

Article

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Relationship of heart rate variability with serum zinc and magnesium in female rheumatoid arthritis patients

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting multiple small symmetrical joints with extra-articular involvement. Altered blood mineral status is associated with the immune-inflammatory rheumatoid process. Reduced heart rate variability (HRV) is a predictor of sudden cardiac death in RA patients. So, the role of minerals for altered HRV needs investigation in RA. **Objectives:** To assess the relationship between HRV and serum zinc (Zn), magnesium and (Mg) levels in RA patients. **Methods:** This cross sectional study enrolled 60 female participants of 30-50 years of age. Among them 30 female RA patients were included in the study group and 30 age matched apparently healthy women constituted control group. Serum Zn, Mg levels were estimated by auto-analyzer and frequency domain parameters of HRV were recorded by a data acquisition device, Powerlab 8/35, AD Instruments, Australia followed by analysis with software, Lab chart. Statistical analyses were done by independent sample 't' test and Pearson's correlation coefficient test. **Results:** In this study, among frequency domain parameters of HRV, total power (TP), low frequency power(LF), high frequency power(HF), HF normalized unit(HF nu) were significantly lower ($p<0.05$) and LF normalized unit (LF nu), LF/HF ratio were significantly higher ($p<0.05$) in RA patients. In addition, significantly ($p<0.05$) lower levels of serum Zn and Mg were found in RA patients as compared to controls. But on correlation analysis, the HF nu showed significant positive correlation and LF nu and LF/HF

ratio demonstrated significant negative correlation ($p < 0.05$) with serum Mg only. **Conclusion:** Results of the present study revealed that low levels of serum Mg was correlated with reduced HRV in patients with RA. Moreover, low serum Mg was related to parasympathetic hypo and sympathetic hyperactivity as well as altered sympathovagal balance in RA.

Keywords: Rheumatoid arthritis, Heart rate variability, Zinc, Magnesium.

Introduction

Rheumatoid arthritis (RA) is the commonest joint disease with considerable disability, compromised quality of life and premature mortality prevalent in the industrialized as well as in developing world.¹ The most prominent feature of RA is symmetrical polyarthritis involving small synovial joints of hand, wrist, feet, ankle, knee.²⁻³

This disabling disease has worldwide distribution, hence is a global public health concern.⁴⁻⁵ Almost all ethnic groups and races are affected by RA.⁶ Overall pooled prevalence of RA in Bangladesh is about 0.7%. This progressive disabling disease impacts heavily upon treatment expenses and productivity of the affected patients. Thus, RA imposes a great economic burden on health outcome.^{2,7-8} Despite high incidence of RA globally as well as locally it is often a neglected medical issue in developing country like Bangladesh.

Progressive disabilities with non articular complications deteriorate patient's quality of life seriously. Among many risk factors, minerals and trace elements disorders have been recognized as risk factors of RA.^{3,5,9} Previous studies reported chronic inflammation induced marked systemic alteration in blood mineral levels causing pathogenesis in RA patients.^{1-3,5,9-13}

In addition to joints, RA adversely affects all the organ and system of the body and cardiovascular morbidity and mortality is well marked in RA patients.¹⁴⁻¹⁵ As because, cardiovascular

involvement is silent, more than 40% of the premature deaths occur in RA due to cardiovascular diseases (CVD)¹⁶

Analysis of HRV has been emerged as most reliable and non-invasive method for assessment of cardiac autonomic activity and reduced HRV is a marker of autonomic imbalance, which is a strong predictor of sudden cardiac death.¹⁷ HRV analysis by frequency domain parameters, is most widely used non invasive tool which distinguishes the original HRV signal into specific frequency band and reflects the amplitude of the signals of heart rate fluctuation at different frequency ranges. This difference in frequency ranges can differentiate the sympathetic and parasympathetic component of autonomic nervous system. Therefore frequency domain analysis represents more precise assessment of cardiac autonomic activity.¹⁸ Previous studies reported that RA was associated with significantly reduced HRV.^{16,19-20} Among the blood minerals, low serum Mg and Zn has been found associated with RA which increases risk of CVD in RA.^{8,11,21-22} Previous studies demonstrated that serum Mg deficiency was found to be associated with autonomic dysfunction. Studies on healthy adult Korean women and hypomagnesemia patients showed that serum Mg was significantly positively correlated with some HRV indices.²³⁻²⁴ whereas no association was observed between serum Zn level and cardiovascular autonomic function in pregnant women with gestational

hypertension.²⁵ But no published data was found regarding the relationship of serum Zn and Mg level with HRV in patients with RA. Therefore, the present study has been designed to assess the relationship between reduced HRV and serum levels of Zn, Mg in patients with RA.

