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# The possible correlation between magnesium deficiency and SARS-CoV-2 infection

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## Abstract

Magnesium (Mg) is an essential electrolyte for living organisms. It is the fourth most abundant mineral in the body. Although Mg is usually found in hard water and high-fiber diets, wide use of soft water and refined flour impose people at risk of Mg deficiency. Imbalances in Mg status and Mg deficiency may result in a variety of complications associated with the immune, cardiovascular, urinary, nervous, and respiratory systems. Because of the important roles of magnesium in the prevention and treatment of many diseases, several studies are focusing on the correlation between Mg status and Coronavirus disease 2019 (COVID-19). The present study reviewed several types of research to indicate the importance of monitoring of Mg status as well as the possible role of Mg supplementation for supportive treatment in COVID-19 patients. The results indicated that Mg deficiency could be a risk factor for multi-organ dysfunction in COVID-19 infection. Mg supplementation improves functions of the immune, cardiovascular, nervous, urinary, and respiratory systems through different mechanisms. Suppression of cytokine storm, bronchodilation, antithrombotic function, a decrease of arterial blood pressure, preventing electrolyte imbalance, increase stress resistance are some of the related mechanisms. These findings may provide a reference regarding the possible beneficial effects of the Mg supplement as an inexpensive, safe, and easily available drug for supportive treatment in COVID-19 patients.

Keywords: Magnesium; Magnesium Deficiency; COVID-19; Magnesium Supplement

## 1. Introduction

Magnesium (Mg) is the fourth and second most abundant mineral in the body and cell, respectively. Mg plays a crucial role in the structure of the human body and in every essential metabolic reaction. Its concentration in the adult human body is about 25 grams (g). Approximately 50-60% of all Mg concentration is found in the skeletal system and the remainder is in soft tissues. Less than 1% of total body Mg is in blood circulation and only the ionized form of magnesium  $(Mg^{2+})$  is physiologically active [1].

Mg is an essential factor for many physiologic mechanisms and pathways like energy production, protein synthesis, ion transport, as well as cell signaling. It has a key role in hundreds of enzymes by its cofactor activity. Mg also affects Vitamin D and Calcium homeostasis. Gastrointestinal diseases, inadequate dietary Mg intake, kidney disorders, chronic alcoholism, and old age are the main risk factors for magnesium deficiency [2].

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Low serum Mg concentration correlates to increased risks of several complications including cardiovascular disease, osteoporosis, and metabolic disorders. It has been indicated that Mg by improving insulin sensitivity can decrease the risk of type 2 diabetes mellitus. The role of Mg supplementation in the prevention of complications following a stroke or heart surgery was also illustrated. Mg compounds (MgSO<sub>4</sub>) are critically administered in obstetric care preventing seizures in pregnant women with eclampsia. The role of magnesium in preventing brain damage in premature infants is also notable. The use of Mg supplementation for the management of other conditions like asthma or pain is currently under investigation [2-4].

Magnesium content is approximately 50% higher in the high-fiber diet (green leafy vegetables, unrefined grains, legumes, beans, nuts) and is found in hard water. The tolerable upper intake level related to Mg supplement is reported about 350 mg/day. Although Mg intoxication is rare, excessive intake may result in several adverse effects especially in subjects with impaired kidney functions. Despite rich sources of dietary Mg, today's wide use of soft water and refined flour puts people at the risk of Mg deficiency [5, 6].

Recently, global attention has focused on the pandemic coronavirus (COVID-19). The mortality and morbidity rates are dramatically increasing by COVID-19 [7]. Few investigations showed Mg deficiency in COVID-19 patients and have suggested the possible supportive effects of Mg on COVID-19 outcomes. It was also reported that low Mg status may result in mild to critical transition of COVID-19 manifestations. The effectiveness of Mg replacement in a variety of disorders may show the possibility of supportive treatment with Mg supplementation in COVID-19 cases [7-9].

