ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2021; 14(1); 595-601

Original Research Article

Does Serum Magnesium Levels Correlates with Serum Ferritin Concentrations in COVID-19 Patients?

Kumari A[1], Sharma V[2], Singh SB[3], Mahajan S[4], Agrawal Y[5]

[1]Assistant Professor, Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana

[2]Demonstrator, Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana

[3]Professor and Head, Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana

[4]Associate Professor, Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana

[5]Assistant Professor, Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Haryana, India

Received: 23-11-2021 / Revised: 10-12-2021 / Accepted: 29-12-2021
Corresponding author: Dr. Asha Kumari
Conflict of interest: Nil

Abstract

Introduction: Serum Ferritin has emerged as an important marker in Covid-19 pandemic. High Serum Ferritin concentrations independently predicts in-hospital mortality. Magnesium is a simple in-vestigation which can be easily done on fully automatic analyser. Few evidence has estimated correlation between Serum Ferritin and Magnesium concentrations.

Material and Method: This study was retrospectively conducted in Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana over a period of two months (Jan -Feb 2021). Data was collected from Covid-19 positive patient's reports available in department. Serum Ferritin and Serum Magnesium levels were statistically analysed.

Results: 85 Covid-19 patients (38 Females and 47 males) were included in the study. Mean age of patients was 42.54 +/- 15.31 (Mean +/-SD). Mean Ferritin level was 360.521ng/ml. Mean serum Magnesium level was 2.20 +/-0.43 mg/dl. Correlation coefficient between Serum Mg and Ferritin is 0.6694. p value is < .00001.

Conclusion: A positive correlation between Serum Magnesium and Serum Ferritin was found in this study and hence Mg may be used as a supplementary test at Biochemistry labs or a substitute test during kit nonavailability of Serum Ferritin during Covid-19 pandemic.

Keywords: Covid-19, Corona virus, Magnesium, Ferritin.

Introduction

COVID-19 spread at an unprecedented speed in world and by 28 Jan 2022, 364,191,494 confirmed cases including 5,631,457 deaths were reported to WHO. Intense vaccination drive helped in administering a total of 9,854,237,363 vaccine doses by this time[1].

Exaggerated immune response in patients was found to be responsible for severe

disease stage. One of the mechanisms, the cytokine storm was characterized by release of massive amount of pro-inflammatory cytokines and chemokines[2]. Markers like interleukin (IL)-6, 7, 10, 1 beta, Tumor necrosis factor alpha, monocyte chemoattractant protein 1 (MCP-1) and granulocyte colony stimulating factor (G-CSF) were found in blood of COVID-19 patients[3]. Other inflammatory markers like serum C-Reactive Protein and serum Ferritin were also investigated and gave promising correlations with disease severity and prognosis. With accruing literature, serum Ferritin emerged as a crucial marker predicting independently the in-hospital mortality[4]. Due to elevation of Ferritin levels in cytokine storm, Covid-19 disease may become subset of hyperferritinemic syndrome[5,6].

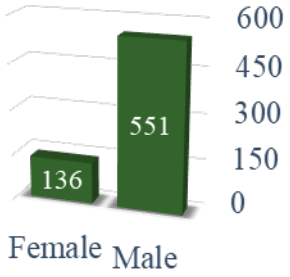

Figure 1: S.Ferritin (Mean ng/ml) in COVID-19 patients: Males had higher mean value of Serum Ferritin

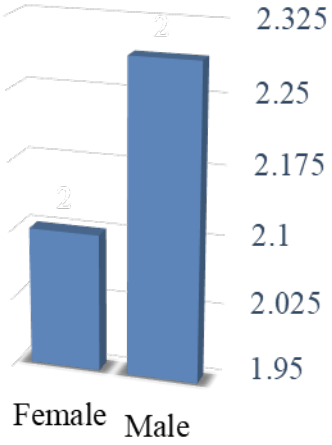

Figure 2: Serum Mg levels (mg/dl) in COVID-19 patients

The immune system is significantly dependent on nutritional status of individual[7]. The research work on the link between nutritional status of patients and COVID-19 severity is scarce[8].

Our body needs many vitamins and minerals for various biological functions including immune response. Magnesium (Mg) is one of such important minerals. Magnesium is a simple investigation which can be easily done on fully automatic analyser. Is there any correlation between serum Mg and other markers like S. Ferritin currently used in COVID-19 assessment? With these questions in mind this study was planned in a tertiary care hospital in North India.

