Importance of Magnesium Status in COVID-19

Subjects: Infectious Diseases

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Magnesium is an essential nutrient, also called an essential mineral or element. Magnesium is vastly important in all life, with vital roles for the healthy functioning of the human immune, metabolic, neurological, psychological, and heart and circulatory systems. Magnesium (Mg) status may have relevance for the outcome of COVID-19 and that Mg could be protective during the COVID disease course: (1) low magnesium status is associated with the severity of COVID-19 outcomes, including mortality, and with several disease-related neurological symptoms, including loss of memory, taste, and/or smell; (2) inhaled magnesium as a therapy may improve oxygen status; and (3) magnesium therapy, alone or in combination with zinc, may increase the effectiveness of anti-COVID-19 medications.

Keywords: COVID-19 ; SARS-CoV-2 ; magnesium ; Mg ; zinc ; Zn ; hypomagnesemia ; dietary magnesium ; magnesium deficit ; serum magnesium

1. Introduction

Mg is an essential trace element that plays a substantial role in physiological, biochemical, and cellular processes [1]. Mg is the second most abundant cation in cells in the body after potassium, with 99% of total-body Mg localized within the intracellular space and approximately 1% in blood and extracellular fluids [2][3].

Mg is involved in all metabolic and biochemical pathways and is required in a large range of vital functions such as bone formation, neuromuscular activity, signaling pathways, bioenergetics, metabolism (of glucose, lipids, and protein), DNA and RNA stability, and cell proliferation and differentiation [4][5][6][7][8][9][10][11]. Enzymatic databases report > 600 enzymes with Mg registered as a cofactor, and there are another 200 in which Mg acts as an activator [12]. However, it must be noted that Mg itself is a substrate rather than a cofactor, as the enzyme substrates are Mg complexes [6][7][8][9].

Mg's role in suitable immune, vascular, and pulmonary function has been highlighted previously [13][14]. In this regard, Mg is required for the following: proper function of neutrophils and macrophages, cytotoxic activity of T lymphocytes, activation of immunocompetent cells, and inhibition of viral replication [15][16]. It is noteworthy that Mg regulates innate and adaptive immune system activity, which may result in potential protective effects against COVID-19. For instance, Mg stabilizes the membranes of mastocytes, regulates neutrophil and macrophage activity, and inhibits the Toll-like receptor a/nuclear factor-κB (NF-κB) axis [17]. Furthermore, Mg modulates the cytotoxic functions of natural killer (NK) cells and $CD8^+$ T lymphocytes [18].

Whereas normal Mg levels exert a protective function against viral infection, Mg deficiency may contribute to viral infection. Mg deficiency has been reported to decrease NK and T-cell cytotoxicity, increase NF-κB expression, and exert proinflammatory activity through upregulation of proinflammatory cytokine production in monocytes [19]. Recently, Lötscher et al. [20] demonstrated that extracellular Mg concentration via lymphocyte function-associated antigen LFA-1 regulates CD8 T-cell function. Mg helps T cells attain an active state, transmit signals, reprogram metabolism, form physical bridges to target cells, and ultimately kill errant or infected cells. Mg deficiency primes phagocytes, improves granulocyte oxidative burst, activates endothelial cells, and increases cytokine level synthesis and release (i.e., cytokine storm) [17]. In addition, hypomagnesemia triggers the inflammatory response by activating phagocytic cells, opening Ca channels, and activating NF-κB and *N*-methyl-d-aspartate receptors (NMDARs) [21]. These findings suggest that Mg deficiency may play a critical role in severe outcomes of COVID-19 infection and may explain the increased risk for COVID-19 among patients who are older or have hypertension, obesity, or diabetes, as these individuals usually present with hypomagnesemia and/or low Mg intakes [22][23][24].

2. Low Serum Mg and COVID-19

Among areas related to Mg and COVID-19 risk requiring further research is the frequency of hypomagnesemia in subjects with SARS-CoV-2 infection. However, information is scarce [25][26]. Quilliot et al. [25] analyzed serum Mg levels in 300 French patients with COVID-19 at hospital admission. The investigators found that 48% of patients exhibited hypomagnesemia (serum Mg < 1.82 mg/dL [<0.75 mmol/L, <1.5 mEq/L]), including 13% with severe hypomagnesemia (serum Mg < 1.58 mg/dL [<0.65 mmol/L, <1.3 mEq/L]). In a study of 1064 Mexican individuals with COVID-19 at hospital admission, Guerrero et al. [26] found that hypomagnesemia frequency (serum Mg ≤ 1.8 mg/dL) was 44.1%.