## 2. Hypothesis

So far, very few studies have assessed the relationship between Mg status andCOVID-19 infection. The present study reviewed and summarized the current knowledge on the possible effects of Mg on the prevention or management of COVID-19 to discuss the challenges. Thus, firstly, the risk factors correlated to Mg deficiency were explained. Then the effects of Mg/Mg deficiency on the immune, cardiovascular, urinary tract, respiratory and nervous systems (which are dramatically affected by COVID-19 infection) were reviewed. Finally, we argued the importance of monitoring of Mg status and treatment of Mg deficiency in COVID-19 patients. The results of this study may provide informative data regarding the effectiveness of Mg supplements as preventative or supportive strategies in populations at risk of COVID-19. Moreover, future clinical trials may design and introduce potentially beneficial effects of Mg supplement for infected cases with COVID-19.

## 3. Risk factors associated with Mg deficiency

Mg deficiency is not common in healthy subjects with consuming a balanced diet. Mg is abundant in plant and animal foods as well as in hard water but the widespread use of soft water and refined flour increases the risk of magnesium deficiency [5, 6]. Based on Mg intake, the kidneys regulate urinary excretion of Mg. Several conditions increase the risk of Mg deficiency. Gastrointestinal disorders (prolonged diarrhea, Crohn's disease, malabsorption syndromes, celiac disease, small intestine inflammations, removal bowel surgeries, radiation), renal disorders, endocrine and metabolic disorders (diabetes mellitus, parathyroid gland disorders, primary aldosteronism), phosphate depletion, excessive lactation, poor dietary intake, alcoholism and long-term use of diuretics may lead to Mg depletion. Furthermore, a decrease of intestinal Mg absorption and an increase of urinary Mg excretion are frequently observed by aging process [10-12].

It seems that COVID-19 disease characterized by multi-organ involvement affects dietary Mg intake, gastrointestinal tract, and renal systems leading to more susceptibility for Mg deficiency. It should be also noted that Mg deficiency by weakening the immune system may make individuals more likely to get COVID-19 infection [13, 14].

## 3.1. Mg/Mg deficiency and immune System

Mg can affect the immune system by suppressing the cytokine storm and coagulation cascade. It also has a protective role against oxidative stress by activating vitamin D. The beneficial effects of Vitamin D for immune system health have been known for decades [15]. Mg also plays a key role in antiviral immunity and low magnesium levels may account for impaired cytotoxicity [16]. It was noted that high serum Mg concentration could enhance antihistaminic and anti-inflammatory responses in patients. Moreover, the association between systemic inflammation and Mg deficiency has been delineated. Mg deficiency causes increases in serum levels of  $TNF\alpha$  and inflammatory cytokines with a concomitant decline of production and release of anti-inflammatory cytokines [17-22]. Mg deficiency with its stressor effect makes the body more susceptible to physiological stress resulting in activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and sympathetic nervous system [23]. This activation may also stimulate the production of oxidative stress and

NFkB leading to cell apoptosis. Mg deficiency by NFkB signaling triggers increases of inflammatory cytokines and reactive oxygen species through the activation of calcium channels [22, 23]. These inflammatory responses were confirmed by an animal model study. Inducing Mg deficiency in rats could show leukocyte and macrophage activation, synthesis of inflammatory cytokines, and extensive production of free radicals. Increasing the extracellular Mg levels could alleviate these inflammatory effects [23]. It was also shown that a drop of intracellular free magnesium could induce defective expression of the natural killer activating receptor NKG2D in NK and CD8+ T cells. Mg deficiency can also stimulate hepatic fibrosis and steatosis, possibly through its effect on mast cells [16]. Mg deficiency could accumulate collagen in the cardiovascular system following stress or inflammatory stimuli such as the administration of a hepatotoxic agent [24]. It was demonstrated that Mg deficiency led to increased proliferation of mast cells in the duodenum and the kidney. The researchers noted that XMEN (X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia) patients carrying MAGT1 (Mg transporter) mutations had lower free intracellular Mg levels and Mg supplementation could recover the cytotoxicity defect in cytotoxic T-lymphocytes and NK cells [16].

