The Magnesium Homeostasis Role in COVID-19 Infection: A Review

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Abstract
The COVID-19 pandemic starting at 2019 cause a hug panic and big challenge to scientist in a large area in the world, SARS-COV-2 is a virus with various targets and causes big health problems, the researches tend their efforts to study virus to understanding pathology and physiopathology of virus, electrolyte is one of the scientist targeting during COVID-19 era belong to its role in immune response and some vital processing functions. Magnesium homeostasis is one of the electrolyte that have role in cell functions and associated with various disease, in this review the role of magnesium level in cases with COVID-19 infection was discussed, reports found that the patients of corona virus infection have low level of Mg, especially in the patients with low oxygen and need ventilation in the Intensive Care Unit, furthermore associated Mg depletion with other disease that considered as a risk factors of COVD-19 mortality like obesity, diabetes, hypertension and cancer. It can be concluded that Mg homeostasis alteration might reasonably contribute to and aggravate long COVID syndrome, thus the flow up the Mg status is necessary and essential to support full recovery in COVID-19 patients.
Keywords: magnesium homeostasis, role, COVID-19, infection

1. Introduction

At the end of 12 may 2023, about 688,188,987 cases were infected by COVID-19 and about 6,873,799 deaths and 660,585,919 were recovered, (world meter, 2023), the nober is vibrated according to the country, the vaccines of COVID-19 contributed in the decreased the severity and approved immunization(Singh et al., 2021). In spite of high number of vaccines administration, the disease eradication still far away, on the other hand some evidences are the proved the lingering effects of COVID-19 patients (Nalbandian et al., 2021), There are some factors involved in the COVID-19 strategies therapy like balance in diet that is essential in immune responses and microbes harmonization (Fan and Pedersen, 2021), the nutrition is very important in patient with COVID-19 in spite of the information limitation (Medeiros , 2021).

During pandemic of COVID-19, the scientists found similarities between risk factors of COVID-19 and magnesium deficiency in human (Iotti et al., 2020; Micke et al., 2020; Wallace et al., 2020), like age, diabetes mellitus, hypertension, thrombosis and cardiovascular diseases, that strong association with high odds of COVID-19 mortality (Harrison et al., 2020; Salinas et al., 2021) in different areas. The lower magnesium level that resulted from food processing losses lead to magnesium redaction in the food chain, in addition to long period of proton pump preventer drugs may precipitate subclinical Mg depletion (Cazzola et al., 2020).

Moreover, Trapani et al., (2022) reasoned that deficiency in Mg have a role in the COVID-19 pathophysiology, in different sites of infection that causes organ failure (Gupta et al., 2020), the mechanism of this disease like viral cytotoxicity, excessive excretion of inflammatory cytokines that proved as vital evident of COVID-19 illness and death, to the point that endothelial markers estimation for diagnosis however, medication are tended to preserve endothelial function (Goshua et al., 2020; Perico et al., 2021). The low level of Mg stimulate a pro-thrombotic and pro-inflammatory in endothelial cells (Maier et al., 2012) furthermore and enhance platelet aggregation, liberate of thromboxanes and beta-thromboglobulin that favor the thromboembolism development(Sheu et al., 2002). The hypercoagulable state and Endothelial injury are key components of the Virchow's triad may be clarified high thromboembolic events incidence in COVID-19 cases. On the other hand, low level of Mg may exacerbate the inflammatory response stimulate by corona virus, development and maintaining the cytokine storm, that causes acute respiratory distress syndrome, dysfunction of accentuates endothelial and coagulopathy, and causes failure in some organs. Furthermore other signs observed by COVID-19 cases, like myalgias, asthenia , depression, anxiety, sleep disorder, may be linked to Mg depletion (Iotti et al., 2020).

In present review the physiological role of Mg, and its role in in a chronic non-communicable diseases risk factor for severe COVID-19 was discussed.

2. Magnesium Metabolite

Studies have been observed that the Mg role in cells and tissues is complex and multi factorial, its represented primarily as a metabolite and key signaling component in the physiology of cells. Whatever, an electrolyte concept of Mg is full studied and obsolete (Kubota et al., 2004; Rubin , 2005; Iotti et al., 2005; Feeney et al., 2016; Li et al., 2012). Magnesium is contributed in different cell function and as enzymes cofactors and activators (Caspi et al., 2019), However,

doi.org/10.31838/hiv23.03.319 Received: 24.11.22, Revised: 17.12.22, Accepted: 15.01.23.