Among tools used to predict the development of severe COVID-19, two studies included serum Mg measurements at hospital admission as a risk factor for adverse prognosis [27][28]. Jia et al. [27] reported that serum Mg levels between 2.19 and 2.26 mg/dL protected from further deterioration. Jia et al. [27] also showed that Mg levels < 2.0 mg/dL are a risk factor for severe COVID-19.

Associations of genetically predicted circulating concentrations of 12 micronutrients (i.e., β-carotene, calcium, copper, folate, iron, magnesium, phosphorus, selenium, vitamin B6, vitamin B12, vitamin D, and zinc) with SARS-CoV-2 risk and COVID-19 severity were investigated in a Mendelian randomization study of 87,870 individuals of European descent with a COVID-19 diagnosis and 2,210,804 controls [29]. Significant effects were found only for Mg, indicating that circulating Mg levels in COVID-19 cases were lower relative to the general population. Nonetheless, the relevance of Mg deficiency in increased risk for developing SARS-CoV-2 infection, as well as severe COVID-19, remains to be clarified [13].

3. Low Dietary Mg Intake and COVID-19

As with hypomagnesemia, risk factors for COVID-19 correspond to those associated with low dietary Mg intake. Mg intake generally diminishes with aging. Mg deficit is associated with cardiovascular disease, hypertension, type 2 diabetes mellitus, and asthma [30]. In addition, nutritional Mg deficiencies are associated with major chronic noncommunicable diseases such as cardiovascular disease and type 2 diabetes mellitus [22]. In patients with chronic kidney disease, Mg deficiency is common because of restricted Mg intake and impaired Mg reabsorption [31]. Obesity can be considered a profound risk factor for greater COVID-19 susceptibility and severity [32]. The Recommended Dietary Allowance (RDA) for Mg increases with body weight [33]. Thus, persons with obesity have higher dietary Mg requirements than individuals without obesity, making it more likely they will incur a dietary Mg deficit. In addition, low dietary Mg is associated with inflammation, especially C-reactive protein (CRP) [28][34][35].

Whole grains, legumes, nuts, fruits, and vegetables are examples of foods with high Mg concentrations. In previous studies, individuals who consumed a plant-based diet showed a 73% lower risk of moderate to severe COVID-19 [36][37]. However, in populations consuming modern processed food diets, inadequate Mg intakes were common [38]. Low dietary Mg intake may lead to low serum Mg concentration, which can be corrected with oral Mg supplementation [39][40].

Handwashing and vaccinations help reduce the spread and impact of infections. Nevertheless, nutrition (including Mg) plays an important and complementary role in immune system support [41]. Strong evidence shows that adequate Mg plays a role in reducing inflammation and disease burden among patients with COVID-19 [42]. Mg intake has been shown to be inversely associated with CRP, interleukin (IL)-6, and TNF-α-R2 [43]. To maintain host immunity, adequate intake of dietary agents including Mg is required [44]. Zinc, calcium, iron, and magnesium have important roles in boosting host system immunity and assist in the development and function of lymphocytes, cytokines, free radicals, inflammatory mediators, and endothelial cells [45]. Some micronutrients, including Mg, have been shown to enhance immune system support to fight respiratory infection; therefore, Mg has a vital role in antiviral defense in patients with COVID-19 and may affect the severity of infection, symptoms, and outcomes [46]. Mg is beneficial in reducing the risk of chronic pulmonary disease and viral infection [47], an area of special import for patients with COVID-19.

Vitamin D status is shown to predict COVID-19 risk, infection severity, and death [48][49]. Serum Mg levels are associated with serum vitamin D levels [50]. Mg status is important in vitamin D metabolism, with Mg being required for proper vitamin D activation and metabolism [51]. Mg deficiency may impair vitamin D metabolism [52], whereas oral Mg supplementation has been shown to increase serum vitamin D levels [53].

