Editorial

Magnesium deficiency and COVID-19 – What are the links? Some remarks from the German Society for Magnesium Research e.V.

Oliver Micke[1]*, Jürgen Vormann[2], and Klaus Kisters[3]**

[1]Department of Radiation Therapy and Radiation Oncology, Franziskus Hospital, Bielefeld, [2]Institute for Prevention and Nutrition, Ismaning, and [3]Internal Medicine I, St. Anna Hospital, Herne, Germany

*President of the German Society for Magnesium Research e.V.
**Vice-President of the Society for Magnesium Research e.V.

The novel coronavirus SARS-CoV-2 is causing an ongoing worldwide pandemic of COVID-19.

The infection with this single-stranded RNA virus appears to be asymptomatic in a large fraction of people, and many other patients may experience mild symptoms such as fever, cough, anosmia, and myalgia. Some German patients need hospitalization, and some will develop acute respiratory distress syndrome (ARDS), and a significant subset will require treatment in the intensive care unit to provide respiratory ventilator support.

Unfortunately, there is no causal curative treatment or a vaccination available, so far.

In this context, the potential prophylactic and therapeutic options for the novel SARS-CoV-2 infection and corresponding COVID-19, as well as interventions with special nutrients like zinc or vitamin D are discussed, especially due to their role in the immune system [1, 2, 3, 4]. Magnesium (Mg) has a strong relation with the immune system as well, and immunological functions are disturbed in case of Mg deficiency [5, 6]. Interestingly, in patients with XMEN disease (X-linked immunodeficiency with Mg defect, Epstein-Barr virus (EBV) infection, and neoplasia) it has been reported that free basal Mg concentration has an important role in regulating cytotoxic immune function [7]. By that, intracellular free Mg concentration contributes significantly to antiviral immunity. Therefore, decreased resistance against infection with SARS-CoV-2 in case of Mg deficiency can be assumed. However, there are some more potential connections between Mg and COVID-19 worth mentioning.

QT interval prolongation – think of Mg

Possible drugs for the treatment of COVID-19 increase the risk of QT interval prolongation, e.g., chloroquine, hydroxychloroquine, azithromycin, lopinavir, ritonavir [8]. QT prolongation can provoke life-threatening torsade-de-pointes arrhythmias (TdP) and sudden cardiac death. Mg deficiency and other electrolyte imbalances also belong to the known risk factors for QT prolongation and TdP [9]. Consequently, it is recommended to obtain baseline assessment of Mg and other electrolytes and to correct deficiencies before using QT-prolonging

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drugs [8]. Keeping serum potassium levels and Mg levels above 4 mmol/L and 3 mg/dL (= 1.23 mmol/L), respectively, in COVID-19 patients treated with QT-prolonging drugs proved to be effective in preventing QT prolongation, and no arrhythmias or sudden cardiac arrest were registered [10]. This is above the upper limit of the reference range (usually ~ 1.1 mmol/L). In a single-center study (n = 524), a specially designed monitoring process in COVID-19 patients (with COVID-19-related medication) identified a high proportion of patients with QT prolongation (n = 103, corresponding to 19.7%) [11]. As part of the medical support, achieving Mg and potassium in the reference range was recommended [11].

Administration of intravenous Mg sulfate is the therapy of choice for hemodynamically stable TdP, regardless of whether the patient is hypomagnesemic or has a normal serum Mg concentration [9]. This may be a relevant reason why the German Federal Institute of Drugs and Medical Devices (BfArM) put Mg (parenteral) on a list with drugs whose need is greatly increased with treatment of COVID-19 patients in intensive care units [12]. On the other hand, hypomagnesemia generally is a common occurrence in intensive care patients (regardless of COVID-19) with a prevalence up to 65%, associated with an increased mortality rate, higher need for ventilator support, increased incidence of sepsis, and longer hospital stays [13, 14].

Mg and lung function

With regard to lung function, lower serum Mg concentrations seem to increase the incidence of exacerbations in chronic obstructive pulmonary disease (COPD) [15, 16, 17, 18, 19, 20]. Possible mechanisms for this relationship are functions of Mg in the relaxation of bronchial smooth muscle and bronchodilatation, anticholinergic, antihistaminic, and anti-inflammatory effects as well as mucociliary clearance. It is therefore believed that hypomagnesemia is associated with increased airway hyperactivity and impaired pulmonary function [20]. Intravenous Mg sulfate is emphasized as an adjunctive therapy for acute asthma in the emergency department [21], whereas oral Mg supplementation may improve the outcome in mild to moderate asthma [22]. Intravenous Mg sulfate is also discussed as an adjunctive therapy in acute exacerbations of COPD and asthma-COPD overlap [19]. However, clinical evidence is poor, and standard guidelines do not recommend Mg sulfate in acute exacerbation of COPD, but it is used by some clinicians in practice [19]. Given the current evidence, harmful consequences of an existing Mg deficiency on lung function in COVID-19 patients can be assumed. Furthermore, there are indications that intravenous Mg may have beneficial pharmacological effects on lung function, regardless of Mg status.

