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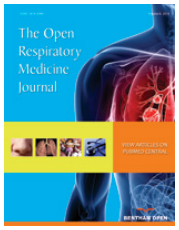

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EDITORIAL

Association between Hypomagnesemia, COVID-19, Respiratory Tract and Lung Disease

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Abstract:

The complexity of COVID-19 is also related to the multiple molecular pathways triggered by SARS-CoV-2, which is able to cause type I pneumocyte death, trigger intravascular coagulation, interfere with the renin-angiotensin system, dysregulate iron metabolism, ending with the insurgence of a cytokine storm which may lead to death. Old adults with obesity, hypertension, and diabetes are among the high-risk category groups more prone to SARS-CoV-2 infection. Magnesium has been reported to play a major role both in physiology and in pathology, particularly in elderly people, regulating cytotoxic functions of natural killer (NK) cells and CD8+ T lymphocytes. In spite of the absence of controlled trials, the possibility of magnesium supplementation for supportive treatment in patients with COVID-19 should be encouraged. This could be useful in all phases of the COVID-19 disease.

Keywords: COVID-19, Magnesium, Effects, Magnesium deficiency, Lung diseases, Obesity.

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The pandemic Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by relevant differences regarding the severity of the disease and the case fatality rate (CFR) across different geographical areas. The high CFR observed in some regions has been hypothesized to be due to multiple factors, such as poor distancing measures, co-morbid conditions, climate [1], pollution [2] health system facilitating access to care [3, 4], genetic characteristics of populations [5, 6] and distribution by the age of populations, with vulnerability for communities with a high percentage of older adults [7]. The complexity of COVID-19 is also related to the multiple molecular pathways triggered by SARS-CoV-2, which is able to cause type I pneumocyte death, trigger intravascular coagulation [8], interfere with the renin-angiotensin system, dysregulate iron metabolism, ending with the insurgence of a cytokine storm which may lead to death [9]. Regarding the co-morbidities, COVID-19 has been hypothesized to may trigger atherosclerotic plaque vulnerability, favoring the invasion of the plaque by inflammatory cells and increasing the risk of developing ischemic stroke and myocardial infarct [10]. The finding that angiotensin-converting enzyme 2 (ACE2), the receptor and the main entry point into human cells for SARS-CoV-2, is a zinc carboxypeptidase, associated with the ability of the virus to dysregulate iron homeostasis with an increase in ferritin serum levels, introduced trace elements among the multiple factors that might explain the marked differences that characterize the clinical course of COVID-19.

Old adults with obesity, hypertension, and diabetes are among the high-risk category groups more prone to SARS-CoV-2 infection, which is often severe or fatal in these subjects [11]. Iron, copper [12], zinc [13], gold [14] and magnesium [15] have been reported to play a major role both in physiology and in pathology, particularly in elderly people. Given that magnesium is an essential trace element involved in over 600 enzymatic reactions in human cells [16] magnesium status might explain, at least partially, why these categories of subjects share an increased risk of severe COVID-19. Hypomagnesemia (serum Mg2+ <0.7 mmol/L) has been described as strongly associated with old age [17] type 2 diabetes mellitus [18] and obesity [19]. Regarding hypertension, hydrochlorothiazide often leads to magnesium deficiency [15]. How could these findings change our

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knowledge on the linkage between magnesium deficiency and the insurgence of severe pulmonary pathology in patients affected by COVID-19? Recently, it has been hypothesized that a low Mg status might favor the transition from mild to critical clinical manifestations of COVID-19 [20]. Magnesium regulates cytotoxic functions of natural killer (NK) cells and CD8+ T lymphocytes [21]. Decreased NK and T-cell cytotoxicity due to magnesium deficiency may explain the susceptibility of older, hypertensive, obese, and diabetic patients to SARS-CoV-2 infection. In addition, magnesium deficiency upregulates pro-inflammatory cytokine production in monocytes and increases NFkB expression [22]. These data taken together support the role of magnesium deficiency in susceptibility to COVID-19. Moreover, the pro-inflammatory activity of hypomagnesemia substantiates the concept that magnesium deficiency is critically involved in the severe outcome of COVID 19 infections in these categories. Aging, the main determinant of Covid-19 mortality, is often associated with magnesium deficit [23], particularly in poor nutrition conditions such as in non-self-sufficient elderly people living in sheltered homes [24].