Material and Method

This cross-sectional, observational retrospective study was conducted in Department of Biochemistry, SHKM GMC, Nalhar, Nuh, Mewat, Haryana over

a period of two months (Jan-Feb 2021). Data of age, gender, serum Ferritin, CRP, Mg, Blood urea, serum creatinine and Lactate dehydrogenase were collected from Covid-19 positive patient's departmental reports. All biochemical parameters were done on fully automatic analyser (Roche C501). Study was ethically approved from institution.

Statistical analysis: Mean, SD, median and Interquartile range were calculated for continuous data using python computer language. Percentages and frequency were calculated for nominal data. Correlation coefficient was calculated to analyse the relation between two parameters. P value <0.05 was taken as significant.

Results

Eighty-five Covid-19 patients (38 Females and 47 males) were included in this study. Mean age of patients was 42.54 ± 15.31 (Mean ± SD) years. Mean Ferritin level was 360.521ng/ml. (Normal range of serum Ferritin in male is 30 - 400 ng/dl and female are 15-150 ng /dl). In female subjects the mean Ferritin was 136.12 ng/dl which was in normal range towards upper limit, however male patients had higher mean (550.76 ng/dl) ferritin levels. Thirty percent patients in this study had Ferritin >400 ng/dl.

Mean serum Magnesium level was 2.20 ± 0.43 (SD) mg/dl. Normal range of serum Mg is 1.6-2.6mg/dl. 5.04% subjects were hypomagnesemia (Mg 1.26-1.7 mg/dl) and 8% were hypermagnesemia (Mg > 2.6 mg/dl). Correlation coefficient (R) between age and ferritin was found to be 1.00. Correlation coefficient between Serum Mg and Ferritin is 0.55 which is statistically significant, and the p value is < .00001 which is highly significant. Strong positive correlation was observed between LDH and MG with value of R being 0.6196. A moderate correlation of 0.3004 was found between Mg and CRP. Very weak correlation between Mg and age of 0.1748 was detected. Mean Blood Urea concentration was 33.52 ± 22.65 (SD) mg/dl and S. Creatinine 0.85 ± 0.644 (SD) mg/dl in the study.

Discussion

This study was proposed to find any correlation between serum Mg and ferritin levels. Very few studies have been conducted in this field. Mean serum ferritin in the present study was raised in male patients. Thirty percent COVID-19 patients had ferritin >400 ng/dl in the current study. Mean Ferritin level was 360.52 ng/ml.

Chen G et al[9] and Liu J et al[10] reported mean ferritin level of 337.4 μg/L and 367.8μg/L in COVID-19 patients respectively. Some authors reported mean ferritin > 480 μg/L[11] and 500 μg/L[3,12,13] in other studies.

Merad et al demonstrated that in non-severe patients, ferritin is within normal range. In contrast, severe disease was associated with ferritin >400 μg/L, on an average >800 μg/L[14]. Another study reported that serum ferritin levels higher than 300 μg/L was associated with 9-fold increased chances of death before discharge of patient[15]. The source of elevation in ferritin concentration is active ferritin production by macrophages during inflammation as well as induction of ferritin synthesis by IL-6[16].

Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm[17]. Complex feedback mechanisms between ferritin and cytokines in the control of pro-inflammatory and anti-inflammatory mediators might exist as cytokines can induce ferritin expression, but ferritin can induce the expression of pro- and anti-inflammatory cytokines as well.

Serum ferritin is not only actively secreted during inflammation, but the death of

hepatocytes also contributes as ferritin is primarily an intracellular protein for iron storage. Ferritin molecule loses iron after secretion, resulting in extreme elevation of free iron levels[18]. Free iron is well proven to aggravate inflammatory process, favouring an intense pro-coagulant state[18]. There are evidences that implicate COVID-19 virus in hepcidin-mimic effects, which can be another mechanism of coagulopathy and hyperinflammation[19].

The second finding of this study is a strong positive correlation between Mg and ferritin levels in COVID-19 patients. Serum Magnesium levels were higher in male subjects than females. In present study, 5.04% subjects were hypomagnesemia and 8% were hypermagnesemia. These results are quite low as compared to a cohort study of 300 patients where 48% had Mg <0.75mmol/L, 13% had Mg <0.65mmol/L and 9.6% were hypermagnesemia (Mg >0.95mmol/L)[20]. Here hypomagnesemia prevalence was found higher in critical cases than moderate cases, but the patients admitted in ICU were more hypermagnesemia[20].

Low Mg levels have been linked with higher risk of mortality in Covid-19 patients. Alamdari et al found in a retrospective study that out of 459 cases, on admission, Mg levels in 63 patients who expired later was significantly lower than cases who survived[21].

