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14 déc. 2020 15:22 (il y a 2 jours)



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Dear Prof Mourad Errasfa,

We are delighted to inform you that your manuscript mag200066 "Magnesium therapeutic potentials against Covid-19: Could it be an "All in one" therapy ?" has been accepted for publication in Magnesium Research.

Many thanks for your contribution.

Sincerely,

Professor Andre Mazur  
Editor-in-Chief

## Letter to the Editor

### **Magnesium therapeutic potential against Covid-19: Could it be an "All-in-one" therapy ?**

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**Running title: Therapeutic potential of magnesium in Covid-19**

**Key words:** Covid-19, SARS-Cov-2, inflammation, blood hemostasis, cytokines, hypoxia, thrombosis, magnesium.

Covid-19 has caused very high scores of deaths in many countries since the pandemic was declared early this year. Many therapeutic protocols were carried out on Covid-19 patients in a large number of participating countries. In a recent paper (1), the authors have analyzed the results of a large study including 11330 patients in 30 countries, and they have concluded that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. Although no specific drug has been declared as efficacious against Covid-19, the physiopathology associated with Covid-19 has been somehow better understood, thanks to many clinical studies, whose results have oriented therapeutic management using prophylactic protocols that include blood thinners, corticoids and antibiotics (2). Vitamin C was also prescribed in many protocols to fight oxidative stress in Covid-19 patients. Other studies have included magnesium, vitamin D, and vitamin B12 as supportive therapies (3).

Covid-19 symptoms can be mild to moderate, including fever and cough (4), although , severe cases can involve multiorgan dysfunction and breathing difficulties that may require oxygen therapy and mechanical respiratory support. Severe Covid-19 cases were found to be

associated with a "cytokine storm", high scores of inflammatory parameters such as CRP and ferritin, thrombosis, microcoagulation events and pneumonia. Higher mortality scores caused by Covid-19 were reported mainly in elderly patients and those who have other serious comorbidities, such as cardiovascular events, high blood pressure, diabetes, respiratory dysfunction, cancer, Alzheimer disease and morbid obesity (5).

Interestingly, some of the hallmarks of Covid-19 disease, mainly those of severe Covid-19 cases (inflammation, blood associated inflammatory factors "CRP, cytokines, ferritin", thromboembolic events, blood microcoagulation, hypoxia, gut microbiota dysbiosis and upper airways infections) remind some pathological events in magnesium deficient people. Among the common risk factors for Covid-19, type 2 diabetes is a metabolic disorder that is associated with many blood hemostasis dysfunctions and inflammation. It was suggested that Covid-19 patients having hyperglycemia and /or hyperinsulinemia may experience vascular thrombosis and endothelium-associated inflammation, magnesium and Vitamin D deficiency, as well as oxidative stress. For the above situation, some authors have suggested to supplement vitamin D, magnesium and zinc (6).

Severe cases of Covid-19 patients can experience an imbalance of their mineral status. Some studies have reported that severe Covid-19 cases have low serum magnesium (7) and calcium levels (8, 9). Thus, SARS-Cov-2 may negatively influence the balance of mineral status in the blood of Covid-19 patients, through a yet to be discovered mechanism. It is not known whether blood mineral imbalance is a cause or a consequence of severe Covid-19 physiopathology.

It should be emphasized that in the inflammatory and abnormal blood clotting processes that were described in severe Covid-19 cases, calcium ions may also play a key role, as they are cofactors for hundreds of enzymes, like many types of phospholipases involved in inflammatory lipid production (10), and many other proteases involved in blood clotting system and thrombosis (11). Interestingly, targeting calcium currents across the host cell membrane by calcium blockers was recently proposed as a possible therapeutic approach, since calcium may affect some vital steps in the life cycle of viruses (12). The results of a recent clinical study have reported a positive effect on mortality in Covid-19 patients who were under calcium blockers Nifedipine and Amlodipine (13). Calcium ions were shown to promote fusion of Middle East Respiratory Syndrome Coronavirus with host cells and to increase infectivity (14). Hence, calcium might also represent a possible target for Covid-19 therapeutic ends. Moreover, magnesium pharmacological and biochemical effects are believed to be a result of its interference with calcium, either at the level of calcium channels

and its influx through cell membranes, or at the level of calcium-dependent enzymatic activities. The above properties of magnesium and its actual therapeutic use in many clinical issues (cardiovascular and neurological pathologies, blood hemostasis, endothelial dysfunction, and muscle relaxation) could justify its use to manage some Covid-19 pathological events, such as blood hemostasis dysfunction, inflammation, oxidative stress and bronchoconstriction.

Magnesium could also have a positive effect on one of the key steps of viral infection, namely, virus binding and fusion with the host cell membrane. Indeed, the molecular process of viral binding and fusion of coronaviruses with the host cell was shown to be dependent on calcium (14). On the other hand, a key step of virus infection is the priming of its surface spike protein by many host serine proteases, located either in the extracellular space or across the host cell membrane. One of these enzymes is the calcium-dependent furin serine protease (15, 16), whose site of cleavage on the spike protein is a unique sequence found only in SARS-Cov-2 among coronaviruses. Host serine proteases involved in the activation of viruses and their cell infection are extensively investigated as possible targets in the therapeutic management of viral infection (17). In relationship to the possible effect of magnesium ions on calcium-dependent furin proteases, *in vitro* studies have shown that magnesium ions enhance the activity of a recombinant furin-like protease on a synthetic peptide substrate (18). However, the activation of furin enzyme by magnesium was not dose-dependent, and it was even lost as magnesium concentrations were increased. The *in vitro* studies may not reproduce the exact molecular and cellular environment for magnesium ion function, and therefore, no clear-cut conclusion can be drawn from *in vitro* studies.

Because calcium ions play a key role in both SARS-Cov-2 fusion with the host cells, and they are cofactors of furin enzyme and other proteases that prime the virus spike protein, it is necessary that further cell infection studies and clinical investigations be carried out to investigate the effect of magnesium supplementation.

Thus, magnesium supplementation could have some positive effects on many pathological aspects associated with Covid-19, in a similar manner to some of its other therapeutic uses for cardiovascular and nervous diseases, blood hemostasis, vessel dysfunction and inflammation. The above hypothesis was indeed suggested recently by Iotti et al. (19), Wallace (20), and Tang et al. (21). Furthermore, as an attractive hypothesis, magnesium ions; being natural antagonists of calcium ions in many biochemical and cellular processes, they could inhibit cell infection by SARS-Cov-2, because both virus

fusion with the host cell membrane and the priming of the virus spike protein are modulated by calcium. Furthermore, the recently described positive outcome of Covid-19 patients under calcium blockers (13) is an encouraging reason to investigate a possible positive effect of magnesium supplementation in hypertensive Covid-19 patients. In conclusion, magnesium might have many clinical therapeutic benefits for some Covid-19 patients, mainly those who are at risk for hypomagnesemia, or patients who have some comorbidities such as cardiovascular and respiratory events, or glycemic metabolism dysfunction. Further clinical studies on magnesium supplementation in Covid-19 patients are warranted.

**Conflicts of interest:** None declared.

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