

The relationship between lower serum Magnesium levels and heart rate variability indices

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Abstract

Introduction: Magnesium is required in muscular contraction, neuromuscular conduction, heart functions, and vascular tone. Heart rate variability (HRV) is a non-invasive assessment method of the autonomic nervous system activity which regulates heart rate (HR). Time-domain, frequency-domain and non-linear analysis of the HRV can establish the autonomic tone balance.

Objectives: The purpose of this study was to investigate the relationship between lower serum magnesium levels and HRV indices, and to observe if magnesium supplementation can corrected autonomic functions.

Methods: We analyzed HRV parameters in 30 patients with hypomagnesaemia and 20 age-related healthy subjects.

Results: In control group we found lower values for HR, LF nu and LF/HF ratio ($p < 0.0002$) and higher values for HF nu, SD1 when compare with patients with magnesium deficiency, resulting that in supine position there is an enhanced heart rate. In magnesium deficiency group we found increase LF nu, LF/HF ratio suggesting that the sympathovagal balance was affected with a sympathetic overactivity. After magnesium supplementation the HR, LF/HF ratio decrease and RMMSD, pNN50%, HF, SD1 increase in these patients. **Conclusions:** Findings from the current study suggest that Mg supplementation may enhance parasympathetic activity and therefore presenting a positive impact on cardiac autonomic function.

Key words: *magnesium, deficiency, supplementation, heart rate variability, sympathetic nervous system, parasympathetic nervous system,*

1. Introduction

Magnesium is a cofactor for more than 300 enzymatic reactions and is required in muscular contraction, neuromuscular conduction, heart functions, and vascular tone [1, 2]. Magnesium (Mg^{2+}) inhibits calcium induced cell death, can regulate the activity of ion channels, and the synthesis of ATP, RNA, DNA [1, 3].

Mg^{2+} deficiency promotes oxidative stress and inflammatory response and can contributes to the pathogenesis of several cardiovascular diseases such as atherosclerosis, hypertension, arrhythmia and sudden death [4-6]. It was reported a high incidence of sudden death on rats with Mg-deficient [7]. Mechanisms of sudden death related to Mg deficiency were arrhythmias, coronary vasospasm and dysfunction of autonomic nervous system [7].

Mg in serum is about 0.76–1.15 mmol/L and when serum magnesium concentration is low then 0.75 mmol/L is defined hypomagnesaemia [8].

Two types of tetany are known: manifest and latent (spasmophilia). The manifest tetany due to hypocalcemia is rare while latent tetany or spasmophilia (normocalcemic tetany) resulting from cellular magnesium deficiency and hyperventilation, occurs much more frequently [9]. Signs of spasmophilia may include symptoms such as weakness, fatigue, insomnia, depress mood, loss of

appetite, nausea, arrhythmias, muscle fasciculation, tremor and generalized seizures. These disorders can be reverse by oral supplementation of magnesium.

Heart rate variability (HRV) is a non-invasive assessment method of the autonomic nervous system activity which regulates heart rate (HR). Time-domain, frequency-domain and non linear analysis of the HRV can establish the autonomic tone balance. Linear parameters are commonly used in clinical trials. Nonlinear parameters such as the Poincaré plot, Detrended fluctuation analysis (DFA), Approximate Entropy (ApEn) and Sample Entropy (SampEn) are rarely analyzed although, there are proves they are more sensitive than linear parameters to smaller heart rate (HR) modulations [10, 11].

Increased HRV reflects a healthy organism which is able to respond appropriately the environmental changes, whereas decreased HRV is a sign of autonomic dysfunction [12]. Recent research has shown that a decreased HRV is associated with risk factors for cardiovascular diseases and sudden cardiac death. The effects of magnesium in reduction of the systolic and diastolic arterial blood pressure are known, but the studies that try to correlate serum magnesium concentration with HRV are very scarce [13].

In the present study we try to explore the relationship between lower serum magnesium levels and HRV indices, and to observe if magnesium supplementation can corrected autonomic functions.