Secondary magnesium deficit in aging largely depends on pathologies and treatments common to elderly persons: i.e. non-insulin-dependent diabetes mellitus and use of diuretics [25]. Thus, several conditions occurring in old adults are recognized as risk factors for Covid mortality (i.e. vascular diseases [26, 27] are well known associated with magnesium deficit. More specifically, the presence of clinical and biochemical correlates of low serum and muscle Mg was found by means of muscle biopsy and blood samples in people consecutively admitted to a pulmonary Intensive Care Unit for chronic obstructive pulmonary disease and acute respiratory failure [28]. This may also suggest a short circuit in Covid respiratory conditions in which the deficit supported by the respiratory impairment may lead to worsening of infection. Although we do not believe that controlling magnesium in the elderly may be the key to solving the Covid, however, these considerations lead us to think that greater attention should be paid to this issue.

CONCLUSION

To conclude, there are several reasons to believe that magnesium deficiency may predispose to COVID-19, ending with severe pulmonary disease, often fatal. What are, in summary, the major links between magnesium deficiency and severe COVID-19? A recent Editorial by the president of the German society for magnesium research lays stress on the role of magnesium in the regulation of antiviral immunity and in the prevention of QT interval prolongation, possibly caused by multiple drugs for the treatment of COVID-19 [29]. More than 30% of COVID-19 patients with QT prolongation show hypomagnesemia [30]. Keeping serum Mg levels above 3 mg/dL in COVID-19 patients was effective in preventing QT-prolonging and sudden cardiac arrest [31]. Hypomagnesaemia due to the use of proton-pump inhibitors has been linked to a worse outcome in patients with COVID-19 [32].

ATP regeneration following the cytokine storm induced by SARS-CoV-2 requires adequate magnesium levels, and is deficient in patients with hypomagnesemia, causing a more severe form of COVID-19 [33]. Hypomagnesemia in COVID-19 patients may cause the calcium “channel blocking effects” played by magnesium ions in physiology, which lead to suppression of interleukin-6 and other endocrine disruptors, leading to the exaggerated inflammatory response typical of more severe COVID-19 patients [34]. A combined oral treatment of older COVID-19 patients with Magnesium, vitamin D and vitamin B12 reduces the proportion of patients requiring oxygen and intensive care support [35].

May these findings change our clinical practice? Data mainly suggests that hypomagnesemia is an issue, so magnesium supplementation may help in a patient who may be magnesium deficient and may not be helpful in patients who have normal magnesium levels. According to these data, a subset of COVID-19 patients with hypomagnesemia may really benefit from magnesium supplementation [36]. Importantly, magnesium supplementation may restore intracellular magnesium, with the recovery of NK cells and CD8 lymphocytes and decreased cytokine production [21]. In spite of the absence of controlled trials, the possibility of magnesium supplementation for supportive treatment in patients with COVID-19 [36 - 38] should be encouraged. This could be useful in all phases of the disease [39] and adequate studies should be conducted on this important aspect both on the therapeutic and preventive side. In fact, this problem can be common to many respiratory conditions as well as COVID-19 infection.

REFERENCES

[1] Carta MG, Scano A, Lindert J, *et al.* Association between the spread of COVID-19 and weather-climatic parameters. Eur Rev Med Pharmacol Sci 2020; 24(15): 8226-31. [http://dx.doi.org/10.26355/eurrev_202008_22512] [PMID: 32767354]

[2] Huang G, Brown PE. Population-weighted exposure to air pollution and COVID-19 incidence in Germany. Spat Stat 2021; 41100480 [http://dx.doi.org/10.1016/j.spasta.2020.100480] [PMID: 33163351]

[3] Wang Z, Duan Y, Jin Y, Zheng ZJ. Coronavirus Disease 2019 (COVID-19) pandemic: How countries should build more resilient health systems for preparedness and response. Glob Health J 2020; 4(4): 139-45. [http://dx.doi.org/10.1016/j.glohj.2020.12.001] [PMID: 33312747]

[4] Abdalla M, Abar A, Beiter ER, Saad M. Asynchrony between individual and government actions accounts for disproportionate impact of COVID-19 on vulnerable communities. Am J Prev Med 2020; S0749-3797(20): 30472-4. [http://dx.doi.org/10.1016/j.amepre.2020.10.012]

[5] Littera R, Campagna M, Deidda S, Angioni G, *et al.* Human leukocyte antigen complex and other immunogenetic and clinical factors influence susceptibility or protection to SARS-CoV-2 infection and severity of the disease course. The Sardinian Experience Front Immunol 2020; 4(11): 605688. [http://dx.doi.org/10.3389/fimmu.2020.605688]