## 3.2. Mg/Mg deficiency and urinary tract system

Mg deficiency increases the risk of several diseases like diabetes mellitus type II that negatively affect urinary tract function. An investigation illustrated that low Mg levels could significantly deteriorate renal function in 550 diabetes mellitus type II cases with not-known kidney disease. The association between different concentrations of Mg in Chronic Kidney Disease (CKD) was also evaluated and results showed that hypomagnesaemia was responsible for more adverse outcomes. It was also suggested that Mg supplementation may have beneficial effects against calcification and mortality in CKD patients [25]. It should be also mentioned that renal diseases like chronic renal failure or nephrolithiasis can alter Mg balance through excess Mg excretion [26].

#### 3.3. Mg/Mg deficiency and respiratory system

Several investigations noted that high serum Mg concentration could decrease the incidence of exacerbations of chronic obstructive pulmonary disease (COPD). The possible involving mechanisms may relate to the influences of Mg on the relaxation of bronchial smooth muscle, bronchodilation, anticholinergic, antihistaminic, anti-inflammatory, and mucociliary clearance properties. This finding can explain the correlations between hypomagnesemia with increased airway hyperactivity resulting in chronic obstructive pulmonary disease (COPD) or impaired pulmonary function [17-19, 21]. Micke et al. also showed the correlation between low serum Mg concentration and the exacerbations of COPD [27]. Mg can also induce bronchial smooth muscle cell relaxation by inhibiting cytosolic calcium release in the cells [28]. The beneficial effects of Mg on activation of Vitamin D and its role in pulmonary epithelial and immune system health have been also shown [15, 29]. The beneficial role of magnesium supplements in respiratory dysfunction was also confirmed by a systematic review with 668 patients. It was shown that hospital admission due to asthma attacks was significantly reduced by the administration of magnesium sulfate. The rates of PEFR (peak expiratory flow rate) and absolute FEV<sub>1</sub> (the exhaled volume in the first second of a forced expiration) significantly increased in cases with severe acute asthma [30]. A meta-analysis study revealed that intravenous Mg sulfate could significantly decrease hospitalization days in asthmatic cases when compared to those treated with a placebo. It also indicated the synergistic effects of Mg sulfate in conjunction with inhaled bronchodilators and systemic steroids in patients with moderate to severe acute asthma [31]. Patients who received nebulized Mg sulfate demonstrated improvement in pulmonary function leading to a decrease in hospitalization. Improved lung function was also significantly notable in cases using nebulized magnesium sulfate with a B2-agonist [32]. The beneficial effect of Mg sulfate in conjunction with B2-agonist agents for adult and children's patients with severe asthma attacks was confirmed by another study [33]. The use of Mg sulfate (nebulized or intravenous) was also recommended for severe and life-threatening asthma exacerbation [34, 35].

#### 3.4. Mg/Mg deficiency and cardiovascular system

Mg is an essential element for endothelial function. It was reported that Mg deficiency causes endothelial dysfunction with impaired endothelial-dependent vasodilation. Results of a randomized controlled trial showed that oral Mg supplementation could improve flow-mediated dilation as a marker of endothelial function [36]. An in-vitro study indicated that Mg deficiency could be a risk factor for cardiovascular diseases through its influences on the increase of pro-inflammatory cytokine interleukin -1a and atherogenesis in endothelial cells [37]. The other study suggested that Mg can act as an antithrombotic agent by inhibiting of platelet reactivity and thrombosis formation [4]. The synthesis of nitric oxide (NO) is also stimulated by Mg resulting in the relaxation of vascular smooth muscle cells [7]. Mg may also play a protective role against vascular calcification via several mechanisms like inhibition of apatite crystals formation, preventing calcium from entering the intracellular space, restoring the balance between the expression of calcification promoters, and inhibitors as well as activating CaSR leading to inhibition of vascular smooth muscle cells calcification [25].