2. Patients and Methods

2.1. Participant recruitment and inclusion criteria

The study involved 30 (12 males and 18 females) patients with hypomagnesaemia and 20 (10 males and 10 females) age-related healthy subjects. The volunteers were recruited mainly from students of the Faculty of Medical Bioengineering, University of Medicine and Pharmacy “Grigore T. Popa” from Iasi. The ages of both groups ranged between 20-35 years. Subjects with medical history of diabetes mellitus, hypertension, heart diseases, arrhythmias, atrioventricular block or bundle branch blocks, seizures in the past 6 months, smoking were excluded from the study. Inclusion criteria for the controls were: the absence of clinical signs of hypomagnesaemia, normal serum Mg^{2+} and normal electrocardiogram.

Patients were enrolled after being given a detailed explanation of the study and after the informed consent was signed either by the patient or the responsible caregiver. The study was carried out in accordance with the Helsinki Declaration.

2.2. Clinical, psychological and biochemical assessment

Detailed history, clinical evaluation, blood tests were assessed for all patients included in the study. Height, weight and body mass index (BMI, kg/m^2 , calculated as weight divided by height squared) were measured in all subjects. Systolic and diastolic blood pressure (SBP and DBP) were measured in a supine and standing position using an Omron MX blood pressure recorder. The mean arterial blood pressure was determined by the formula: diastolic blood pressure + [(systolic blood pressure – diastolic blood pressure)/3].

2.3. Clinical autonomic function tests and measurement of heart rate variability

For this study short term electrocardiogram recording was acquired during supine for 10 min using the BIOPAC MP 150 data acquisition system. AcqKnowledge Software version 4.1.1. (BIOPAC Inc., Goleta, CA, USA) was used to analyze and remove from the recorded ECG all noise and ectopic beats. Kubios HRV[®] Analysis Software 2.0 for Windows (The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied

Physics, University of Kuopio, Finland) was used to generate the HRV parameters. Data acquisition was performed in a quiet room with temperature between 20 and 22°C. The data were recorded between 9 and 10 am, after an adaptation period of 15 minutes. All individuals were asked to avoid caffeine and alcohol 24 hours before the tests.

Time-domain indices, such as mean heart rate, SDNN (reflects the overall cyclic components of HRV during the recording period), RMSSD (square root of the mean squared differences of successive normal to normal intervals) and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) were calculated [14]. Using Fast Fourier Transform we analyzed frequency domain indices, such as very low frequency (VLF, 0.0033 to 0.04 Hz - influenced by the thermoregulatory and renin-angiotensin system), low-frequency (LF, 0.04-0.15 Hz, ms^2 - represent both sympathetic and parasympathetic activities) and high-frequency (HF, 0.15-0.4 Hz, ms^2 - characteristic to parasympathetic activity) powers, LF in normalized units (LF nu = LF/ (TP-VLF), HF in normalized units (HF nu = HF/ (TP-VLF) and the ratio between LF/HF (considered an index of cardiac sympathetic/ parasympathetic tone balance) [15].

For non-linear Poincare plot, Approximate Entropy (ApEn), Sample Entropy (SampEn) and the Detrended Fluctuation Analysis (DFA) parameters were reported. Plotting the RR values of N on the x axis, and the RR values of N+1 on the y axis we obtained Poincare plot. Index SD_1 obtained from the Poincare plot was used to determine short-term variability of a nonlinear system [16]. SD_1 was correlated with RMSSD and high frequency [17]. We also used short-term α_1 (calculated from 4–16 beats) scaling exponents of DFA to reveal short-term fluctuation. Normal values of α around 1 are found in healthy subjects; lower values indicate a reduced fractal property of heart rate and have been correlated with mortality in elderly subjects [18].

ApEn was used to quantify the overall complexity and predictability of the signal. A large value of ApEn indicated a regular signal and high values indicate a more irregular signal. This parameter was demonstrated to be influenced by record length; therefore Richman and Moorman developed SampEn which is not record length dependent [19].

HRV was done before and after Mg supplementation with magnesium citrate in

combination with Vitamin B6 for 30 days. The amount of magnesium administered per day is still in the discussion, although we preferred to administer ≥ 300 mg Mg^{2+} with adjustment dosages for age, sex and nutritional status [20].

2.4. Statistical analysis

Statistical analyses were performed using SPSS, version 4.0.1 (SPSS, USA). The results were expressed as mean \pm standard deviation for normally distributed continuous variables. To determine the differences between the groups the following variables were used: the Mann-Whitney U-test for skew-distributed continuous variables, Test t — Student or variance analysis (ANOVA) for normally distributed continuous variables. The Pearson correlation coefficient r was used for determining relationship between parameters. The values $p < 0.05$ were considered statistically significant.

