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CLINICAL STUDY

Effect of serum magnesium levels on outcomes of patients hospitalized with COVID-19

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ABSTRACT
BACKGROUND: The coronavirus disease 2019 (COVID-19) causes acute respiratory illness and multi-organ failure. The critical roles of magnesium in human health suggest that it could have an active role in the prevention and treatment of COVID-19. We measured magnesium levels in hospitalized COVID-19 patients concerning disease progression and mortality.
MATERIALS AND METHODS: This study was conducted in 2321 hospitalized COVID-19 patients. Clinical characteristics from each patient were recorded, and blood samples were collected from all patients upon their first admission to the hospital to determine serum magnesium levels. Patients were divided into two groups based on discharge or death. The effects of magnesium on death, severity, and hospitalization duration were estimated by crude and adjusted odds ratio using Stata Crop (version 12) software.
RESULTS: Mean magnesium levels in patients who died were higher than in discharged patients (2.10 vs 1.96 mg/dl, $p < 0.0001$). Among patients who died, 13.4 % had low, 66.1 % normal, and 20.6 % high magnesium levels. Of admitted patients with COVID-19, 61.1 % had at least one additional disorder. Magnesium deficiency was unrelated to death or duration of hospitalization ($p > 0.05$).
CONCLUSIONS: We found no relation between hypomagnesaemia on COVID-19 progression, although hypermagnesaemia could affect COVID-19 mortality *(Tab. 4, Ref. 34)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, coronavirus, magnesium, hospital duration, mortality.

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by a new *coronavirus* known as *SARS-CoV-2* (severe acute respiratory syndrome coronavirus 2 (1). One of the leading causes of the high mortality in COVID-19 patients is respiratory failure due to acute respiratory distress syndrome (2). Some patients with severe COVID-19 rapidly develop acute respiratory distress syndrome (ARDS) and multi-organ failure, including severe respiratory failure, heart failure, and renal failure (3).

Immune responses to SARS-CoV-2 infection are critical in controlling a patient's pathogenicity and clinical symptoms and include innate and adaptive immune responses (4).

The immune system is a central defense mechanism against the *coronavirus* (5). The function of the immune system is modulated by nutrients such as proteins, vitamins (A, C, and E), and minerals such as zinc, iron, and magnesium (6).

Nutrients such as vitamins C, D, and E, zinc, selenium, and omega-3 fatty acids may help support COVID-19 patients (7). Clinical evidence is lacking for the role of magnesium in preventing or treating COVID-19 by modulating the immune system m(8).

Magnesium regulates several cellular functions and signaling pathways and has anti-inflammatory, anti-spasm, and vasodilatory effects that affect oxygen uptake, energy production, and electrolyte balance (9–11). A magnesium deficiency is associated with impaired function of T cells, increased plasma concentrations of inflammatory cytokines, and endothelial dysfunction(12, 13).

As an enzymatic activtor, magnesium regulates many physiological functions, including systemic inflammation and cytokine production, while reducing the production of TLR- mediated TNF-α, IL-6, and IL-1β (14, 15). These cytokines are raised in severely infected COVID-19 patients who experience cytokine release syndrome or a 'cytokine storm' associated with respi-

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Tab. 1. Baseline characteristics of the study subjects (n=2321) with COVID-19.

Patient and clinical characteristics	
Age (yr)	
Median (IQR)	64 (52–76)
Mean ± SD	63.1±16.7
Gender– number (%)	
Female	1019 (43.9)
Male	1302 (56.1)
Coexisting disorder – number (%)	
At least one disorder	1417 (61.1)
Chorionic blood disease	69 (3.0)
Cancer	47 (2.0)
Asthma	44 (1.9)
Pulmonary diseases	174 (7.5)
Diabetes Mellitus	607 (26.2)
Coronary vascular disease	394 (17.0)
Hypertension	802 (34.6)
Chorionic kidney disease	141 (6.1)
Other chronic diseases	115 (4.9)
Patients who died	277 (11.9)
Severely ill patients*	141 (6.7)
Duration of hospitalization & (days)	
Mean ± SD	7.3± 6.7
Median (IQR)	5±3–9
>5 days – number (%)	1137 (49.0)