#### 3.5. Mg/Mg deficiency and nervous system

Several studies have demonstrated the cerebroprotective, glioprotective, and neuroprotective effects of Mg. The roles of Mg in nerve transmission, synaptic plasticity, and excitotoxicity were also well defined. It was indicated that neurological trauma and events may lead to a decrease of Mg concentration through the intracellular shift and increased urinary excretion. There are notable correlations between hypomagnesaemia and various types of neurological complications like depression, stroke, Parkinson's disease, migraine cerebral vasospasm, convulsion, and Alzheimer's disease [38-42]. Divers' neurological manifestations such as muscle tremor, tetany, hyperreflexia, dystaxia, delirium, headache, and convulsion are also observed with severe hypomagnesemia [41]. An investigation reported that Mg supplementation by its role in brain revascularization can improve outcomes related to cerebral ischemia. The possible involving mechanisms may be associated with calcium antagonist and neuroprotective effects of Mg [43]. Another study demonstrated poor outcomes in traumatic brain injury patients with low serum and high cerebrospinal fluid magnesium levels compared to patients with normal magnesium levels [44]. It has been also shown that daily Mg intake for more than 8 weeks could improve depression status in depressed cases [42].

#### 3.6. Mg/Mg deficiency and COVID-19 infection

Multiple organs are affected by COVID-19 but the involvement of respiratory, cardiovascular, nervous, immune systems, and kidneys are responsible for the main manifestations and outcome [45]. It is supposed that Mg deficiency could be a risk factor for COVID-19 infection like other complications (cardiovascular disease, diabetes, chronic respiratory disease, old age, and obesity [27]. Hypomagnesemia was reported in 32% of 134 in- and out-patient cases with COVID-19 without underlying disease [46]. An investigation pointed to Mg deficiency as a risk factor for a severe COVID-19. It was indicated that people with low energy reserves due to Mg deficiency were prone to develop severe COVID-19 symptoms. The authors suggested the role of monitoring of Mg status and supplementation in deficient cases for preventing COVID-19 and its complications [9]. It was demonstrated that regular monitoring of ionized magnesium status with subsequent repletion of Mg may be an effective strategy preventing disease progression [13].

Previous investigations suggested that Mg supplementation may help COVID-19 patients by its effects on different systems. Regarding its influences on the immune system, the possible immunomodulatory and anti-inflammatory effects of Mg compounds (Mg sulfate) on the cytokine phase of COVID-19 have been demonstrated [47]. Mg with "calcium-channel blocking" effect may lead to downstream suppression of nuclear factor-K $\beta$ , interleukin-6, and C-reactive protein resulting in suppression of life-threatening events like cytokine storm in COVID-19 disease. Furthermore, Mg by its ability to activate vitamin D may improve immune system health and protect the body against COVID-19 infection [13, 15].

COVID-19 patients severely suffer from respiratory symptoms. The impacts of Mg supplements on alleviation of respiratory complications in COVID-19 subjects have been reported by Sahin et al. The authors demonstrated that the involved mechanism may be relating to the shift of M1 to M2 type macrophages and stimulation of anti-inflammatory cytokine secretion in the respiratory tract [48]. Another study showed that intravenous administration of Mg could suppress severe inflammatory responses in the respiratory tract and prevent worsening the disease courses in COVID-19 patients [27]. Mg as a calcium antagonist can inhibit bronchospasm and results in bronchodilation. Mg by suppression of inflammatory response and oxidative stress can also alleviate pulmonary symptoms in the COVID-19 patients [7]. The other mechanisms may be associated with mucociliary clearance effects of Mg that can decrease resistance in the airways and improve lung function in COVID-19 patients. The beneficial pharmacological effects of intravenous Mg administration have been demonstrated on lung function [27]. It was suggested that serum Mg level should be monitored and supplementation of Mg should be initiated in deficient cases during the early phase of COVID-19. As Mg may diminish the secondary co-morbidities, prophylaxis with Mg may also be beneficial in populations at risk [9].

It was revealed that COVID-19 like other viral infections influences the endothelial cells and plays a key role in the pathogenesis of cardiovascular dysfunction and associated consequences [49-51]. Mg deficiency may also cause frequent occurrences of thrombotic embolism and coagulation cascade in COVID-19 patients. Mg administration may act as an antithrombotic agent (by suppression of platelet reactivity) to prevent or improve cardiovascular manifestations [4, 52, 53]. These findings show the importance of stabilizing the endothelial status particularly in high-risk patients like COVID-19 patients with pre-existing endothelial dysfunction [48]. The effectiveness of Mg on a variety of cardiovascular complications associated with COVID-19 disease has been also reported by the previous investigation. Decrease of systolic, diastolic, and mean arterial blood pressure, an increase of endothelium-derived NO levels, lowering the risk of ventricular dysfunction, and atrial fibrillation have been shown by Mg supplementation in COVID-19 patients [7].