3. Results

3.1. Clinical, biochemical features in the groups study

30 students with hypomagnesaemia (Group 1; 18 women, 12 men) with mean age 24.621 ± 3.396 years and 20 healthy subjects (Control; 10 women and 10 men) with mean age 25.050 ± 3.170 years were investigated in our study. The groups did not differ by age ($p < 0.6571$) Table 1. The values of the serum magnesium were decrease in Group 1 when compare with Control group (0.53 ± 0.13 mmol/L vs 1.06 ± 0.14 mmol/L, $p < 0.0001$). All students with hypomagnesaemia received Mg^{2+} supplementation with magnesium citrate in combination with vitamin B6 for 30 days (Group 2). After supplementation the values of Mg^{2+} increase at 0.92 ± 0.14 mmol/L (Table 1).

Table 1. General parameters in study groups

Parameters	Control N=20	Group 1 Hypomagnesaemia N=30	Group 2 Mg supplementation N=30	Group 1 vs. Control	Group 1 vs. Group 2	Group 2 vs. Control
				p value		
Age (years)	25.050 ± 3.170	24.621 ± 3.396	24.724 ± 3.422	0.6571	0.9084	0.7373
Height (cm)	169.850 ± 7.962	168.345 ± 6.821	168.379 ± 6.863	0.4818	0.9848	0.4327
Weight (Kg)	68.895 ± 10.964	62.172 ± 8.665	62.641 ± 7.802	0.0223	0.8293	0.0254
BMI (kg/m^2)	23.970 ± 3.431	21.898 ± 2.384	22.067 ± 2.072	0.0172	0.7739	0.0206
SBP (mmHg)	118.300 ± 15.048	126.700 ± 16.957	117.567 ± 15.624	0.0793	0.0341	0.8697
DBP (mmHg)	72.550 ± 10.107	79.367 ± 15.305	74.900 ± 12.078	0.0864	0.2146	0.4763
HR (b/min)	78.900 ± 12.887	89.033 ± 15.103	81.933 ± 9.826	0.0296	0.0351	0.5102
Magnesaemia (mmol/L)	1.06 ± 0.14	0.53 ± 0.13	0.92 ± 0.14	< 0.0001	< 0.0001	0.2691
Values are expressed as a mean \pm standard deviation p-value < 0.05 was considered to be statistically significant BMI – body mass index, SBP-systolic blood pressure, DBP-diastolic blood pressure, HR-heart rate						

The body mass indices was decrease in Group 1 (21.898 ± 2.384 Kg/m^2) when compare with Control (23.970 ± 3.431 Kg/m^2) with statistical signification ($p < 0.0172$). After magnesium supplementation the body mass indices increase in Group 2 (22.067 ± 2.072 Kg/m^2) but the difference remains when comparing with Control group with $p < 0.0206$.

The values for systolic and diastolic blood pressures did not differ between Group 1 and Control, but after magnesium supplementation we observed a reduction of the systolic blood pressure (126.700 ± 16.957 mmHg vs 117.567 ± 15.624 mmHg) with $p < 0.0341$. It is also noted that increased heart rate in the hypomagnesaemia group is reduced after supplementation of this ion ($p < 0.0351$).

3.2. Clinical autonomic function tests and measurement of heart rate variability

Mean RR was 789.746 ± 67.622 ms in the control group and 719.151 ± 85.777 ms in the Group 1 with $p < 0.0033$. After the magnesium supplementation the RR mean increase at 793.950 ± 92.339 ms with $p < 0.0019$.

SDNN, RMSSD, pNN50%, parameters which correlate with the parasympathetic activity, were decrease in hypomagnesaemia group and after magnesium administration these parameters increase reaching values similar to those in the control group Table 2.

Analysis of frequency domain indices revealed that before magnesium supplementation LF indices did not differ between the groups (Group 1: 1348.700 ± 822.231 ms² vs 1813.55 ± 880.67 ms² control group, $p < 0.0629$), but LF nu were increase in Group 1 (66.317 ± 11.359) vs control (53.035 ± 8.858) with $p < 0.0001$. After Mg²⁺ administration the value of LF increase 2243.033 ± 1775.669 ms² with $p < 0.0151$ and LF nu decrease (55.383 ± 6.464 , $p < 0.0001$) when compare with the value before Mg²⁺ intake.