Consumption of high-Mg drinking water has long been associated with lower risks of cardiovascular death [54]. In addition, US researchers found that COVID-19 infection risk during early transmission was greater in populations in areas low in Mg [55]. The main mechanisms of the effects of drinking mineral water on the rehabilitation of new coronavirus infection convalescents are nonspecific hormone-stimulating effects in the form of pronounced activation of the gastroenteropancreatic endocrine system, which is capable of integrating substance and energy exchange following the

current needs of the body and also excreting vasoactive factors modulating vital functional system activity. Intake of mineral water with a high content of hydrocarbonate ions, magnesium, sodium, and carbon dioxide saturation with general water mineralization from between 5 and 6 to between 11 and 13 g/L has the maximum effect [56]. As a result of food refining and processing, the Western diet is often low in Mg [57].

4. Mg Supplements and COVID-19

The role of Mg supplements in preventing or treating chronic disorders related to the respiratory system (asthma), reproductive system (preeclampsia), nervous system (migraine), digestive system (constipation), cardiovascular system (hypertension), and endocrine system (diabetes) has been shown previously [58], just as oral Mg supplements been shown to lower serum CRP [59]. After the global COVID-19 outbreak, scientists focused on approaches to prevent or treat this infectious disease. They also strove to introduce supplements or medications to reduce COVID-19 symptoms in patients [60]. Essential supplements to modulate the immune system and interferon (IFN) signaling pathway (e.g., vitamin D, Zn, and Mg) were offered in this regard [61]. Mg was highlighted as an element involved in the immune and inflammatory pathways of COVID-19 [62]. Accordingly, Mg supplements were suggested to prevent and treat COVID-19 [58]. In a previous study, a short course of a Mg supplement in combination with vitamins B12 and D was administered to 17 patients with COVID-19 [63]. These patients showed decreased requirements for oxygen therapy and ICU support compared with controls [63]. Mg supplements may decrease symptoms in patients with hypomagnesemia, whereas they may not be helpful for patients with normal serum Mg levels [64]. Administration of Mg supplements may restore intracellular Mg, which leads to regulation of the cytotoxic functions of NK and $CD8^+$ T cells and reduction in cytokine overproduction [65]. There are two important issues to discuss when recommending Mg supplements as a supportive treatment for patients with COVID-19: (1) measurement of serum Mg levels and (2) bioavailability of Mg supplements. Ionized serum Mg (iMg) or total serum Mg (tMg) can be measured to assess Mg status. Although iMg may better predict clinical outcomes, especially in critically ill patients, it cannot be measured in many clinical settings because specialized equipment is required [66].

The bioavailability of Mg supplements varies within a broad range and depends on various factors. The type of salt and the formulation of Mg supplements are two known factors that may affect the absorption rate. Some studies have shown that the bioavailability of organic Mg salts (lactate, aspartate, amino acid chelate, and citrate) is slightly higher than inorganic products; however, other studies have not confirmed these results [2]. The different study designs on the bioavailability of Mg salts make it difficult to predict which type of Mg supplement has a better absorption rate. Solubilized Mg formulations (e.g., effervescent tablets) have more bioavailability than slow-release formulations [67], and it is better to recommend these to patients who need a rapid increase in Mg serum levels. Drug-drug and drug-food interactions are also important factors influencing the absorption and bioavailability of Mg supplements. Mg absorption is pH dependent and mostly occurs in the small intestine via a passive pathway [68]. Changing gastric acid secretions and intestinal pH with drugs such as proton-pump inhibitors can decrease Mg absorption [69].

5. Mechanisms of Action of Mg in Pulmonary Complications of COVID-19

The respiratory system is the main organ involved in COVID-19, and hypoxia is a significant cause of morbidity and mortality resulting from this disease. According to previous studies, the primary cause of hypoxia in COVID-19 is ventilation–perfusion (VQ) mismatch [70][71]. The phenomenon of VQ mismatch occurs in the alveolar-capillary unit due to airflow incompatibility in the alveoli and pulmonary capillary blood flow around these alveoli. Some lung areas, such as nearly normal ventilated alveoli with microvascular thrombosis and vasoconstriction, have high V/Q. In other parts of the lung, blood flow is diverted to dilated vessels around poorly ventilated alveoli, which show low V/Q. Therefore, these events lead to VQ mismatch; awareness of this mechanism is helpful for determining therapeutic solutions [72].

