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Correlation of serum zinc and magnesium with reduced heart rate variability in male Parkinson's disease patients

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Abstract

Background: Parkinson's disease (PD) is a neurological disorder associated with altered cardiac autonomic function. Heart rate variability (HRV) analysis is a tool to assess the cardiac autonomic status. Altered serum zinc (Zn) and magnesium (Mg) levels are observed in PD. The serum Zn and Mg alteration is associated with nerve function impairment. **Objective:** To evaluate the relationship between serum zinc, magnesium, and time domain measures of HRV in male patients with PD. **Methods:** This observational analytical cross-sectional study was conducted in 2023 on 30 newly diagnosed male PD patients aged 50-60 years. In this study, 30 healthy volunteers were the control. The 30 patients were divided into different categories based on serum mineral levels. The HRV was recorded by Power Lab 8/35, AD Instruments, Australia and the time domain measures of HRV were used in data analysis. The serum Zn and Mg levels were measured by atomic absorption spectrophotometry. Independent sample 't' test and Pearson's correlation coefficient test were used for statistical analysis and $p<0.05$ was considered statistical significance. **Results:** Significantly higher mean HR (Heart rate) ($p<0.01$) and significantly lower mean RR (Normal to normal QRS complex) interval, CVRR (Coefficient variation of RR interval) ($p<0.01$), SDRR (Standard deviation of the RR intervals), SDSD (Standard

deviation of the difference between successive RR intervals), RMSSD (Square root of mean squared differences of successive RR intervals), pRR50% (Proportion of RR interval with duration >50 ms) ($p<0.001$) were observed in PD patients compared to control. In PD patients, significantly lower ($p<0.001$) serum Zn and significantly higher ($p<0.01$) serum Mg were observed compared to control. In addition, significant decrement was observed in SDRR, CVRR ($p<0.05$), SDSD, RMSSD, and pRR50% ($p<0.01$) in hypozincemic PD patients compared to normozincemic patients. On correlation analysis, significant positive correlations of serum Zn were observed with SDRR ($p<0.05$), SDSD ($p<0.001$), RMSSD ($p<0.001$) and pRR50% ($p<0.01$). Moreover, serum Mg was positively correlated with SDRR ($p<0.05$) in PD patients. **Conclusion:** Hypozincemia and magnesium were directly related to reduced HRV in male PD patients.

Keywords: HRV, Serum zinc, Serum magnesium, Time domain analysis.

Introduction

Parkinson's disease (PD) is a neurological disorder that develops due to neuronal loss in the substantia nigra. The risk of PD increases with advancing age. It is a male predominant disease and male to female ratio is 3:2.[1] The typical age of onset of PD is around 60 years. The prevalence of PD in the UK is 180 per 1 million and the incidence is about 18 per 1 million.[2] In 2016, the incidence in north India was close to 0.58 million.[3] The identifying feature of PD is the degeneration of dopaminergic neurons in the substantia nigra projecting to the putamen that results in diminished striatal dopamine and also the formation of Lewy bodies which are some inclusions containing the protein alpha-synuclein in nerve cells initiates degeneration of basal ganglia, different areas of the brain and peripheral nerves. In PD patients, some motor features such as bradykinesia, rigidity, rest tremor and gait are observed. The associated non-motor complications develop due to autonomic dysfunction that affects the cardiovascular system.[4,5] In a previous study, the ANS dysfunction in the early stage of PD was evaluated by heart rate variability (HRV) analysis and reduced HRV was evident in PD patients.[6] The reduced HRV reflects cardiac autonomic dysfunction (CAD) due to compromised parasympathetic and sympathetic nerve activity.[7,8] In HRV analysis, the time domain method is the simplest one in which the beat-to-beat intervals are determined from an RR interval tachogram from a 5-minute electrocardiographic (ECG) record. The time domain variables, calculated from it, include mean normal to normal QRS complex (RR) interval which represents the fine-tuning between the vagal and sympathetic activity of the autonomic nervous system (ANS), mean heart rate (HR) that reflects the relative balance of the sympathetic and parasympathetic nervous system, the standard deviation of all RR interval (SDRR) in millisecond (ms) that estimates the overall variability, the square root of mean squared difference of RR intervals (RMSSD), the standard deviation of successive RR interval (SDSD) and the number of R-R intervals differing >50 ms from adjacent intervals divided by the total number of all R-R intervals (pNN50%)