* Admitted to the intensive care unit with pO2 < 94 mmHg
& Days between admission to discharge of surviving patients

ratory failure, ARDS, and adverse clinical outcomes (16). Extra- and intracellular magnesium concentrations are essential for the activation and proliferation of lymphocytes (17), and a deficiency in magnesium affects the function of lymphocytes and decreases immunoglobulin production (18–20). Magnesium imbalance can also alter the differentiation and maturation of myeloid cells such as neutrophils (21). Alterations in intracellular magnesium levels and its compartmentalization may be the main mechanisms of neutrophilia observed during hypomagnesemia *in vitro* (22).

On the other hand, studies show that high magnesium levels are usually caused by iatrogenic causes and are associated with poor renal function, gastrointestinal problems, and advanced age (23).

As Magnesium disorders are associated with many adverse health outcomes, we aimed to investigate the effect of magnesium serum levels on the progression and mortality rates of hospitalized Covid-19 patients.

Subjects and methods

Study design and patients

The Ethics Committee approved this case-control study of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.709). We enrolled 2321 patients with confirmed COVID-19 admitted to Isfahan University of Medical Sciences hospitals in Iran. The baseline characteristics of patients were extracted from the Isfahan COVID-19 registry database (I-CORE) (24). All participants were asked to sign an informed consent form before enrollment in the study.

Diagnosis and classification

A definitive diagnosis of COVID-19 pneumonia was made based on the positivity of respiratory specimens for SARS-CoV-2 using reverse real-time polymerase chain reaction (RT-PCR) analysis. Only subsequent laboratory-confirmed COVID-19 cases were included in the analysis. Blood samples were taken from all patients at their first admission to the hospital for measurements of serum levels of magnesium. Serum levels of magnesium are reported as low (< 1.7 mg/dl), normal (1.7–2.3 mg/dl) and high levels (> 2.3 mg/dl) (25).

Patients were divided into two groups: deceased patients (case) and recovered patients (control). All data were collected for each patient by reviewing medical records: age, gender, medical history, length of stay in the intensive care unit (ICU) and hospital, comorbid disorders, and mortality.

Statistical analysis

We used mean, SD, median, quartiles, and interquartile range (IQR) to describe continuous variables and the frequencies and percentages in various categories of data from medical records. The severity and hospitalization duration were used to analyze the relationship between magnesium levels on mortality and morbidity with logistic regression. It estimated odds ratios (OR) and 95% confidence interval (CI). All data were analyzed using Stata Crop software (Version 12).

Results

This study enrolled 2321 hospitalized patients with COVID-19, of which 1302 were males, and the mean (SD) age of all patients was 63.1 ± 16.7 years. Sixty-one percent of COVID-19

Tab. 2. Magnesium distribution.

	Patients			
	Total (n=2321)	Dead (n=277)	Severe* (n=141)	Hospitalized>5 days& (n=1137)
Magnesium (ng/ml)				
Median (IQR)	1. 97 (1.80–2.10)	2.00 (1.80–2.30)	2.10 (1.90–2.30)	1. 97 (1.80–2.12)
Mean ± SD	1. 98 ± 0.32	2.10 ± 0.38	2.10 ± 0.31	1. 98 ± 0.32
Magnesium Level – number of patients (%)				
Low (<1.7 mg/dl)	298 (12.84)	37 (13.36)	9 (6.38)	145 (12.75)
Normal (1.7–2.3mg/dl)	1805 (77.78)	183 (66.06)	111 (78.72)	885 (77.84)
High (>2.3mg/dl)	218 (9.39)	57 (20.58)	21 (14.89)	107 (9.41)

* Admitted to intensive care units with pO2 < 94 mmHg
& days between admission to discharge (for survivors)

Tab. 3. Magnesium levels and duration of hospitalization, severity of disease, and death.