To improve ventilation and perfusion and to reduce VQ mismatch in patients with severe COVID-19, nebulization of several agents (e.g., prostacyclin analogues, nitric oxide [NO], and Mg sulfate) has been proposed [73][74][75]. Among these medications, Mg sulfate is a more accessible and inexpensive compound with multiple effects to improve the oxygenation of patients with COVID-19. Mg sulfate has anti-inflammatory, bronchodilatory, vasodilatory, and antithrombotic effects [76][77]. Treatment with inhaled Mg sulfate may play the best role in improving the oxygenation of hypoxic patients with COVID-19 due to better lung accumulation with direct effects. In this regard, inhalation of Mg sulfate causes bronchodilation and improves ventilation; the accumulation of Mg sulfate in well-ventilated alveoli then causes vasodilation and increases perfusion in the capillaries around these alveoli. As a result, increased perfusion in well-ventilated alveoli could reduce VQ mismatch and improve oxygenation [75]. Based on this theory, a multicenter, open-label, randomized controlled trial was conducted in Iran during 2020 and 2021 to investigate the effect of inhaled Mg sulfate in hospitalized patients with COVID-19 [75].

6. Mg in Neurological and Psychiatric Complication of COVID-19

6.1. Guillain-Barré Syndrome and Encephalopathies

Guillain-Barré syndrome is a very severe acute paralytic neuropathy. This syndrome is the most frequent paralytic neuropathy worldwide [78]. Guillain-Barré syndrome has been reported as a complication of COVID-19 [79] that persists long after recovery from the disease [80]. About 25% of these patients develop not only rapidly progressive weakness of the extremities but also respiratory insufficiency [81]. This impairment is difficult to differentiate from the respiratory insufficiency produced by COVID-19 through its direct action in the respiratory system.

Acute flaccid paralysis is essentially an acute inflammatory neuropathic disease [82]. The mechanisms by which Mg can reduce disease severity include anti-inflammatory action, cytokine storm reduction when it occurs, and protective action at the myelin of the peripheral nerves.

Cerebral hypoxia and the genesis of acid metabolites through the increase in anaerobic metabolism are also involved in the occurrence of toxic encephalopathy in some patients with COVID-19 [83]. Encephalopathy degrades patients' mental states to different degrees, varying from patient to patient. Severe forms of necrotizing encephalitis are considered to be produced by the cytokine storm. By reducing this storm, Mg suppresses one of the essential mechanisms of encephalopathies.

6.2. Memory and Cognition

Memory and cognition are complex multifactorial processes in which there is a complicated relationship between genetic and nongenetic factors [84]. Cognition and memory disorders have been observed in patients with COVID-19 [85][86]. Accurate quantification of severity and frequency is difficult because even if these disorders are observed during hospitalization, it is only sometimes known whether the patient presented them before SARS-CoV-2 infection. Mg plays a major role in the mechanisms of memory and cognition, and Mg deficiency is involved in a significant reduction in memory [87][88].

6.3. Taste and Gustatory Dysfunction, Loss of Smell, and Loss of Appetite

The molecular mechanism of taste sensation is not completely known. Experimental studies have shown that the TAS2R7 taste receptor is activated by $MgCl_2$ (and by $MnCl_2$ and $ZnSO_4$) [89]. There are other taste receptors (TAS2R14, TAS2R10, TAS2R38, and TAS2R16) but they are not activated by Mg or Zn salts. Reduced Mg in patients with COVID-19 can cause a decrease in, change in, or complete loss of taste [90].

Loss of smell is common in patients with COVID-19, both in hospitalized patients and in those with mild forms of the disease that do not require hospitalization. Restoration of the acuity of the olfactory senses occurs mainly under the action of Mg and Zn [91]. A low Mg level contributes to the loss of smell in patients with COVID-19 [90][92].