Methods

Setting and study participants

This cross sectional study was carried out in the Department of Physiology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March, to February, 2021. Thirty female RA patients aged 30-50 years were enrolled by purposive sampling from the Outpatient Department of Rheumatology, BSMMU, Dhaka according to selection criteria. Thirty age and BMI match apparently healthy female subjects were also studied as control. Protocol was approved by Institutional Review Board (IRB) of BSMMU.

Selection criteria

The patients who had history or currently suffering from- cardiovascular disorders, respiratory disorders, renal insufficiency, liver disease, arthritis other than RA, neurological disorders, thyroid disorders, psychiatric disorders, malignancy, pregnancy and also the patients under medications for cardiac disease or respiratory disease or for other reasons which might interfere with autonomic nervous system balance or serum mineral status, current smokers were excluded from this study.

Data collection procedure

For this study, informed written consent was taken from each participant after briefing the aim, benefit and procedure of the study.

Then detailed history was taken and thorough physical examination was done and information was documented in a preformed standard data sheet. Then under aseptic precaution, venous blood was collected for estimation of some biochemical parameters. Fasting blood glucose and serum creatinine as well as serum levels of Zn, Mg were estimated by standard laboratory

technique in the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka. Finally selected subjects were then instructed about proper preparation before recording of HRV data. The subjects were instructed to take their meal by 9:00 pm and to have a sound sleep at the previous night, without any physical or mental stress and not to take any sedatives, hypnotic medication. Then on the test day, patients were requested to take light breakfast in the morning without tea or coffee and then attend to the autonomic nerve function laboratory in the Department of Physiology, BSMMU between 8-9 a.m. After that, the subjects were given complete bed rest in supine position for 10-15 minutes in a temperature and sound controlled laboratory environment. Then HRV was recorded by a digital data acquisition device (Powerlab 8/35, AD instruments, Australia) to assess cardiac autonomic nerve function. During the procedure, any talking, eating or drinking as well as performing physical or mental activity even sleep were prohibited.

Statistical analysis

Data were expressed as mean \pm SD. For statistical test, independent sample 't' test and Pearson's correlation coefficient test were applied by using SPSS version 16. Value of probability $P < 0.05$ was considered as level of statistical significance.

Results

General characteristics of the subjects were presented in Table I. In this study, age and BMI were comparable between groups but resting pulse rate, systolic and diastolic blood pressure were significantly higher ($p < 0.01$) in RA patients compared to controls. In this study, significantly ($p < 0.01$) lower values of TP, LF power, HF power, HF nu and higher value of LF nu, LF/HF ratio were observed in RA patients compared to controls (Table II). In addition, significantly ($p < 0.05$) lower serum Zn and Mg levels were found in RA (Table II). On correlation analysis, only serum Mg showed significant ($p < 0.05$) positive correlation with HF power and significant ($p < 0.05$) negative correlation with LF nu, LF/HF ratio in RA patients (Figure 1, 2, 3).

Table II: Frequency domain measures of HRV, serum Zn and Mg levels in two groups (N=60)

Variables	RA (n=30)	Control (n=30)	p value
TP (ms ²)	649.19±736.92 (15.7-3246)	1736.66±1239.94 (176.23-4695)	0.000***
LF power (ms ²)	300.36±323.11 (9.24-1541)	617.08±486.26 (57.7-1941)	0.005**
HF power (ms ²)	144.53±227.71 (2.05-997.8)	705.21±671.81 (41.14-3234)	0.000***
LF norm (n.u.)	66.73±12.89 (26.21-83.12)	45.88±15.32 (17.29-64.7)	0.000***
HF norm (n.u.)	32.59±12.33 (16.57-73.22)	53.01±14.50 (33.26-81.44)	0.000***
LF/HF ratio	2.42±1.12 (0.36-5.02)	0.99±0.52 (0.22-1.95)	0.000***
Zn (µgm/dL)	87.9±22.85 (50-139)	102.17±27.48 (57-146)	0.033*
Mg (mg/dL)	1.91±0.21 (1.5-2.2)	2.05±0.26 (1.5-2.6)	0.024*