reflects vagal modulation.[9] The coefficient variation of RR interval (CVRR) measures the variation of RR interval between diseased and healthy groups.[10] In PD, the alterations in serum Zn and Mg are evident in previous studies.[11-18] Excess Zn causes neurotoxicity and damage to neurons that can hamper nerve functions Zn binds with the Parkin gene related to PD and maintains the normal conformation of the protein which is associated with the ubiquitination of other proteins that interact with alpha-synuclein. Zn plays an important role in nerve signal transmission and cell protection from oxidative stress.[19-21] Magnesium (Mg) is essential for nerve signal transmission, neuromuscular coordination and protection against excessive excitation that leads to cell death. Hypomagnesemia causes excess nerve and muscular excitation whereas hypermagnesemia results in muscle tremors, tetany, convulsions etc.[22] It participates in many physiological processes that control cardiovascular function. Mg is required for the synthesis of some human unsaturated fatty acids that improve parasympathetic nerve function and maintain sympathovagal balance.[23] It also regulates the excitability of cell membranes.[24] Many researchers from different countries investigated serum zinc[11-14] and magnesium[15-18] in PD patients. Many studies reported a decrease in the serum Zn level in PD patients[11-13,15] whereas some researchers reported an increase in the serum Zn level in PD compared to healthy control.[16] A few researchers observed no significant changes from the controls.[14] In a previous study, lower serum magnesium level was reported in PD patients[25] whereas some researchers observed higher serum levels of magnesium in PD than in healthy subjects.[16-18] Moreover, in a research study, no significant differences were also observed.[15] In the past, the relationship between Zn and HRV was reported in prior studies.[21,29] A positive relationship was observed between magnesium deficiency and CAD in hypomagnesemic participants and young adults.[22,23] Therefore, It is crucial to investigate more due to the controversial outcome of these minerals in previous studies. That is why, this study was designed to assess the relationship between serum Zn, Mg and heart rate variability in PD to gain new insights for the physicians and in reducing the advancement of cardiac autonomic complications in this particular group of patients.

Methods

Study design & setting

This observational analytical cross-sectional study was conducted in the Department of Physiology, BSMMU, Dhaka from March 2022 to February 2023

Study participants

The study was conducted on 30 newly diagnosed male patients with PD visiting the Out Patients Department (OPD) of Neurology, BSMMU, aged between 50-60 years, Hoehn and Yahr (H-Y) scale stage I to III, diagnosed by a neurologist according to the UK Parkinson's Disease Society Brain Bank diagnostic criteria[30] constituted the study group and to compare, 30 apparently healthy male subjects with similar age and BMI constituted the control group.

Sampling

Purposive sampling was adopted to select the patients as well as the control subjects. The study group was selected from Neurology OPD, BSMMU. The control group was selected through personal contact.

Exclusion criteria

The subjects with a history of head injury, alcoholism, any other systemic illness, vitamin, mineral supplements and intake of drugs that hamper ANS functions were excluded from this study.

Data collection procedure

Informed written consent was taken from all selected participants. A detailed medical history and anthropometric measurements were taken. Then a thorough clinical examination was done. Under aseptic precaution, 4 ml of venous blood was taken for random blood glucose (RBS), serum creatinine and thyroid stimulating hormone (TSH). The finally selected participants were given instructions for the preparation for HRV recording. For HRV recording, the subjects were asked to finish their

dinner by 9:00 pm, to have a sound sleep the previous night, to avoid any physical or mental stress and also to take any sedatives or any other drugs that could affect the central nervous system. They were requested to have a light breakfast in the morning without tea or coffee and then report to the Department of Physiology, BSMMU between 8-9 a.m. Before performing the test, the subjects were allowed to relax in the supine position for 15-20 minutes in a noise-free, comfortable temperature-controlled environment with dim light in the laboratory. The HRV recording was done by a data acquisition device Power Lab 8/35, AD instrument, Australia for the next 5 minutes refraining from any talking, eating, drinking, performing physical or mental activity or even sleeping. Then, under aseptic precautions, 2 ml of venous blood was taken to estimate serum minerals.

Statistical analysis

Data were expressed as mean±SD. For statistical analysis, Independent sample 't' test and Pearson's correlation coefficient test were done using SPSS version 25, and $p<0.05$ was considered as the significance level.