Table 2. Heart rate variability parameters in resting state in groups study

HRV parameters in resting state	Control N=20	Group 1 Hypomagnesaemia N=30	Group 2 Mg supplementation N=30	Group 1 vs. Control	Group 1 vs. Group 2	Group 2 vs. Control
				p value		
RR	789.746 ± 67.622	719.151 ± 85.777	793.950 ± 92.339	0.0033	0.0019	0.8622
SDNN	72.200 ± 23.647	56.103 ± 20.383	68.513 ± 22.143	0.0143	0.0362	0.5772
HR	73.550 ± 7.207	81.517 ± 13.276	75.833 ± 7.670	0.0184	0.0479	0.1602
RMSSD	77.214 ± 33.541	54.580 ± 32.675	72.840 ± 35.940	0.0216	0.0440	0.6671
pNN50%	15.300 ± 11.449	9.040 ± 7.084	12.409 ± 7.336	0.0207	0.0755	0.2813
VLF	536.333 ± 474.814	275.450 ± 220.629	462.667 ± 377.294	0.0263	0.0513	0.5085
LF	1813.55 ± 880.67	1348.700 ± 822.231	2243.033 ± 1775.669	0.0629	0.0151	0.3222
HF	1595.100 ± 814.888	736.667 ± 682.566	1757.133 ± 1525.387	0.0002	0.0014	0.6659
LF nu	53.035 ± 8.858	66.317 ± 11.359	55.383 ± 6.464	< 0.0001	< 0.0001	0.2837
HFnu	46.474 ± 9.202	33.467 ± 11.414	44.430 ± 6.828	< 0.0001	< 0.0001	0.3717
LF/HF	1.113 ± 0.387	2.403 ± 1.087	1.345 ± 0.278	< 0.0001	< 0.0001	0.0173
SD1	54.605 ± 23.792	38.607 ± 23.196	45.457 ± 20.477	0.0221	0.2302	0.1534
Alfa1	1.111 ± 0.270	0.882 ± 0.168	0.977 ± 0.213	0.0014	0.0527	0.0696
SampEn	0.858 ± 0.208	0.812 ± 0.251	1.007 ± 0.392	0.4760	0.0541	0.0714
ApEn	0.802 ± 0.195	0.879 ± 0.215	0.875 ± 0.292	0.2073	0.9505	0.3361
Values are expressed as a mean \pm standard deviation						
p-value <0.05 was considered to be statistically significant						

The value of HF and HF nu were decrease in Group 1 (736.667 ± 682.566 ms²; 33.467 ± 11.414) in comparison to Control group (1595.100 ± 814.888 ms²; 46.474 ± 9.202) with $p < 0.0002$ and

$p < 0.0001$ indicating that the parasympathetic branch of the autonomic nervous system was affected in hypomagnesaemia group. After Mg²⁺ intake the HF and HF nu increase significantly

($p < 0.0014$, $p < 0.0001$) reaching values similar to those in the control group Table 2.

LF/HF ratio was significantly increased in Group 1 (2.403 ± 1.087) compared with control group (1.113 ± 0.387) with $p < 0.0001$, indicating enhanced sympathetic activity and reduced vagal activity in magnesium deficiency group in resting state. After Mg^{2+} intake the LF/HF ratio decrease at 1.345 ± 0.278 , with $p < 0.0173$ when compare with Control group (Table 2).

Poincare plot index SD1 was greater in healthy controls vs Group 1 ($p < 0.0221$), confirming the enhancement of vagal modulation in supine rest. After the Mg^{2+} supplementation the SD1 mean in group 1 normalized. The increase in alfa 1 of DFA was found in healthy subjects ($p < 0.0014$) when compare with hypomagnesaemia subjects. SampEn, ApEn weren't significantly modified in healthy subjects and Group 1. After Mg^{2+} intake the alfa 1 and SampEn increased with $p < 0.05$.