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample 't' test; RA-Rheumatoid arthritis; TP- total power; LF power- low frequency power; HF power- high frequency power; LF norm- low frequency power in normalized unit; HF norm- high frequency power in normalized unit; LH/HF ratio- low frequency and high frequency power ratio; n=number of subjects in each group; *p<0.05 ** p <0.01; *** p <0.001;

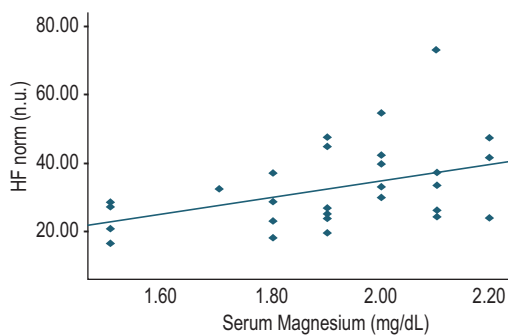


Figure 1: Correlation of HF nu (ms²) with serum Mg level (mg/dL) in group RA. HF nu was positively correlated with serum Mg. RA = Rheumatoid arthritis, HF norm = High frequency power in normalized unit.

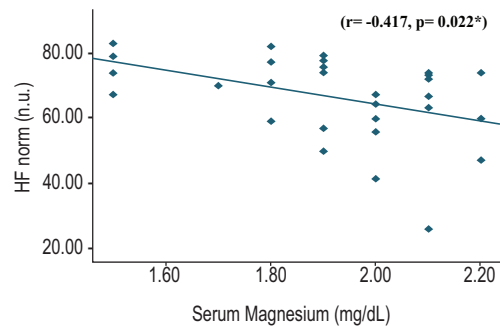


Figure 2: Correlation of LF nu (ms²) with serum Mg level (mg/dL) in group RA. LF nu was negatively correlated with serum Mg level. RA = Rheumatoid arthritis, HF norm = High frequency power in normalized unit.

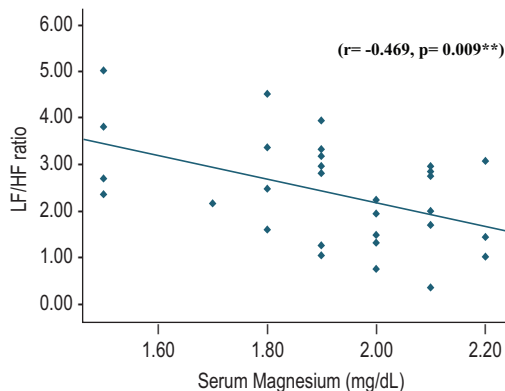


Figure 3: Correlation of LF/HF ratio with serum Mg level (mg/dL) in group RA. LF/HF ratio was negatively correlated with serum Mg level. RA = Rheumatoid arthritis, LH/HF ratio = Low frequency and high frequency power ratio.

Discussion

The present study investigated the relationship of HRV with serum Zn, Mg level in 30-50 years of age female RA patients. Almost similar age range but both genders RA patients were enrolled in a previous study.⁵ This particular age range was chosen for this study because RA is most frequently diagnosed around this age as it is highly prevalent in between 35-50 years.¹ However, BMI was slightly lower in RA patients compared to controls but that difference was statistically non-significant. Therefore, two important confounding factors- age and BMI were adjusted in both groups.^{1,2-3} In this study, higher resting pulse rate, SBP and DBP in RA patients agree to others and suggest slight derangement of cardiovascular autonomic regulation.^{20,26-27} Among the results of frequency domain HRV variables, lower values of TP, LF power, HF power, HF nu suggest hypo parasympathetic tone and higher value of LF nu, LF/HF ratio suggestive of hyper sympathetic tonic activity and shifting of sympathovagal balance towards more sympathetic dominance in the present series of RA were consistent with the findings of other researchers.^{20,27-28} This demonstrates impaired cardiac autonomic