Results

This study observed a significantly higher ($p<0.05$) resting pulse rate in PD patients compared to the control. Data of all general characteristics and BP were similar ($p>0.05$) in both groups (Table I).

Again, a significantly higher Mean HR ($p<0.01$) and significantly lower Mean RR, CVRR ($p<0.01$), SDRR, SDSD, RMSSD and pRR50% ($p<0.001$) were observed in PD patients compared to control (Table II)

Moreover, serum Zn was significantly lower ($p<0.001$) and serum Mg was significantly higher ($p<0.01$) in PD patients compared to the control even though Mg was within the normal range in both groups (Table III).

Again, significantly lower SDRR, CVRR ($p<0.05$), SDSD, RMSSD and pRR50% ($p<0.01$) were observed in hypozincemic PD patients compared to normozincemic patients (Table IV). There was no subjects with high serum Mg observed in PD patients and healthy subjects.

Furthermore, serum Zn showed significantly positive correlations with SDRR ($p<0.05$), SDSD, RMSSD ($p<0.001$), pRR50% ($p<0.01$) (Table V) and serum Mg showed a significant positive correlation with SDRR ($p<0.05$) of time domain measures in PD patients (Table VI).

Table I : General characteristics, resting pulse rate, and BP in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Age (Years)	55.33±3.23 (50-60)	54.83±3.28 (50-60)	0.554
BMI(Kg/m^2)	22.01±0.88 (20.78-24)	22.44±1.08 (20.10-24.20)	0.095
Pulse rate(beats/min)	80.20±4.15 (72-88)	77.30±4.76 (68-86)	0.015
SBP(mm Hg)	124.30±6.83 (110-135)	127.33±5.52 (120-135)	0.064
DBP(mmHg)	81.50±3.97 (70-85)	80.66±4.09 (70-85)	0.427

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by independent sample t-test; PD- Parkinson's disease, BMI- Body Mass Index; SBP- systolic blood pressure; DBP- diastolic blood pressure; N- Total number of subjects; n- Number of subjects in each group.

Table II : Time domain measures in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Mean heart rate(beats/min)	83.12±6.98	76.41±7.20	0.001
	(69.93-99.42)	(65.48-88.73)	
Mean RR Interval (ms)	726.38±60.74	788.33±73.75	0.001
	(604-858.60)	(677.76-993.80)	
SDRR(ms)	27.55±6.69	36.67±6.25	0.000
	(14.36-41.42)	(25.20-49.41)	
CVRR	0.038±0.010	0.046±0.009	0.002
	(0.022-0.062)	(0.031-0.072)	
SDSD(ms)	16.72±6.57	24.93±3.36	0.000
	(7.24-32.52)	(20.45-32)	
RMSSD(ms)	16.71±6.59	24.76±3.08	0.000
	(7.24-32.48)	(20.42-31.96)	
pRR50(%)	0.45±0.56	5.68±5.08	0.000
	(0.00-2.00)	(0.00-25.22)	

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by independent sample t-test; PD- Parkinson's disease, SDRR- Standard deviation of all RR interval; CVRR- Coefficient variation of RR interval; SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects; n- Number of subjects in each group.

Table III : Serum Zn and serum Mg in two groups (N=60)

Variables	PD (n=30)	Control (n=30)	p value
Serum Zn (µg/dL)	53.43±10.38	80.60±14.51	0.000
	(40-80)	(44-105)	
Serum Mg(mg/dL)	2.09±0.16	1.95±0.13	0.001
	(1.80-2.40)	(1.70-2.30)	

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by independent sample t-test; PD- Parkinson's disease, Serum Zn- Serum Zinc, Serum Mg- Serum Magnesium; N- Total number of subjects; n- Number of subjects in each group.