One of the reasons of less hypomagnesemia in cases may be age factor. The mean age of Covid cases in our study was 42.54 ± 15.31 (Mean ± SD) years. Hypomagnesemia has a strong association with old age[22]. With progressing age, Mg becomes more important in pathological conditions along with physiology. Insufficient Mg levels may increase the transition of COVID-19 from mild to severe state[23].

Direct viral cytotoxicity, dysfunction of endothelium and cytokine storm contributed to the pathophysiology of COVID-19[24,25]. Hypomagnesemia favours thromboembolism by promoting platelet aggregation, increasing beta-thromboglobulin and thromboxane secretion[26,27]. Mg have important immunological functions like during viral infection, Mg induces T cell proliferation, Natural killer cell activation and proper secretion of IL-2[28]. Cytotoxic functions of CD8+ T lymphocytes and natural killer cells (NK) cells is regulated by Mg[29]. In deficiency of Mg, this activity is hampered making the elderly prone to severe COVID-19 infection. Hypomagnesemia favours NFkB expression and increases pro-inflammatory cytokine production[30].

Second confounding factor in various studies on this topic may be presence of co-morbidities like diabetes mellitus, cardiovascular diseases, hypertension and obesity in enrolled cases which are more susceptible to Mg derangements.

Due to anti-inflammatory, anti-oxidative and relaxation of bronchial smooth muscle, Tang et al supported the cautious Mg supplementation in COVID-19 patients with airway hyper-reactivity, hypertension and cardiovascular morbidities[31].

It is important to note that Mg is an essential trace element and is involved in myriad metabolic pathways like cell signaling, cell multiplication, bone formation, neuromuscular activity, carbohydrate, lipid and protein metabolism, genetic material stability, and bioenergetics. More than 600 enzymes need Mg as cofactor, kinases being the commonly known[32]. Assessing magnesium status is difficult because most magnesium is present inside cells or in bone[33]. Serum levels have little correlation with total body magnesium levels or concentrations in specific tissues. An adult has 25 g total Mg content chiefly deposited in bone and soft tissues. Blood carries just 1% of total Mg content[28].

Mg^{2+} homeostasis depends on three organs: 1. Intestine (mainly small intestine), facilitating Mg^{2+} uptake; 2. bone, the main Mg^{2+} storage system of the body and 3. kidneys, which are responsible for Mg^{2+} excretion via controlling Mg transporters[34]. Serum Mg concentration is fine-tuned by its excretion from kidneys and release from bones[35]. Subclinical Mg deficiency may result from low dietary intake because of poor Mg content in soil and drugs like Proton pump inhibitors [36].

In COVID-19 patients, when Mg levels fall in serum, kidney compensates by Mg reabsorption. In our study mean BU was 33.52 ± 22.65 mg/dl and mean S. Creatinine was 0.85 ± 0.644 mg/dl. These indicate overall good renal functioning in the subjects. Probably due to this reason, Mg levels were increased in correlation with increasing inflammation as indicated by raising serum ferritin concentrations. So, Magnesium levels in COVID patients' needs to be monitored during the course of disease.

Similar occurrence of hypermagnesemia in absence of nephropathy was observed by two studies in ICU patients[20,37]. Mechanisms explaining this finding are rapid mobilization of Mg from soft tissue in septic patients or microvascular thrombosis leading to necrosis. Further studies are needed to explore the role of Mg in COVID-19 and its strong association with ferritin levels.

Conclusion

S. Mg levels are found to be elevated as a compensatory mechanism in COVID-19 in positive correlation with S.Ferritin in renal sufficient patients. Serum Magnesium should be added as a supplementary test at Biochemistry labs or a substitute test during kit nonavailability of Serum Ferritin during Covid-19 pandemic to assess level of inflammation.

References

1. WHO, (2022 Jan 28), WHO Coronavirus (COVID-19) Dashboard. Retrieved Jan 31, 2022, from https://covid19.who.int/
2. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet. 2020:395(10223): 497–506.
3. Zhou, F. et al. Lancet Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020:395(10229), 1054–1062.
4. Conti, P. et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. J. Biol. Regul. Homeost Agents. 2020:34(2), 327–331.
5. Alunno, A., Carubbi, F. & Rodriguez-Carrio, J. Storm, typhoon, cyclone or hurricane in patients with COVID-19? Beware of the same storm that has a different origin. RMD Open.2020: 6(1), e001295.
6. Ruan, Q. et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. China. Intensive Care Med. 2020:46(5), 846–848 (2020).
7. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021; 19:55–71.
8. Medeiros de Morais C. Nutritional therapy in COVID-19 management. Kompass Nutr Diet. 2021; 1:10–12.
9. Chen G., Wu D., Guo W., Cao Y., Huang D., Wang H., Wang T., Zhang X., Chen H., Yu H., Zhang X., Zhang M., Wu S., Song J., Chen T., Han M., Li S., Luo X., Zhao J., Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. J. Clin. Invest. 2020.

