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Corresponding author:
Mahua Mannan, Department of Physiology, ShahidTajuddin Ahmed Medical College, Gazipur, Bangladesh. E-mail: mahuamanna@gmail.com

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Association of Cardiac Autonomic Nerve Function with Serum Zinc, Calcium Magnesium in Female Hypothyroid Patients

Mahua Mannan[1],Shamima Sultana[2], Bipasha Sarkar[3], Nandita Sarkar[1]

1. Department of Physiology, Shahid Tajuddin Ahmed Medical College, Gazipur, Bangladesh.
2. Department of Physiology, Bangabandhu Sheikh Mujib Medical University, Dhaka
3. Department of Physiology, Satkhira Medical College, Satkhira, Bangladesh

Abstract

Background: Hypothyroidism is related to impaired cardiac autonomic nerve activity with altered levels of serum Zinc (Zn), Calcium (Ca) Magnesium (Mg).Altered Serum Zn,Caand Mg levels are also associated with autonomic imbalance and may raise cardiovascular risk.Heart rate variability (HRV) is an important marker for assessing cardiac autonomic nerve function(CANF). **Objectives:** To evaluate the association of serum Zn, Cal and Mg levels with CANF in female hypothyroid patients. **Methods:** This analytical cross-sectional study was conducted on 40 female hypothyroid patients aged 18-45 years. Thirty apparently healthy women were control. Serum Zn, Ca and Mg levels were estimated by autoanalyzer and CANF was assessed by time domain analysis of HRV recorded by Power Lab 8/35 AD Instruments, Australia. Statistical analysis was done by Independent sample‘t’ test, One way ANOVA followed by post-hoc Bonferroni test and Pearson’s correlation coefficient test. **Results:** Among time domain parameters of HRV, standard deviation of the RR intervals (SDRR), coefficient variation of RR interval (CVRR), SD rate, standard deviation of the difference between successive RR intervals (SDSD), square root of mean squared differences of successive RR intervals (RMSSD), proportion of RR interval with duration >50 ms (pRR50%) were

significantly lower ($p<0.05$) in all hypothyroid patients as compared to control. On correlation analysis, serum Zn, Ca and Mg were significantly positively correlated with SDSD($p<0.01$, $p<0.001$,$p<0.01$) RMSSD($p<0.01$, $p<0.001$, $p<0.01$), pRR50%($p<0.01$, $p<0.01$, $p<0.05$)and serum Ca was also positively correlated with SDRR($p<0.05$) in hypothyroid patients. **Conclusion:**Serum ZnCa and Mg were associated with cardiac autonomic dysfunction. in female hypothyroid patients.

Keywords: Hypothyroid patients, Heart rate variability, Serum Zinc, Calcium, Magnesium.

Introduction

Hypothyroidism is one of the leading endocrine disorders that occur due to insufficient production of thyroid hormone or inadequate action of this hormone on target cells to meet the metabolic demands of the body.[1] This common endocrine disease has a worldwide distribution and raising global health concerns. The prevalence of hypothyroidism in the general population of Europe (0.2% -5.3%), the USA (0.3%- 3.7%)[2], India (10.95%)[3], Pakistan (4.1%)[4] and 7.0% (M/F=4.1/8.3%) in Bangladesh with female predominance[5].

Over the last decade, there is a dramatic increase in coronary vascular disease(CVD). Multiple risk factors contribute to the pathogenesis of CVD in hypothyroid patients and it becomes the major cause of death.[6]Myocardium and vascular endothelial tissue have thyroid hormone receptors and minor changes in circulating thyroid hormone concentration can adversely affect not only the cardiovascular system but also its autonomic regulation.[7-8] Recent investigation found hypothyroid patients developed autonomic dysfunction with sympathetic over activity and reduced parasympathetic activity.[9-12]The autonomic nervous system which consists of the sympathetic and parasympathetic nervous systems controls HRV. Slight changes in cardiac autonomic regulation can significantly change HRV. In comparison with the other cardiovascular reflex tests the analysis of HRV is a more sensitive method, which can discover subclinical forms of autonomic dysfunction.[13]According to Task force certain time domain parameters CVRR, SDSD, RMSSD, and pRR50% are the markers of cardiac vagal tone, while overall variability is represented by SDRR[13]

Recent investigation on mineral metabolism in hypothyroids demonstrated zinc and calcium deficiency and excess magnesium in the blood of hypothyroid patients due to altered metabolism of these minerals as a result of in adequate thyroid hormone in hypothyroid patients[14-15]

Though, serum Zn, Ca and Mg levels in hypothyroid patients were reported. In addition, many cross-sectional studies observed the cardiac autonomic dysfunction in hypothyroid patients. But there is very little evidence for the association of serum Zn Ca and Mg with cardiac autonomic dysfunction in hypothyroid patients. So the objective of the present study is to observe the association of Zn, Ca and Mg with CANF in female hypothyroid patients.