[6] Martín Giménez VM, Ferder L, Inserra F, García J, Manucha W. Differences in RAAS/vitamin D linked to genetics and socioeconomic factors could explain the higher mortality rate in African Americans with COVID-19. Ther Adv Cardiovasc Dis 2020; 141753944720977715 [http://dx.doi.org/10.1177/1753944720977715] [PMID: 33283618]

[7] Ramani VK, Shinduja R, Suresh KP, Naik R. A study on the global scenario of COVID-19 related case fatality rate, recovery rate and prevalence rate and Its implications for india-a record based retrospective cohort study. Adv Infect Dis 2020; 10(3): 233-48. [http://dx.doi.org/10.4236/aid.2020.103023]

[8] Marongiu F, Grandone E, Barcellona D. Pulmonary thrombosis in 2019-nCoV pneumonia? J Thromb Haemost 2020; 18(6): 1511-3. [http://dx.doi.org/10.1111/jth.14818] [PMID: 32293083]

[9] Saba L, Gerosa C, Fanni D, *et al.* Molecular pathways triggered by COVID-19 in different organs: ACE2 receptor-expressing cells under attack? A review. Eur Rev Med Pharmacol Sci 2020; 24(23): 12609-22. [http://dx.doi.org/10.26355/eurrev_202012_24058] [PMID: 33336781]

[10] Saba L, Gerosa C, Wintermark M, *et al.* Can COVID-19 trigger the plaque vulnerability-a Kounis syndrome warning for “asymptomatic subjects”. Cardiovasc Diagn Ther 2020; 10(5): 1352-5.

[http://dx.doi.org/10.21037/cdt-20-561] [PMID: 33224760]

[11] Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506. [http://dx.doi.org/10.1016/S0140-6736(20)30183-5] [PMID: 31986264]

[12] Fanni D, Fanos V, Gerosa C, *et al.* Effects of iron and copper overload on the human liver: an ultrastructural study. Curr Med Chem 2014; 21(33): 3768-74. [http://dx.doi.org/10.2174/0929867321666140601163244] [PMID: 24934354]

[13] Faa G, Nurchi VM, Ravarino A, *et al.* Zinc in gastrointestinal and liver disease. Coord Chem Rev 2008; 252: 1257-69. [http://dx.doi.org/10.1016/j.ccr.2007.09.024]

[14] Faa G, Gerosa C, Fanni D, Lachowicz JI, Nurchi VM. Gold - Old Drug with New Potentials. Curr Med Chem 2018; 25(1): 75-84. [http://dx.doi.org/10.2174/0929867324666170330091438] [PMID: 28359231]

[15] Nurchi VM, Zoroddu MA, Crisponi G, *et al.* Magnesium: Relevant in physiology but overlooked in human pathology? Biomolecules In Press

[16] Fanni D, Gerosa C, Nurchi VM, *et al.* The role of magnesium in pregnancy and in fetal programming of adult diseases. Biological Trace Element Research 2020. [http://dx.doi.org/10.1007/s12011-020-02513-0]

[17] Lo Piano F, Corsonello A, Corica F. Magnesium and elderly patient: the explored paths and the ones to be explored: A review. Magnes Res 2019; 32(1): 1-15. [http://dx.doi.org/10.1684/mrh.2019.0453] [PMID: 31503001]

[18] Gommers LMM, Hoenderop JGJ, Bindels RJM, de Baaij JHF. Hypomagnesemia in type 2 diabetes: A vicious circle? Diabetes 2016; 65(1): 3-13. [http://dx.doi.org/10.2337/db15-1028] [PMID: 26696633]

[19] Guerrero-Romero F, Flores-García A, Saldaña-Guerrero S, Simental-Mendía LE, Rodríguez-Morán M. Obesity and hypomagnesemia. Eur J Intern Med 2016; 34: 29-33. [http://dx.doi.org/10.1016/j.ejim.2016.06.015] [PMID: 27353277]

[20] Iotti S, Wolf F, Mazur A, Maier JA. The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives. Magnes Res 2020; 33(2): 21-7. [http://dx.doi.org/10.1684/mrh.2020.0465] [PMID: 32554340]

[21] Chaigne-Delalande B, Li FY, O'Connor GM, *et al.* Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science 2013; 341(6142): 186-91. [http://dx.doi.org/10.1126/science.1240094] [PMID: 23846901]

[22] Weglicki WB. Hypomagnesemia and inflammation: Clinical and basic aspects. Annu Rev Nutr 2012; 32: 55-71. [http://dx.doi.org/10.1146/annurev-nutr-071811-150656] [PMID: 22404119]

[23] Barbagallo M, Belvedere M, Dominguez LJ. Magnesium homeostasis and aging. Magnes Res 2009; 22(4): 235-46. [http://dx.doi.org/10.1684/mrh.2009.0187] [PMID: 20228001]