Mg deficiency also causes loss of appetite [93], which is frequently encountered in both hospitalized patients [94] and outpatients [95] with COVID-19.

6.4. Ataxia

Among various neurological diseases in which their pathogenesis involves hypomagnesemia are cerebellar syndromes, which include ataxia [29]. In a previous study, Mg administration contributed to the improvement of cerebellar clinical manifestations in these patients [96]. Mg administration also rapidly improved the ataxic manifestations [97][98].

6.5. Confusion, Delirum, and Consciousness Disturbances

One clinical manifestation of hypomagnesemia is the presence of confusional states and, more rarely, delirium [29]. Hypomagnesemia is one of the electrolyte disorders that are sometimes associated with the appearance of delirium [99]. The problem of disturbed consciousness is very complex because it can evolve from dysphoria and disorientation to loss of consciousness [83]. Impaired consciousness occurs in about 14% of patients with COVID-19 [100][101]. Because the exact mechanism of the production and maintenance of consciousness is unknown, it is difficult to indicate where Mg is involved. Both hypomagnesemia and hypermagnesemia sometimes cause severe disturbances of consciousness [102] [103]. Hypomagnesemia is common in patients with COVID-19, but there are no consistent data regarding the presence of significant hypermagnesemia in these patients.

6.6. Cranial Nerve Deficits and Cranial Nerve Palsy

Peripheral autonomic nervous system disorders are due to the direct action of the virus on peripheral nervous structures and occur in about 2.5% of hospitalized patients. Demyelination, cranial nerve palsy, and axonal neuropathies are present in some patients with COVID-19 [104]. Complications of this disease include damage to the cranial nerves, especially lesions of the bulbar cranial nerves [105].

6.7. Convulsions, Child Epilepsy, and Hallucinations

In patients with COVID-19, convulsions occur mainly due to encephalic inflammation and hypoxia, which lower the convulsive threshold. Some patients experience focal seizures, whereas others have generalized seizures [106]. These seizures can be tonic or tonic-clonic and appear in children and in some adults. The mechanisms of producing convulsions are different [107]. Hypomagnesemia is associated with the production of convulsions. Lack of Mg lowers the convulsive threshold, increases the glutamate concentration in the brain, and reduces the action of inhibitory GABAergic systems [108].

6.8. Demyelination and Axonal Neuropathies

Both genetic and epigenetic factors are involved in the mechanism of producing demyelination [109]. One of those in the last category is Mg deficiency.

One disease in which a significant Mg deficit is evident is multiple sclerosis. Demyelination plays an essential pathogenic role in the progression and evolution of this disease. In patients with multiple sclerosis, the most marked reduction in Mg^{2+} content has been observed in the CNS white matter and demyelinated plaques. Mg deficiency is involved in nerve dysfunction and demyelination [110][111]. This reduction in Mg concentration at the level of demyelinated areas and multiple sclerosis plaques is associated with general hypomagnesemia in these patients [112]. In other CNS diseases with demyelination, low Mg levels have also been reported. Mg has a stabilizing effect on myelin. Mg administration to patients with multiple sclerosis has been shown to decrease the frequency of relapse [113]. Demyelination from multiple sclerosis is associated not only with a low level of plasma Mg but also with a reduction in the concentration of this element in the cerebral spinal fluid [114].

6.9. Headache and Dizziness

Headache is common in patients with COVID-19 and has been reported in numerous studies. For example, headache was reported in 11–34% of hospitalized patients with COVID-19 [101][115]. Previous studies suggest that the main pathogenic mechanism is the entry of the virus into the CNS and the increased synthesis and release of cytokines [116].

After SARS-CoV-2 fixes on the receptors at olfactory mucosa by transsynaptic migration through the olfactory route from the nasal cavity, the virus affects both the trigeminal branches and the trigeminal ganglion [117].

6.10. Immunity

Mg deficiency is involved in the pathogenesis of COVID-19 complications due to decreased intracellular and extracellular Mg that leads to decreased antiviral immunity [118]. Although hypomagnesemia is involved in the occurrence of some COVID-19 complications [65], there are no data to show a therapeutic benefit of hypermagnesemia in this disease [119].