Mg can interact or its represented as substrate rather than cofactors (Feeney et al., 2016; Li et al. 2012; Caspi et al., 2020; Fiorentini et al., 2021). Indeed, since Mg2+ associate with phosphate moieties of metabolites, the phosphorylated component form a complex with Mg. its suggests that the biochemical interaction substrates contributing these metabolites are Mg complexes. This is the reason why Mg considered as a metabolite and not as cofactor representing in ancillary fashion in biochemical reactions (Iotti et al., 2010) [20]. As a paradigmatic instance, the association between Mg2+ and ATP form in an adequate structural that causes weaken terminal O–P bond of ATP, thus it facilitates the phosphate transport (Caspi et al., 2020). therefore, the active species is MgATP2− not ATP (Iotti et al., 2010), This proved by different from other ions by maintain transmembrane gradients of the cell, extracellular and intracellular free Mg2+ level are comparable (Fiorentini et al., 2021), The total Mg level in the cell is about (10-30) mM. Moreover, several Mg is bound to ATP, polynucleotides, proteins and phosphorylated metabolites, the intracellular ionic Mg level (free) form is ranged (0.5–1.2) mM (de Baaij et al., 2015).

The total concentration of Mg in the adult body is about 25 g, about (50–60%) in bone, (40%–50%) is in the soft tissues, and lower than 1% in the blood (de Baaij et al., 2015).

Unfortunately, the level of Mg in serum is still not detected in daily clinical practice. The importantly of Mg in some health disorder, hence, strongly proposed to enrolled Mg in the estimation of the blood ionogram.

The role of Magnesium in non-communicable chronic diseases and aging

The hypomagnesemia prevalence in geriatric cases about 36% (Arinzon et al., 2009), among DM cases is about (19% - 29%) (Hyassat et al., 2014; Rabeea et al., 2020), and in hypertension cases is reached to 63.8% (Rodríguez-Ramírez et al., 2015). Furthermore the mortality is increased among cardiovascular cases in cases with hypomagnesemia as compared with normal Mg levels cases (Reffelmann et al., 2019).

Among elderly cases with DM type 2 there were high risk of severe disease or death belong to COVID-19 infection than age-matched healthy people, notably, some studies observed a relation between Mg deficiency with insulin sensitivity in metabolic syndrome and T2DM (Barbagallo et al., 2015; Piuri et al., 2021; Barbagallo et al., 2021). Overall there was an association of Mg intake and decreased risk of T2DM (Veronese et al., 2022). Also Mg is associated with bronchial smooth muscle cells contractile state (Britton et al., 1994). As a results of its vasodilatory, anti-thrombotic and anti-inflammatory impacts, Mg can improve lung function and reduce the respiratory symptoms of COVID-19 cases. The impacts might involve to the decreased the ventilation-perfusion mismatch, that is a vital events for hypoxemia in COVID-19 cases, and to the enhancing of oxygenation in cases (Pooransari et al., 2020). In addition, the Mg role in reduction mastocyte degranulation and decreased inflammatory, pro-thrombotic and fibrotic mediators (Zierler et al. 2016).

The Magnesium role in infectious diseases

Some findings found strong correlation between Mg and immune response in animal model. In humans, the relation concept of Mg with immune function was observed by primary immunodeficiency XMEN (X-linked immunodeficiency with magnesium defect, Epstein–Barr virus infection, and neoplasia) (Ravell et al. 2020). There were many studies proved the relation between magnesium deficiency and a higher predisposition to infectious diseases is mostly indirect (Dominguez et al.,2021). The Mg is an important in the generate, transfer, and vitamin D activation (Dai et al., 2018). The strong association between vitamin D and Mg found that the higher infectious diseases incidence related with deficiency in vitamin D and it can be at least in part clarified by Mg depletion, and this perhaps particularly relevant in the respiratory tract.

The Mg level alteration also have a vital role in older individuals affected by pneumonia bacteria. hypermagnesemia and hypomagnesemia that contributed in the excessive short-term mortality, in compared with Mg normal values (Nasser et al., 2018). Meanwhile in a retrospective study on older adults the low Mg level was a significant predictor of frequent readmissions for acute exacerbation of chronic obstructive pulmonary disease (Bhatt et al., 2008).

Furthermore, in patient with SARS-CoV-1 in 2003, the hypomagnesemia was observed in some cases on admission, and tended to worsen through hospitalization (Booth et al. 2003). The ribavirin medication is used in 306 SARS cases and its strongly correlated with hypomagnesemia, it has been found that the risk of hypomagnesemia attributable to ribavirin use was 45% (Muller et al., 2007). It's also used for compassionate in corona cases with respiratory distress (Mak et al., 2018).

Trapani et al., (2022) concluded that there were little information about the role of hypomagnesemia in infectious diseases, therefore significant efforts were tended after COVID-19 pandemic to detected relationships between Mg status and COVID-19 infection.