	Odds Ratio (95% CI)					
	Hospitalization Duration>5 days[&]		Severity		Death	
	Crude	Adjusted[#]	Crude	Adjusted[#]	Crude	Adjusted[#]
Magnesium(continuous) (mg/dl)	1.02 (0.79–1.31)	1.01 (0.78–1.30)	2.64 (1.71–4.09) *	2.55 (1.70–4.08) *	2.22 (1.56–3.14) *	2.30 (1.63–3.31) *
Category of magnesium level (mg/dl)						
Normal (1.7–2.2mg/dl)	1	1	1	1	1	1
Low (< 1.7 mg/dl)	0.98 (0.77–1.25)	0.98 (0.76–1.25)	0.47 (0.23–0.94) *	0.46 (0.23–0.92) *	1.25 (0.86–1.83)	1.17 (0.82–1.77)
High (> 2.2 mg /dl)	1.00 (0.76–1.32)	0.98 (0.74–1.32)	1.62 (1.00–2.65) *	1.56 (0.94–2.55)	3.13 (2.23–4.40) *	3.15 (2.21–4.48) *

* Significant if ($p < 0.05$).
[&] Days between admission to discharge (just for alive patients)
[#] considering just "have at least one underlying disease" for adjusted OR

patients in our study had at least one additional comorbid disorder, with hypertension and diabetes mellitus being the most common comorbid disorders. Several patients (6.7 %) were hospitalized in the intensive care unit with respiratory distress ($pO_2 < 94$ mmHg); 277 patients died during the study period, of whom 20 were in the severe group ($p < 0.0001$). The median duration of hospitalization in surviving patients was ~5 days (Tab. 1).

The mean serum magnesium level in all COVID-19 patients was 1.98 ± 0.32 mg/dl, while it was 2.10 ± 0.38 mg/dl in patients who died compared to 1.96 ± 0.31 mg/dl in survivors ($p < 0.0001$) (Tab. 2). Only 13.4 % of patients who died had magnesium deficiencies, and no differences in magnesium deficiency were noted between the discharged and dead patients. However, a high level of magnesium was measured in 57 (20.6 %) patients who died and 128 patients (7.9 %) patients who were discharged from the hospital (Tab. 3).

Stratified analysis indicated two groups of people with magnesium deficiency: one group with symptoms of diarrhea and the other group without diarrhea. Magnesium deficiency in COVID-19 patients without diarrhea reduced mortality ($p < 0.05$) (Tab. 4). Magnesium deficiency increased mortality in patients whose pO_2 was < 94 % but had no effect on mortality in patients whose pO_2 was > 94 %. Magnesium deficiency in male patients with and without normal creatinine levels (0.9–1.3 mg/dl) had significant effects on mortality ($p < 0.05$) but was without effect on mortality of female patients with normal creatinine levels (0.6–1.1 mg/dl). Magnesium deficiency with average plasma urea nitrogen (BUN) (5–20) had no significant effect on mortality, but a considerable mortality rate was observed in patients without normal BUN ($p < 0.05$).

Tab. 4. Effect of Magnesium and existence of symptoms on the hospitalization duration and death.

			Odds Ratio(95% CI)	
			Hospitalization Duration >5 days[&]	Death
Diarrhea		Yes	1.23 (0.39–3.84)	2.89 (0.38–22.10)
		No	0.97 (0.74–1.28)	2.02 (1.39– 2.93)*
pO_2 (mm Hg)		<94%	1.09 (0.81–1.47)	2.68 (1.77–4.07) *
		94%	0.85 (0.52–1.37)	1.37 (0.69–2.70)
Normal Creatinine	Men (0.9–1.3 mg/dl)	Yes	0 .81 (0.48–1.35)	2.93 (1.65–5.19) *
		No	1.23 (0.77–1.95)	2.60 (1.13–5.95) *
	Women (0.6–1.1 mg/dl)	Yes	1.11 (0 .63–1.96)	1.67 (0.58–4.75)
		No	0.88 (0.52–1.51)	1.27 (0.67–2.41)
Normal plasma urea nitrogen (BUN) (5–20 mg/dl)		Yes	0.98 (0.68–1.40)	1.07 (0.53–2.18)
		No	0.96 (0.66–1.38)	2.20 (1.42–3.40) *