Mg and function of the epithelium

There is increasing evidence that viral infection of the endothelial cells plays a key role in multi-organ involvement, and severe courses of COVID-19 [23, 24, 25]. This finding provides a rationale for therapies to stabilize the endothelium, in particular for vulnerable patients with pre-existing endothelial dysfunction which can be found for example in cardiovascular disease, diabetes, hypertension, obesity, all of which are associated with adverse outcomes in COVID-19 [23]. Interestingly, Mg is known to be crucial for endothelial function, and its deficiency causes endothelial dysfunction with impaired endothelial-dependent vasodilation [26, 27]. In a meta-analysis of randomized, controlled trials (RCTs), oral Mg supplementation was shown to improve flow-mediated dilation as a marker of endothelial function [28]. It is therefore plausible to assume that Mg deficiency further worsens the consequences of an infection with SARS-CoV-2 via induction of endothelial dysfunction. In this context the frequent occurrence of thrombotic embolism in COVID-19 is worth mentioning [29, 30]. Animal and human data suggest that Mg functions as an antithrombotic agent. Hence, increased platelet reactivity and thrombosis are possible cardiovascular manifestations of Mg deficiency [31].

Table 1. Relevant research questions for magnesium related to COVID-19.

Is the prevalence of Mg deficiency or hypomagnesemia increased in COVID-19 patients?
Is Mg deficiency or hypomagnesemia associated with more severe courses of disease in COVID-19 and why? (e.g., endothelial dysfunction, more cases of thromboembolism)
In case of new infection with SARS-CoV-2: Does oral Mg supplementation have an impact on the course of the disease or the occurrence of complications?
Does the therapeutic induction of hypermagnesemia via Mg infusion provide clinical benefits for COVID-19 patients in the intensive care unit (for example with regard to lung function)?

Mg and inflammation

Furthermore, increased inflammation in Mg deficiency has to be kept in mind. Experimental studies show an increased incidence of markers for inflammation in case of Mg deficiency, e.g., leukocyte and macrophage activation, pro-inflammatory molecules such as interleukin-1, interleukin-6, tumor necrosis factor, vascular cell adhesion molecule-1, plasminogen activator inhibitor-1, and excessive production of free radicals [26, 32]. Generally, Mg deficiency is considered a significant contributor to chronic low-grade inflammation and, therefore, risk factor for a variety of pathological conditions, such as cardiovascular disease, hypertension, and diabetes [32]. In meta-analyses of RCTs, Mg supplementation was shown to reduce C-reactive protein levels [33, 34]. Whether Mg deficiency or Mg supplementation may impact the inflammatory event in COVID-19 has to be investigated in clinical studies.

Mg status and COVID-19

To our knowledge, there are no systematic studies so far examining Mg status in COVID-19 patients. In a pooled analysis, Lippi et al. [35] confirmed that COVID-19 severity was associated with lower serum concentrations of sodium, potassium, and calcium. Therefore, measuring of electrolytes at initial presentation and monitoring during hospitalization is recommended in order to be able to take appropriate corrective measures in good time [35]. Unfortunately, serum Mg was not determined in the studies analyzed. In the above mentioned study of Jain et al. [11], 30.1% of the COVID-19 patients with QT prolongation showed hypomagnesemia.

Conclusion

In view of the relationships described, it is plausible to assume that Mg deficiency may decrease the resistance against infection with SARS-CoV-2 and, most notably, may worsen the course of COVID-19. Hence, Mg deficiency could be a risk factor for severe COVID-19, comparable to cardiovascular disease, diabetes, chronic respiratory disease, older age, obesity, amongst others. Interestingly, Mg deficiency is often associated with these risk factors or seen as comorbidity. However, relevant research questions need to be addressed (Table 1) before definitive conclusions can be drawn.

Diagnosis and treatment of Mg deficiency

As a pathological situation, Mg deficiency should generally be avoided and is in need of treatment per se. According to new scientific data, an evidence-based reference interval for total serum Mg concentration of ≥ 0.85 mmol/L is proposed [36]. However, the informative value of serum Mg is limited as normal serum Mg concentrations can be seen in the presence of intracellular Mg deficiency. Therefore, the clinical symptoms of Mg deficiency (e.g., cramps, cardiac arrhythmias, headache, and excitability) and medical history (e.g., diabetes mellitus, diuretics, proton pump inhibitors) are of great importance for the diagnosis [37, 38, 39]. Mg deficiency should be treated by oral ingestion, if possible. Daily doses of 10 – 20 mmol (243 – 486 mg) over several weeks are recommended. Contraindications are severe renal failure (GFR < 30 mL/min), exsiccation, and anuria. Parenteral therapy is reserved for clinical specialists and special areas of indication in which hypermagnesemia is induced as a therapeutic principle.

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Conflict of interest

None.

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Prof. Dr. med. Oliver Micke
Department of Radiation Therapy and Radiation Oncology
Franziskus Hospital
Kiskerstraße 26
33615 Bielefeld, Germany
oliver.micke@franziskus.de