Hypomagnesemia is statistically significantly associated with increased mortality of patients with COVID-19. The causes of death among these patients are multiple, but CNS dysfunctions are also involved (without the existing data to identify the frequency of these involvements) [120].

A potentially important consideration is the ratio of Mg and Ca concentrations in patients with COVID-19. There are little data in this regard, but some studies show that a weight ratio of Mg:Ca serum concentrations ≤ 0.2 (or molar Mg/Ca serum ratio ≤ 0.33) determines the occurrence of serious complications and is strongly associated with mortality in patients with severe COVID-19 [26]. Unfortunately, there are no studies showing the importance of the Ca/Mg ratio in the occurrence of neuropsychiatric complications of COVID-19 or regarding their severity.

7. Interrelationships between Mg, Zn, and Agents Used to Treat COVID-19

Several agents have been used or are still used today to treat COVID-19. Some examples include ivermectin, azithromycin, chloroquine, hydroxychloroquine, casirivimab, dexamethasone, imdevimab, sotrovimab, tocilizumab, remdesivir, amantadine, moxifloxacin, mefloquine, molnupiravir, anticoagulants, favipiravir, and others [121][122][123][124][125]

[126]. Important interrelationships with Mg and Zn—two of the most important biometals in the human body—are known for some of these agents. With regard to their use in COVID-19 treatment, the interrelationships between these medications and two of the main electrolytes in the human body, Mg and Zn, are complex. The four groups of interrelationships are as follows:

- pharmacodynamic interactions between Mg^{2+} and Zn^{2+} and the action of anti-COVID-19 drugs, including a) direct influence on the drug mechanism of action and b) indirect influence through the influence on the body immunity of patients with COVID-19;
- pharmacokinetic interactions (related to the influence of Mg and Zn on the absorption, transport in the blood, and elimination from the body) of the drugs used;
- influence of anti-COVID-19 medication on the plasma or tissue concentration of these two cations; and
- influence of Mg^{2+} and Zn^{2+} on the adverse effects of anti-COVID-19 medication.

Mg and Zn can indirectly influence the efficacy of anti-COVID-19 drugs by reducing the intensity and frequency of some adverse effects and by their involvement in the immune response, which, together with the action of these drugs, plays an essential role in the evolution and prognosis of patients with COVID-19. In evaluating the interrelationships of Mg^{2}, Zn^{2+}, and anti-COVID-19 drugs, the following factors must also be considered:

- Among the numerous drugs that are or have been used to treat COVID-19, these interrelations are partially known only for some. Future studies are needed.
- Many drugs that have been or are used in anti-COVID-19 therapy are also used to treat other diseases. Their pharmacokinetic characteristics and mechanism of action remain the same and are intrinsically determined by their molecular structure. Some pharmacokinetic characteristics could be modified if new pharmaceutical forms are used.
- Frequently, patients with COVID-19 receive not only anti-COVID-19 therapy but also treatment for preexisting chronic diseases. Drugs used to treat these conditions can change Mg and Zn plasma concentrations and thus indirectly influence anti-COVID-19 therapy.
- Extracellular and intracellular Mg levels and Zn plasma levels in hospitalized patients with COVID-19 are highly variable. Many patients have hypomagnesemia or hypozincemia (or both) upon admission, and many develop imbalances of these elements during the disease course.
- Determinations of serum Mg and Zn concentrations at admission and during hospitalization are inconsistent (and in many cases, only sporadically undertaken).
- Oral nutrition of these patients can be deficient, and the solutions administered parenterally rarely aim to correct Mg deficiency.

Patients with COVID-19 receive anti-COVID-19 treatment (usually made up of several associated medications) and medications used to treat any preexisting diseases. With all of these medications, there can be interactions of various types independent of interactions of the anti-COVID-19 medication with Mg and Zn.

Mg and Zn homeostasis is important [13], but all of the factors shown previously affect pharmacotherapy against COVID-19. Disturbances of the hydroelectrolyte balance during hospitalization of patients with COVID-19 have been observed not only for Mg and Zn but also for other electrolytes. Sodium and potassium serum concentrations are significantly lower in these patients compared with healthy individuals of the same age [127]. Serum concentrations of the main electrolytes must be determined for all patients, both at admission and during treatment.

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