Table IV : Time domain measures in two study groups based on serum zinc level (N=30**)**

Variables	Hypozincemic PD (n=26)	Normozincemic PD (n=4)	p value
Mean heart rate(beats/min)	82.39±6.74 (69.93-99.42)	87.83±7.62 (81.97-98.54)	0.150
Mean RR Interval (ms)	732.13±60.24 (604-858.60)	688.60±56.89 (610-733.70)	0.187
SDRR (ms)	26.53±6.54 (14.36-41.42)	34.15±2.85 (30.51-37.43)	0.031
CVRR	0.03±0.010 (0.021-0.062)	0.049±0.003 (0.046-0.054)	0.014
SDSD (ms)	15.36±5.95 (7.24-32.52)	25.52±1.68 (23.75-27.14)	0.002
RMSSD (ms)	15.37±5.99 (7.24-32.48)	25.49±1.67 (23.72-27.10)	0.003
pRR50 (%)	0.33±0.47 (0.00-2.00)	1.17±0.56 (0.41-1.76)	0.004

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by independent sample t-test; PD- Parkinson's disease, SDRR- Standard deviation of all RR interval; CVRR- Coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects; n- Number of subjects in each group.

Table V : Correlations of time domain HRV measures with serum zinc level in the study group (N=30)

Variables	r value	p value
Mean heart rate(beats/min)	-0.036	0.849
Mean RR Interval(ms)	0.072	0.707
SDRR(ms)	0.428	0.018
CVRR	-0.065	0.732
SDSD(ms)	0.736	0.000
RMSSD(ms)	0.735	0.000
pRR50(%)	0.552	0.002

Statistical analysis was done by Pearson's correlation coefficient (r) test; PD- Parkinson's disease, SDRR- Standard deviation of all RR interval; CVRR- Coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects.

Table VI : Correlations of time domain HRV measures with serum magnesium level in the study group (N=30)

Variables	r value	p value
Mean heart rate(beats/min)	-0.160	0.399
Mean RR Interval (ms)	0.310	0.095
SDRR(ms)	0.414	0.023
CVRR	-0.303	0.104
SDSD(ms)	0.187	0.324
RMSSD(ms)	0.192	0.310
pRR50(%)	0.232	0.217

Statistical analysis was done by Pearson's correlation coefficient (r) test; PD- Parkinson's disease, SDRR- Standard deviation of all RR interval; CVRR- Coefficient variation of RR interval, SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; N- Total number of subjects.

Discussion

In this study, a significantly higher resting pulse rate, Mean HR and lower Mean RR, SDRR, CVRR, SDSD, RMSSD, and pRR50% were observed in PD. Similar findings were also reported in the previous studies.[5-7,27,31] The lower values of these time domain variables suggest the reduced overall variability with decreased vagal tone. The accelerated HR was contributed by decreased parasympathetic modulation and increased sympathetic stimulation.[9] The current study also revealed lower serum Zn and higher serum Mg in PD patients which is supported by several previous.[11-13,15-18] Again, the significantly lower SDRR, CVRR, SDSD, RMSSD, and pRR50% in hypozincemic PD patients compared to normozincemic PD patients strongly suggested that hypozincemia had an association with reduced variability and cardiac parasympathetic hypoactivity in PD. On correlation analysis, the significantly positive correlations of SDRR, SDSD, RMSSD and pRR50% with serum Zn observed in PD patients suggested that lower parasympathetic modulation of ANS was associated with hypozincemia in PD patients which agrees with previous reports.[21,29] In addition, a significant positive correlation between SDRR and serum Mg in PD patients, suggesting overall variability was related to serum Mg in PD patients, supported by previous studies.[22,23] The exact mechanism to describe the relationship between serum Zn, Mg, and HRV in PD is unknown even though different research studies could suggest many hypothesised explanations. Loss of Zn causes the unfolding of the genes related to PD that may result in the induction of PD. Oxidative stress is evident in Zn deficiency as it is associated with decreased superoxide dismutase activity that causes neuronal cell death in PD.[20] Some previous studies also revealed the association of PD with the Zn disbalance resulting from the dysfunction of Zn transporters that was observed in PD and considered it as the cause of the low circulating Zn level in the particular group of patients.[13] The previous evidence also reported that alterations in Mg transporter protein expressions were associated with PD patients. The transport of Mg into the cells became hampered due to decreased expression of transporter proteins that were specifically responsible for influx leading to an increased Mg in the circulation.[18] Mg acts as a cofactor for the synthesis of some fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that have a possible association with vagal function. Nevertheless, an excess increase in the serum Mg was considered as a possible cause that could reduce parasympathetic activity and sympathetic tone.[23] Hence, the alteration in serum Zn and Mg could be the potential indicators for the risk of PD.