* $p < 0.05$
[&] days between admission to discharge (for surviving patients)

Discussion

In this study, we investigated the relationship between the serum levels of magnesium and disease progression and mortality in hospitalized COVID-19 patients. Of 2321 patients hospitalized due to COVID-19 during the study period, 277 died, and 2044 were discharged. Magnesium deficiency was not different between these two groups, and COVID-19 progression and mortality were not affected by magnesium deficiency. Our findings agree with those of Sravazad et al. They reported that while 38 % of COVID-19 patients had hypomagnesemia upon hospital admission, the serum levels of magnesium did not differ in the frequency in patients with severe and less severe diseases (26).

Our study indicates that the mean serum levels of magnesium in all COVID-19 patients were lower (1.98± 0.32 mg/dl) than in patients who died from the infection (2.10 ± 0.38 mg/dl). A study on serum magnesium levels of hospitalized patients with SARS-CoV-2 by Sharma et al. reported that of 193 patients, 104 patients (54 %) were identified with hypermagnesemia, of which 46 % were admitted to intensive care units (27). Age-adjusted logistic regression analysis suggested an association between hypermagnesemia and mortality, indicating that hypermagnesemia can be used as a marker of disease severity in hospitalized COVID-19 patients (27). Another study by Stevens et al. demonstrated an association

between the incidence of hypermagnesemia and disease outcomes of hospitalized COVID-19 patients; of 1685 hospitalized patients, 21 % had hypermagnesemia with a greater incidence of respiratory failure (requiring mechanical ventilation) and acute kidney injury. Survival probability at 30 days for COVID-19 patients with hypermagnesemia was lower (34 %) than for patients with normal serum levels of magnesium (65 %) (28). In addition, another study with a small cohort reported that the incidence of hypermagnesemia was higher in COVID-19 non-survivors compared with survivors (29).

Given magnesium's critical role in cellular functions, hypermagnesemia can be caused by either increased total body storage (due to exogenous consumption, impaired clearance, or both) or a magnesium shift across compartments (30).

Increased cell turnover could explain elevated magnesium levels rather than a total body surplus. Another factor to consider is that these patients may had hypermagnesemia due to lower renal clearance (31).

So, the high rate of hypermagnesemia in COVID-19 patients can be due to a combination of higher cell turnover and reduced renal clearance. Another possibility that could justify the adverse effect of hypermagnesemia is its vasoplegic impact on the vascular smooth muscle, which can be a plausible physiologic explanation for the bad outcomes reported in hypermagnesemia (32).

Also, magnesium has significant calcium antagonistic effects and acts as a physiologic calcium channel blocker, lowering blood pressure (e.g., the standard of care in treating pre-eclampsia) (33).

Researchers are of the opinion that magnesium can prevent pro-inflammatory and oxidative stress conditions, which make people more prone to infections and states of exaggerated inflammation. Also, it has been shown that magnesium supplementation in post-COVID-19 patients may prevent fatigue and dyspnea linked to inflammation and oxidative stress (34).

Only a few researches have looked into whether magnesium has a role in COVID-19 outcomes, but they all have methodological flaws (e.g., small sample size, not randomized, selection bias, and confounding).

According to this content, more studies should be done in this field. Before giving magnesium supplements to Covid-19 patients, it is recommended that their serum magnesium levels be measured and consumed only in case of magnesium deficiency.

Study limitations

We studied only hospitalized COVID-19 patients, and other patients who did not require hospitalization were not included. Thus, there remains a needs to be checked in a broader population.

Conclusion

Although many studies suggest that magnesium deficiency affects immune responses and homeostasis, the findings of our study do indicate that hypomagnesaemia can alter COVID-19 progression. On the other hand, hypermagnesemia may have a significant effect on COVID-19 mortality. Well-designed, powered randomized controlled trials are needed to elucidate the role of magnesium in the progression and severity of infection with COVID-19.

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