regulation with sympathetic dominance and decreased parasympathetic modulation is associated with RA. The current study also revealed association lower serum Zn and Mg with RA. This result is also supported by some previous studies.^{1-3,8,11,21-22} On further analysis, significant positive correlation of HF nu and negative correlation of LF nu and LF/HF ratio with serum Mg suggest that decreasing level of serum Mg is related to reduced parasympathetic activity and increased cardiac sympathetic, altered sympathovagal balance to sympathetic dominance in Rheumatoid arthritis. This finding is novel and it demonstrated the contribution of Mg deficiency to cardiac autonomic dysregulation in RA. Scientific literature suggested that Mg deficiency promotes oxidative stress, inflammatory response which could contribute to the pathogenesis of several cardiovascular diseases such as atherosclerosis, hypertension, arrhythmia and sudden cardiac death. It was reported that a high incidence of sudden death in Mg-deficient rats was related to arrhythmias, coronary vasospasm and ANS dysfunction.²⁴ The role of low Mg for cardiac autonomic derangement in the present study can be explained by the chronic inflammation and immune modulation that are chiefly involved in RA pathogenesis. Thus, low levels of serum magnesium may be considered as potent risk factors for CVD events in patients with RA.

Conclusion

The results of the present study revealed that low levels of serum Mg was related to reduced HRV in patients with RA. Moreover, low serum Mg was related to parasympathetic hypo and sympathetic hyperactivity as well as altered sympathovagal balance in this particular patient cohort. Association of serum Mg status alteration with reduced HRV is an important predictor of increased risk of sudden cardiac death in patients with RA.

Conflict of interest: Declared none

References

1. Das DC, Jahan I, Uddin MG, Hossain MM, Chowdhury MAZ, Ferdous Z, Rahman MM, Kabir AKMH, Deb SR, Siddique MAB, Das A. Serum CRP, MDA, vitamin C and trace elements in Bangladeshi patients with rheumatoid arthritis. *Biol Trace Elem Res* 2021; 199:76–84. doi:10.1007/s12011-020-02142-7.
2. Xin L, Yang X, Cai G, Fan D, Xia Q, Liu L, Hu Y, Ding N, Xu S, Wang L, Li X, Zou Y, Pan F. Serum levels of copper and zinc in patients with rheumatoid arthritis: a meta-analysis. *Biol Trace Elem Res* 2015; 168: 1-10. doi: 10.1007/s12011-015-0325-4.
3. Ma Y, Zhang X, Fan D, Xia Q, Wang M, Pan F. Common trace metals in rheumatoid arthritis: a systematic review and meta-analysis. *J Trace Elem Med Biol* 2019; 56:81-89. doi: 10.1016/j.jtemb.2019.07.007.
4. Ali HM, Al-Zubaidi MA. Evaluation of trace elements in Iraqi patients with rheumatoid arthritis by using atomic absorption spectrophotometer (AAS). *Iraqi J Pharm Sci* 2012; 21(2): 77- 84.
5. Strecker D, Mierzecki A, Radomska K. Copper levels in patients with rheumatoid arthritis. *Ann Agric Environ Med* 2013; 20 (2): 312-6.
6. Ralston SH, McInnes IB. Rheumatology and bone disease. In: Walker BR, Colledge NR, Ralston SH, Penman ID, editors. *Davidson's Principles and Practice of Medicine*. Edinburgh: Elsevier;2014. p.1057- 1136.
7. Khanna S, Jaiswal KS, Gupta B. Disease modifying antirheumatic drugs: The new treatment modalities for rheumatoid arthritis. *EMJ Rheumatol* 2018; 5(1): 93-99.
8. Manole C, Mihaela CI, Lucia M, Isabela S, Minerva G. Changes of serum magnesium levels in patients with rheumatoid arthritis stage i-ii before treatment. *Med Con* 2011; 6(2): 9-12.
9. Ullah Z, Ullah MI, Hussain S, Kaul H, Lone KP. Determination of serum trace elements (Zn, Cu and Fe) in Pakistani patients with rheumatoid arthritis. *Biol Trace Elem Res* 2017; 175(1): 10-16. doi: 10.1007/s12011-016-0746-8.
10. Onal S, Nazýroglu M, Colak M, Bulut V, Flores-Arce MF. Effects of different medical treatments on serum copper, selenium and zinc levels in patients with rheumatoid arthritis. *Biol Trace Elem Res* 2011; 142(3):447–455. doi:10.1007/s12011-010-8826-7.
11. Afridi HI, Kazi TG, Kazi N, Shah AQ, Khan S, Kolachi NF, Wadhwa SK, Shah F. Evaluation of calcium, magnesium, potassium and sodium in biological samples (scalp hair, serum, blood and urine) of Pakistani referents and arthritis patients of different age groups. *Clin Lab* 2012; 58 (1-2):7-18.
12. Sahebari M, Ayati R, Mirzaei H, Sahebkar A, Hejazi S, Saghafi M, Saadati N, Ferns GA, Ghayour-Mobarhan M. Serum trace element concentrations in rheumatoid arthritis. *Biol Trace Elem Res* 2016; 171: 237–245. doi: 10.1007/s12011-015-0501-6.
13. Saptarini NM, Wibowo MS, Gusdinar T. Correlation study of serum calcium levels and serum cartilage oligomeric matrix protein levels in rheumatoid arthritis patients in Bandung, Indonesia. *Asian J Pharm Clin Res* 2017; 10(11):401-403. doi:10.22159/ajpcr.2017.v10i11.18493.
14. Masoud S, Lim PB, Kitas GD, Panoulas V. Sudden cardiac death in patients with rheumatoid arthritis. *World J Cardiol* 2017; 9(7):562-573. doi: 10.4330/wjcv.9.i7.562.
15. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. *Eur Heart J* 2017; 38: 1717-1727. doi:10.1093/eurheartj/ehw208.
16. Saminathan MB, Sharma R, Gogna A, Rani A, Kapoor R. Correlation of inflammatory markers and disease severity with cardiovascular autonomic dysfunction in Indian patients with rheumatoid arthritis. *Indian J Rheumatol* 2019; 14:123-6. doi:10.4103/injr.injr_171_18.
17. Task force of the European Society of Cardiology and the North American Society of pacing and electro physiology. Heart rate variability. Standards of measurement, physiological interpretation and clinical use. *Eur Heart J* 1996; 17: 354-381.
18. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front psycho* 2014;5:1040. doi: 10.3389/fpsyg.2014.01040
19. Adlan AM, Lip GYH, Paton JFR, Kitas GD, Fisher JP. Autonomic function and rheumatoid arthritis- a systematic review. *Semin Arthritis Rheum* 2014; 44(3): 283-304. doi:10.1016/j.semarthrit.2014.06.003.