Conclusion

From the result of this study, it can be concluded that hypozincemia and magnesium level are directly related to reduced heart rate variability in male patients with Parkinson's disease.

Conflict of interest None

Ethical clearance

The protocol of this study involved human subjects following the ethical rules of Helsinki (1964) and was first approved by the departmental ethical and academic committee. It was further reviewed by the Institutional Review Board (IRB) of BSMMU.

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References

1. Scorza FA, Fiorini AC, Scorza CA, Finsterer J. Cardiac abnormalities in Parkinson's disease and Parkinsonism. J Clin Neurosci 2018; 53:1–5. doi:10.1016/j.jocn.2018.04.031
2. Hunt DPJ, Connor MD. Neurology. In: Penman ID, Ralston SH, Strachan MWJ, Hobson RP, editors. Davidson's principles and practice of medicine. United Kingdom: Elsevier; 2023. p. 1165-1167

3. Bamon A, Raina R, Sharma S, Chauhan N. A clinical-epidemiological profile of Parkinson's disease patients attending the tertiary care hospital of hilly state of North India: a hospital-based cross-sectional study. Int J Res Med Sci 2021; 9(8):2397. doi:10.18203/2320-6012.ijrms20213088

4. Olanow CW, Schapira AHV. Disease and other Extrapyramidal movement disorders. In: Hauser SL, Josephson S, editors. Harrison's Neurology in Clinical Medicine. United States. McGraw-Hill; 2017. p. 333-338

5. Suzuki M, Nakamura T, Hirayama M, Ueda M, Katsuno M, Sobue G. Cardiac parasympathetic dysfunction in the early phase of Parkinson's disease. J Neurol 2017; 264(2):333–40. doi:10.1007/s00415-016-8348-0

6. Arnao V, Cinturino A, Mastrilli S, Buttà C, Maida C, Tuttolomondo A, et al. Impaired circadian heart rate variability in Parkinson's disease: a time-domain analysis in the ambulatory setting. BMC Neurol 2020; 20(1):152. doi: 10.1186/s12883-020-01722-3

7. Rocha RSB, De Oliveira Rocha LS, Pena ESM, Caldas LCP, Moreno MA. Analysis of autonomic modulation of heart rate in patients with Parkinson's disease and elderly individuals submitted to game therapy training. Geriatr Gerontol Int 2018; 18(1):20–5. doi: 10.1111/ggi.13130

8. Gonçalves VC, Cuenca-Bermejo L, Fernandez-Villalba E, Martin-Balbuena S, Fernandes MJ, Scorza CA, et al. Heart Matters: Cardiac Dysfunction and Other Autonomic Changes in Parkinson's Disease. The Neuroscientist 2021;

9. Task force of the European Society of Cardiology and the North American Society of Pacing and electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Eur Heart J 1996; 17: 354-381.PMID: 8737210

10. Chang CCJ, Hsiao TCR, Chiang YY, Hsu HY. The usefulness of the coefficient of variation of electrocardiographic RR interval as an index of cardiovascular function and its correlation with age and stroke. Tungs' Med J 2012; 6: 41-48.

11. Zhao H-W, Lin J, Wang X-B, Cheng X, Wang J-Y, Hu B-L, et al. Assessing plasma levels of selenium, copper, iron and zinc in patients of Parkinson's disease. PLoS One 2013; 8(12):e83060. doi: org/10.1371/journal.pone.0083060

12. Asad T, Aamir M, Haroon ZH, Munir MU, Kirmani SI, Awan A. Comparison of serum copper, Zinc, lead, aluminium and iron levels in patients with Parkinson's disease with healthy controls in tertiary care hospital. Pak Armed Force Med J 2022; 72(5):1673–7. doi: 10.51253/pafmj.v72i5.6535

13. Du K, Liu M-Y, Zhong X, Wei M-J. Decreased circulating Zinc levels in Parkinson's disease: a meta-analysis study. Sci Rep 2017; 7(1):3902. doi: 10.1038/s41598-017-04252-0

14. Ajsuvakova OP, Tinkov AA, Willkommen D, Skalnaya AA, Danilov AB, Pilipovich AA. Assessment of copper, iron, zinc and manganese status and speciation in patients with Parkinson's disease: a pilot study. J Trace Elem Med Biol 2020; 59. doi: 10.1016/j.jtemb