Magnesium Status and COVID-19 Pathogenesis

the COVID-19 pathogenesis has been developed, potential role of Mg status was observed in different clinical cases of patients, Mg regulates neutrophils and macrophages activity, prevent oxidative burst and their priming, and also hinders the Toll-like receptor 4/NFκB axis (Maier et al., 2020). Mg regulate amount of IP3 and DAG, second messengers stimulation after the association of B and T cell receptors (Brandao et al., 2013). On the other hand, Mg protects against viral infections belong to adequate intracellular Mg level are needed for the cytotoxic activity of T lymphocytes and natural killer cells (Minton et al., 2013). In addition to enhance the immune response

by Mg, it's also influenced initial events of covid-19 infection through spike protein and ACE2 receptors (Gupta et al., 2020). This processing's happened by cell proteases activity mainly the transmembrane protease serine protease 2 (TMPRSS2) and the pre-protein convertase furin (Hu et al., 2021). It has been found that Mg contributed in prevent these enzymes activity. Some evidences found that Mg causes promoter methylation of TMPRSS2 that lead to decreased gene expression (Fan et al., 2021). furthermore, belong to Mg antagonistic to calcium function, Mg might prevent the calcium-dependent furin activity (Errasfa et al., 2021). It follows that deficiency of Mg may enhance virus infectivity. When the infection is ongoing, the deficiency in Mg may contribute in the inflammatory response that resulted to cytokine storm in sever COVID-19 pathogenesis. In some cases the immune response may be so overwhelming that causes organs disruption. Importantly, the low Mg concentration related with elevation in inflammatory mediators amount (Maier et al., 2012; Maier et al., 2021).

Recently, reports found that the deficiency of Mg change the balance between gut microbiota and the host (Gommers et al., 2019; Fan et al., 2020). Therefore influencing the immune response and airway microbiota (Gasmi et al., 2021).

Clinical studies of Magnesium in COVID-19

as mention above and according to previous studies conclusions, the role of Mg is maintaining proper immune, the magnesium levels analyzed in COVID-19 cases, significant lower Mg level was observed in 300 patients with severe infection than moderate and mild patients Zeng et al. (2021) moreover same results were seem to be as mortality risk of COVID-19. There are confounding factor mentioned by studies like cardiovascular diseases, hypertension, obesity and diabetes that have more predisposed to develop sever infection by COVID-19, a study implemented by Sarvazad et al. (2020), the Mg level in COVID-19 patients without any other disease, they found 32% were observed to be hypomagnesemic (1.26%–1.7 mg/dl), 6% were severely hypomagnesemic (< 1.25 mg/dl) and 14% were hypermagnesemic (> 2.6 mg/dl).

The Post-Acute COVID-19 Syndrome and Mg status

The prolonged impacts of COVID-19 in the lung, brain, heart gastrointestinal system and kidney, the common experiences are loss of hair, fatigue, weakness in muscles and pain in joint, and some neurological disorder like sleep disorders, headache, cognitive disturbances and anxiety/depression, belong to epidemiological reports, a high percentage of COVID-19 cases have at least one signs up to 2–6 months after infection, however, these signs result to life quality decline and increase frailty. The long COVID-19 syndrome pathophysiology is multifactorial included alteration stimulate by direct virus inflammatory damage and immunologic aberration in response to the acute infection, like ischemia. Some symptoms refer to alteration in brain like dyspnea, fatigue, pain and cough. Importantly, COVID-19 has neuro-invasion capacity and sensory neurons seem to be its entry point to the central nervous system, Lead to neuroinflammatory, cytokine storm that impact in central nervous system (Song et al., 2021).

it is noteworthy the role of Mg in the brain can impact in various biochemical processes like in cognitive functions, NMDA-receptor stimulate by excitatory stimuli, cell membrane stability and integrity, in addition to exerts a calcium-antagonist action and combats neuroinflammation (Barbagallo et al., 2021). Interestingly, the deficiency in Mg causes anxiety, hyperemotionality, insomnia, depression, light-headedness and headache (Barbagallo et al., 2021). in addition to the post-acute COVID-19 syndrome. furthermore, Mg deficits have been found to weakness and muscle pain causing. This is not surprising since Mg is a key for enzymes involved in ATP synthesizing in muscle, therefore generation muscle energy, and also control on relaxation and contraction (de Baaij et al., 2015).

Conclusion: belong to the previous evidences we can conclude that the Mg homeostasis alteration perhaps reasonably contribute to and aggravate long COVID syndrome, thus the flow up the Mg status is necessary and essential to support full recovery in COVID-19 patients. Moreover Mg supplementation is an important for health maintains.

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