20. Ahamed S, Sheriff R. Analysis of heart rate variability in patients with chronic rheumatoid arthritis. *Int J Clin Exp Physiol* 2016; 3: 204-8. doi:10.4103/2348-8832.196914.
21. Chavan VU, Ramavaram DVSS, Patel PA, Rupani MP. Evaluation of serum magnesium, lipid profile and various biochemical parameters as risk factors of cardiovascular diseases in patients with rheumatoid arthritis. *J Clin Diagnos Res* 2015; 9(4): 1-5. doi: 10.7860/JCDR/2015/12206.5740.
22. Moustafa SR, Al-Taweel N, Mohsen F. Association of Boron, Copper, Germanium, Magnesium, Selenium and Zinc with incidence of rheumatoid arthritis. *Am J Intern Med* 2015; 3(3):132-140. doi: 10.11648/j.ajim.20150303.17.
23. Kim YH, Jung KI, Song CH. Effect of serum calcium and magnesium on heart rate variability in adult women. *Biol Trace Elem Res* 2012;150:116-122.
24. Matei D, Luca C, Andritoi D, Sardaru D, Corciova C. The relationship between lower serum magnesium levels and heart rate variability indices. *Balneo Res J* 2018; 9(4): 426-432. doi:10.12680/balneo.2018.226.
25. Mohan P, Udayakumar KP, Hiramath PB. Does the frequency domain parameters among pregnant women with gestational hypertension associated with levels of serum zinc, magnesium and copper? A cross sectional study. *Natl J Physiol Pharm Pharmacol* 2020; 10 (9): 1-5. doi: 10.5455/njppp.2020.10.04099020201062020.
26. Rensburg DCJV, Ker JA, Grant CC, Fletcher L. Autonomic impairment in rheumatoid arthritis. *Int J Rheum Dis* 2012; 15(4):419-426.
27. Yadav RK, Gupta R, Deepak KK. A pilot study on short term heart rate variability and its correlation with disease activity in Indian patients with rheumatoid arthritis. *Indian J Med Res* 2012; 136(4):593 8.
28. Adlan AM, van Zanten JJCSV, Lip GYH, Paton JFR, Kitas GD, Fisher JP. Cardiovascular autonomic regulation, inflammation and pain in rheumatoid arthritis. *Auton Neurosci* 2017; 208 :137–145. doi:10.1016/j.autneu.2017.09.003.