10. Liu J., Li S., Liu J., Liang B., Wang X., Wang H.et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55.
11. Qin C., Zhou L., Hu Z., Zhang S., Yang S., Tao Y., Xie C., Ma K., Shang K., Wang W., Tian D.S. Dysregulation of Immune Response in Patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin. Infect. Dis. 2020.
12. Chen T., Wu D., Chen H., Yan W., Yang D., Chen G., Ma K., Xu D., Yu H., Wang H., Wang T., Guo W., Chen J., Ding C., Zhang X., Huang J., Han M., Li S., Luo X., Zhao J., Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368.
13. Bai T., Tu S., Wei Y., Xiao L., Jin Y., Zhang L., Song J., Liu W., Zhu Q., Yang L., Chen H., Hou X. Clinical and laboratory factors predicting the prognosis of patients with COVID-19: an analysis of 127 patients in Wuhan, China. Lancet. 2020.
14. Ji D., Zhang D., Chen Z., Xu Z., Zhao P., Zhang M., Zhang L., Cheng G., Wang Y., Yang G., Liu H., Li B., Ji J., Lau G., Qin E. Clinical characteristics predicting progression of COVID-19. Lancet. 2020.
15. M. Merad, J. Martin. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat. Rev. Immunol. (2020).
16. Rosário C., Zandman-Goddard G., Meyron-Holtz E.G., D'Cruz D.P., Shoenfeld Y. The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013; 11:185.
17. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. Research J Med Sci. 2014;19(2):164–174.
18. E. Pretorius, D. Kell. Diagnostic morphology: biophysical indicators for iron-driven inflammatory diseases. Integr. Biol. (Camb) (2014).
19. A. Cavezzi, et al. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin. Pract. (2020).
20. Quilliot D, Bonsack O, Jaussaud R, Mazur A. Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors. Magnes Res. 2020; 33:114–122.
21. Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. Tohoku J Exp Med. 2020; 252:73–84.
22. 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.
23. 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.
24. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020;7:e575–e582.
25. Perico L, Benigni A, Casiraghi F, et al. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021; 17:46–64.
26. Maier JAM. Endothelial cells and magnesium: implications in atherosclerosis. Clin Sci (Lond) 2012; 122:397–407.
27. Sheu J-R, Hsiao G, Shen M-Y, et al. Mechanisms involved in the antiplatelet activity of magnesium in human platelets. Br J Haematol. 2002; 119:1033–1041.

28. de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: Implications for health and disease Physiol Rev. 2015; 95:1–46.
29. 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.
30. Weglicki WB. Hypomagnesemia and inflammation: Clinical and basic aspects. Annu Rev Nutr 2012; 32: 55-71.
31. 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; 886:173546.
32. Caspi R, Billington R, Keseler IM, et al. The MetaCyc database of metabolic pathways and enzymes - a 2019 update. Nucleic Acids Res. 2020;48: D445–D453.
33. Dibaba DT, Xun P, He K. Dietary magnesium intake is inversely associated with serum C-reactive protein levels: Meta-analysis and systematic review Eur J Clin Nutr. 2014; 68:510–6.
34. Huang Y, Jin F, Funato Y, et al. Structural basis for the Mg(2+) recognition and regulation of the CorC Mg(2+) transporter. Sci Adv. 2021;7: eabe6140.
35. Workinger JL, Doyle RP, Bortz J. Challenges in the diagnosis of magnesium status. Nutrients. 2018; 10:1202.
36. Cazzola R, Della Porta M, Manoni M, et al. Going to the roots of reduced magnesium dietary intake: a tradeoff between climate changes and sources. Heliyon. 2020;6: e05390.
37. Sarvazad H, Cahngaripour SH, Eskandari Roozbahani N, Izadi B. Evaluation of electrolyte status of sodium, potassium and magnesium, and fasting blood sugar at the initial admission of individuals with COVID-19 without underlying disease in Golestan Hospital. Kermanshah New Microbes New Infect. 2020; 38:100807.