[24] Woods JL, Walker KZ, Iuliano Burns S, Strauss BJ. Malnutrition on the menu: Nutritional status of institutionalised elderly Australians in low-level care. J Nutr Health Aging 2009; 13(8): 693-8. [http://dx.doi.org/10.1007/s12603-009-0199-2] [PMID: 19657552]

[25] Durlach J, Bac P, Durlach V, Rayssiguier Y, Bara M, Guiet-Bara A. Magnesium status and ageing: An update. Magnes Res 1998; 11(1): 25-42. [PMID: 9595547]

[26] Pan WH, Lai YH, Yeh WT, *et al.* Intake of potassium- and magnesium-enriched salt improves functional outcome after stroke: a randomized, multicenter, double-blind controlled trial. Am J Clin Nutr 2017; 106(5): 1267-73. [http://dx.doi.org/10.3945/ajcn.116.148536] [PMID: 28877896]

[27] Pearce A, Lockwood C, van den Heuvel C, Pearce J. The use of therapeutic magnesium for neuroprotection during global cerebral ischemia associated with cardiac arrest and cardiac surgery in adults: A systematic review. JBI Database Syst Rev Implement Reports 2017; 15(1): 86-118. [http://dx.doi.org/10.11124/JBISRIR-2016-003236] [PMID: 28085730]

[28] Fiaccadori E, Del Canale S, Coffrini E, *et al.* Muscle and serum magnesium in pulmonary intensive care unit patients. Crit Care Med 1988; 16(8): 751-60. [http://dx.doi.org/10.1097/00003246-198808000-00004] [PMID: 3396369]

[29] Micke O, Vormann J, Kisters K. Magnesium deficiency and COVID-19. What are the links? Some remarks from the German society for magnesium research e.V. Trace Elem Electr 2020; 3(37): 103-7. [http://dx.doi.org/10.5414/TEX01651]

[30] Jain S, Workman V, Ganeshan R, *et al.* Enhanced electrocardiographic monitoring of patients with Coronavirus Disease 2019. Heart Rhythm 2020; 17(9): 1417-22. [http://dx.doi.org/10.1016/j.hrthm.2020.04.047] [PMID: 32387247]

[31] Habibzadeh P, Moghadami M, Lankarani KB. The effect of potential therapeutic agents on QT interval in patients with COVID-19 Infection: The importance of close monitoring and correction of electrolytes. Med Hypotheses 2020; 143109847 [http://dx.doi.org/10.1016/j.mehy.2020.109847] [PMID: 32460209]

[32] Lee SW, Ha EK, Yeniova AÖ, *et al.* Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: A nationwide cohort study with propensity score matching. Gut 2021; 70(1): 76-84. [http://dx.doi.org/10.1136/gutjnl-2020-322248] [PMID: 32732368]

[33] van Kempen TATG, Deixler E. SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19. Am J Physiol Endocrinol Metab 2021; 320(1): E2-6. [http://dx.doi.org/10.1152/ajpendo.00474.2020] [PMID: 33174766]

[34] Wallace TC. Combating COVID-19 and building immune resilience: A potential role for magnesium nutrition? J Am Coll Nutr 2020; 39(8): 685-93. [http://dx.doi.org/10.1080/07315724.2020.1785971] [PMID: 32649272]

[35] Tan CW, Ho LP, Kalimuddin S, Cherng BPZ. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVIDS-19 patients. medR xiv 2020. [http://dx.doi.org/10.1101/2020.06.01.20112334]

[36] Tang CF, Ding H, Jiao RQ, Wu XX, Kong LD. Possibility of magnesium supplementation for supportive treatment in patients with COVID-19. Eur J Pharmacol 2020; 886173546 [http://dx.doi.org/10.1016/j.ejphar.2020.173546] [PMID: 32931782]

[37] Tangvoraphonkchai K, Davenport A. Magnesium and cardiovascular disease. Adv Chronic Kidney Dis 2018; 25(3): 251-60. [http://dx.doi.org/10.1053/j.ackd.2018.02.010] [PMID: 29793664]

[38] Carta MG, Romano F, Orrù G. The true challenges of the COVID-19 epidemics: The need for essential levels of care for all. Open Respir Med J 2020; 14: 8-9. [http://dx.doi.org/10.2174/1874306402014010008] [PMID: 32509035]

[39] Domingo Ribas C. COVID-19: A therapeutic approach based on pathophysiological staging. Open Respir Med J 2020; 14: 32-7. [http://dx.doi.org/10.2174/1874306402014010032]