Previous studies have shown that patients with chronic kidney disease were at higher risk of severe COVID-19 disease. A wide range of kidney complications from proteinuria or haematuria to renal failure and the need for haemodialysis has been also indicated among hospitalized COVID-19 patients [54-56]. As all these urinary tract complications are frequently observed among Mg deficient patients, thus it seems Mg supplementation can prevent COVID-19 patients from further deterioration of their condition [7]. Moreover, Covid-19 infection may also exacerbate the hypomagnesaemia through an excess increase of stress hormones and urinary Mg excretion. Preventing or treatment of such an electrolyte imbalance may provide optimal supportive therapy for Covid-19 patients [45, 57].

Regarding the influence of Coronavirus on the nervous system, it should be noted that Coronavirus is detected in the brain tissue as well as in cerebrospinal fluid that can severely impact the nervous system through diverse pathways [58]. COVID-19 patients complain of a wide range of mild to severe neurological manifestations like headache, dizziness, hypogeusia, myalgia, hyposmia, polyneuropathy, myositis, complications related to cerebrovascular events or intracranial infections [59, 60]. Moreover, COVID-19 patients severely experience acute and chronic emotional tensions which result in an increase of stress hormones catecholamines and corticosteroids [46, 61,62]. As mentioned before, all these events may lead to the loss of more and more Mg. Besides that, Mg deficiency is one of the main factors for decrease of stress and immune resistance as well as adaptive body reserves. So, it seems that using Mg supplements to correct Mg level in COVID-19 patients can beneficially increase stress resistance and prevent neurological diseases [61]. It was also indicated that Mg by antagonizing calcium can interfere with calcium functions either at the level of calcium channels, cytosolic influx, calcium-dependent enzymatic activities, inflammatory and blood clotting processes. These properties of Mg may significantly prevent neurological and cerebrovascular pathologies in COVID-19 patients [63].

In brief, there are no pharmacological strategies for the treatment of COVID-19; however, in the present study, we have shown the importance of nutritional strategies. Previous research has demonstrated that magnesium has a wide-range of systemic effects on the body. On the other hand, Mg deficiency has been shown as one of the pathogenic factors for decreasing stress resistance and body's adaptive reserves, thrombotic events, bronchospasm, ETC. So, it is supposed that Mg supplementation may be beneficial in vulnerable populations such as COVID-19 patients. However, relevant research questions such as the prevalence rate of Mg deficiency in COVID-19 patients, correlation between Mg deficiency with the severity of disease or the occurrence of co-morbidities, and the therapeutic doses need to be discussed and determined by future studies and clinical trials.

## 4. Conclusion

In the present study, previous studies were reviewed and the results indicate the positive correlations between Mg deficiency and multi-organ dysfunctions in COVID-19 disease. The effectiveness of Mg supplementation on improved functions of immune, cardiovascular, urinary tract, respiratory, and nervous systems may provide a reference regarding the possible beneficial effects of Mg for supportive therapy in COVID-19 cases. However, future studies should determine the prevalence rate of Mg deficiency in COVID-19 patients, the therapeutic doses, and the correlation between Mg supplementation and the severity, co-morbidity, and outcome of the disease.

#### **Compliance with ethical standards**

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Dr. L. N and Dr. M.S carried out the design and coordinated the study, participated in most of the experiments. Dr. S.D, Dr. Z.F. and Dr. M.M.S.D. participated in manuscript preparation. All authors have read and approved the content of the manuscript.

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Our study was approved by the institutional review board of Tehran University of Medical Sciences and according to Helsinki declaration.

#### Disclosure of conflict of interest

The authors declare that there is no conflict of interests.

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