In Pearson correlation Mg^{2+} correlated positively with RMSSD ($r = 0.48$, $p < 0.0032$), HF ($r = 0.45$, $p < 0.001$), HF nu ($r = 0.45$, $p < 0.0008$), SD1 ($r = 0.47$, $p < 0.0033$) and negatively with heart rate ($r = -0.48$, $p < 0.003$), LF nu ($r = -0.46$, $p < 0.0007$), LF/HF ratio ($r = -0.57$, $p < 0.0001$), systolic blood pressure ($r = -0.26$, $p < 0.0173$). Frequency domain measures of heart rate variability analysis revealed that LF nu and HF nu were correlated with LF/HF ($r = 0.86$, $p < 0.0001$) and ($r = -0.85$, $p < 0.0001$) respectively.

Discussions

Lower magnesium concentration was associated with increased risk of cardiovascular mortality [21, 22], while magnesium supplementation was found to reduce the risk of cardiovascular events [23, 24]. Magnesium concentration is correlated directly with parasympathetic indices of HRV and may enhance the parasympathetic activity [21-23].

Mg deficiency produces accumulation of intracellular Ca^{2+} and may lead to enhanced automaticity, which can increase arrhythmogenic activity and can contribute to cardiac cell hypertrophy, necrosis, or apoptosis [25].

Low Mg^{2+} levels have been shown to adjust the expression of interleukin-6, TNF- α , and C-reactive protein (CRP), thereby producing inflammation and endothelial dysfunction [26, 27].

Normally, the sympathetic and parasympathetic nervous system activities are in dynamic balance thus indicating a healthy physiological system. The

autonomic imbalance described by increased sympathetic activity and suppressed parasympathetic activity is associated with an increased risk of diseases such as cardiovascular, neuroendocrine, digestive and psychiatric disorders.

Spectral analysis of HRV provides a sensitive non-invasive measure of cardiac autonomic regulation. High frequency (HF) power reflects vagal activity and low frequency (LF) power is thought to measure a combination of vagal and sympathetic nervous system activity. As such, the LF component is less easily interpretable, although the LF/HF ratio is accepted as an indicator of sympathovagal balance [15].

In the present study, the HRV analysis revealed that control group had significantly lower values for HR ($p < 0.0184$), LF nu ($p < 0.0253$) and LF/HF ratio ($p < 0.0002$) when compare with patients with Mg^{2+} deficiency. Also in the same patients we found higher values of HF nu ($p < 0.0273$) and SD1 ($p < 0.0471$) resulting that in supine position there is an enhanced heart rate vagal modulation in control group. A significant increase in LF nu, LF/HF ratio and significant decrease in HF nu and SD1 were found in Mg deficiency suggesting that the sympathovagal balance were affected with a sympathetic overactivity in these patients. Increase in non-linear indexes was associated with vagal modulation and its decrease is usually interpreted by the result of an increased sympathetic drive and vagal withdrawal [28].

After Mg supplementation the HR ($p < 0.0479$), LF/HF ratio ($p < 0.0014$) decrease and SDNN ($p < 0.0453$), RMMSD ($p < 0.0447$), pNN50% ($p < 0.0005$), HF ($p < 0.0065$), SD1 ($p < 0.0401$) were found increase in these patients. Findings from the current study suggest that Mg supplementation may enhance parasympathetic activity and therefore presenting a positive impact on cardiac autonomic function. In Pearson correlation we found a negative correlation between serum Mg^{2+} levels and LF/HF.

Our study is in agreement with other studies demonstrating that Mg administration improves cardiac function [28, 29]. More over it has been proved that magnesium supplementation was inversely associated with mortality from ischemic strokes, coronary heart disease, and heart failure in women [30].

The main limitation of our study was the relatively small sample size, which makes it difficult

to draw more specific conclusions. Also the very short time of treatment (1 month) is another factor which contributes to the analysis of recorded data. Therefore, further studies are needed to track the influence of Mg supplementation on HRV parameters over a longer period of time and to establish the role of magnesium in the prevention and treatment of cardiovascular diseases.

5. Conclusions

In conclusion, both linear and non-linear parameters of HRV measured in our study demonstrated an increased vagal influence on heart rate and an attenuated sympathetic tone in patients with normal values of serum Mg. The Mg deficiency group was characterized by a high sympathetic tone, expressed by high heart rate, LF/HF ratio and altered nonlinear dynamic parameters. After one month of Mg supplementation the autonomic balance has been restored. Mg²⁺ by stimulating parasympathetic activity with effect over cardiac function has important role in cardiac protection.

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Conflict of Interest Statement:

The authors declare that have no conflict of interests.

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