15. Ahmed SSSJ, Santosh W. Metallomic profiling and linkage map analysis of early Parkinson's disease: a new insight to aluminium marker for the possible diagnosis. PLoS One 2010; 5(6):e11252. doi: 10.1371/journal.pone.0011252

16. Ogunrin AO, Komolafe MA, Sanya EO, Osubor C, Ajose OA, Akande AA, et al. Trace metals in patients with Parkinson's disease: A multi-center case-control study of Nigerian patients. J Neurol Epidemiol 2013; 1(1):31–8. doi: 10.12974/2309-6179.2013.01.01.4

17. Sanyal J, Ahmed SS, Ng HK. Metallomic biomarkers in cerebro-spinal fluid and serum in patients with Parkinson's disease in Indian population. Sci Rep 2016; 6.

18. Jin X, Liu M-Y, Zhang D-F, Gao H, Wei M-J. Elevated circulating magnesium levels in patients with Parkinson's disease: a meta-analysis. Neuropsychiatr Dis Treat 2018; 14:3159–68. doi: 10.2147/NDT.S186209

19. Stelmashook EV, Isaev NK, Genrikhs EE, Amelkina GA, Khaspekov LG, Skrebitsky VG, et al. Role of zinc and copper ions in the pathogenetic mechanisms of Alzheimer's and Parkinson's diseases. Biochem (Mosc) 2014; 79(5):391–6. doi: 10.1134/S0006297914050022

20. Sikora J, Ouagazzal A-M. Synaptic zinc: An emerging player in Parkinson's disease. Int J Mol Sci 2021; 22(9):4724. doi: 10.3390/ijms22094724

21. Spann MN, Smerling J, Gustafsson H, Foss S, Altemus M, Monk C. Deficient maternal zinc intake but not folate is associated with lower fetal heart rate variability. Early Hum Dev 2015;91(3):169–72. doi: 10.1016/j.earlhumdev.2015.01.007

22. Matei D, Luca C, Andrioi D, Sărdaru D, Corciovă C. The relationship between lower serum Magnesium levels and heart rate variability indices. Balneo Research Journal. 2018;9(4):426-32.

23. Kim Y-H, Jung K-I, Song C-H. Effects of serum calcium and magnesium on heart rate variability in adult women. Biol Trace Elem Res 2012; 150(1–3):116–22. doi: 10.1007/s12011-012-9518-2

24. Xue W, You J, Su Y, Wang Q. The effect of magnesium deficiency on neurological disorders: A narrative review article. Iran J Public Health 2019; 48(3):379–87. doi: 10.18502/ijph.v48i3.880

25. Oyanagi K, Hashimoto T. Magnesium in Parkinson's disease: an update in clinical and basic aspects. Magnesium in the Central Nervous System. Adelaide: University of Adelaide Press; 2011.

26. Soares F, Rebouças GM, Lopes P, Felipe TR, Bezerra J, Filho A. Measures of heart rate variability in patients with idiopathic Parkinson's disease. J Alzheimers Dis Parkinsonism 2013; 3

27. Miyagi T, Yamazato M, Nakamura T, Tokashiki T, Namihira Y, Kokuba K, et al. Power spectral analysis of heart rate variability is useful as a screening tool for detecting sympathetic and parasympathetic nervous dysfunctions in Parkinson's disease. BMC Neurol 2022; 22(1). doi: 10.1186/s12883-022-02872-2

28. Maetzler W, Karam M, Berger MF, Heger T, Maetzler C, Ruediger H, et al. Time- and frequency-domain parameters of heart rate variability and sympathetic skin response in Parkinson's disease. J Neural Transm (Vienna) 2015; 122(3):419–25. Available from: doi: 10.1007/s00702-014-1276-1

29. Lopresti AL. Association between micronutrients and heart rate variability: A review of human studies. Adv Nutr 2020; 11(3):559–75. doi: 10.1093/advances/nmz136

30. Zesiewicz TA. Parkinson disease. Continuum (Minneap Minn) 2019; 25(4):896–918. doi: 10.1212/con.0000000000000764

31. Ke JQ, Shao SM, Zheng YY, Fu FW, Zheng GQ, Liu CF. 2017. Sympathetic skin response and heart rate variability in predicting autonomic disorders in patients with Parkinson's disease. Medicine (Baltimore); 96(18):e6523. doi:10.1097/MD.0000000000006523