Methods

Study design and setting

This cross-sectional study with comparative analysis was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU),Dhaka from March 2021 to February 2022.

Study participants

Forty(40) female newly diagnosed hypothyroid patients with18-45 years of age in this study and 30 age BMI-matched apparently healthy females were control . Hypothyroid patients were further subdivided into groups with either normal or low level of serum Zn, Cal and high serum Mg levels.

Exclusion criteria

In this study pregnant women, subjects with a history of medication or illness affecting autonomic functions, subjects with a history of or currently suffering from cardiovascular disorders, endocrine disease other than hypothyroidism, respiratory disorders,arthritis, acute or chronic liver disease, kidney disease, psychiatric disorders, parathyroid disorder, neurological disorders, malignancy, current use of zinc, calcium, magnesium supplementation were excluded.

Sampling

A purposive sampling procedure was used to select both the patients and the controls. Hypothyroid patients were selected among the patients visited outpatient department of Endocrinology BSMMU, Shahbag, Dhaka. Age and BMI-match apparently healthy female volunteers were selected from different areas of Bangladesh through personal contacts.

Data collection Procedure

After enrollment, The aim, benefit of the study and procedure for participation was explained to them and a informed written consent was taken from all participants. A detailed medical history, anthropometric measurements were taken and a thorough clinical examinations were done. . On the next day, venous blood was collected for the estimation of fasting blood glucose, serum creatinine and ALT. Preparation for the HRV test was explained to all study participants.On the following day after getting the biochemical test reports the final selection was done. When the participant was found non-diabetic with normal renal and liver function, a measurement of HRV was done for assessing CANF. For HRV recording, the subject took their meal by 9:00 pm and had a sound sleep the previous night. They were advised to avoid taking any sedatives or any other drugs that could affect the central nervous system.[13]From the previous night up to the test period, they were requested not to undergo any physical or mental stress. The participants were requested to take light breakfast but no tea or coffee in the morning and then report to the Noorzahan neurophysiology research lab in the Department of Physiology, BSMMU between 8-9 am on the next day for HRV recording. The temperature of the laboratory was maintained at 25ÚC-28ÚC. The room light was kept dim and noise free laboratory environment was ensured with sound proof wall The short-term (5 minutes) recording of HRV measures was done by 8 active channels, Power Lab 8/35 (AD instrument, Australia), in relaxed supine position. Time domain measures of HRV were a analyzed by in-built automation based Lab Chart software. After that 03ml of venous blood was collected by trained laboratory staff with proper aseptic precautions and immediately sent to the laboratory of the Department of Biochemistry and Molecular Biology, BSMMU for the measurement of serum Zn, Ca and Mg levels.

Statistical analysis

Data were checked by Shapiro wilk test for its normal distribution and expressed as Mean±SD. For statistical analysis One-way ANOVA followed by Bonferroni post-hoc test, Independent sample 't-test and Pearson's correlation coefficient test were done, by using SPSS version 22.Value of probability $p<0.05$was considered statistically significant.

Results

The general characteristics of the subjects were presented in Table I. In this study, mean diastolic blood pressure (DBP) of hypothyroids was found significantly higher compared to the control but nosignificant difference in, resting pulse rate and SBP was noted compared to control.Here, all time domain measures were significantly lower in all patients with either normal or low level of serum Zn and Ca or high Mg level except HR and RR which did not change significantly compared to control. In addition, there were no significant differences in all these time domain measures between patients with normal or abnormal level of these minerals (Table

II, III, IV). Correlation analysis of time domain measures with serum minerals showed significant positive correlation of SDSD, RMSSD, and pRR50% with serum Zn (Table V), Ca(Table VI) and Mg (Table VII) level and SDRR was positively correlated with only serum Ca level (Table VI).

Table I : Age,BMI, resting pulse rate and BP in two groups (N=70)

Variables	Hypothyroids (n=40)	Control (n=30)
Age(Years)	33.68±6.95	32.07±5.07
	(19-45)	(21-48)
BMI(Kg/m^2)	25.78±4.07	24.08±3.47
	(18.26-34.85)	(18.49-33.25)
Pulse rate(beats/min)	76.53±7.96	73.10±8.41
	(60-90)	(58-98)
SBP(mm Hg)	114.25±8.26	110.50±9.94
	(100-130)	(90-135)
DBP(mmHg)	77.13±6.01**	71.50±7.21
	(60-85)	(60-85)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; BMI- Body Mass Index;SBP- systolic blood pressure; DBP- diastolic blood pressure; N- Total number of subjects; n- Number of subjects in each group.*This depicts control vs hypothyroid group, **p<0.01

Table II : Time domain parameters in different groups (N=70)

Variables	Hypothyroid (n=40)		Control(n=30)
	Normal Zn (n=15)	Low Zn (n=25)	
Mean heart rate(beats/min)	75.21±6.44	78.30±8.58	73.43±8.55
	(60.19-85.89)	(62.33-91.86)	(58.25-99.37)
Mean R-RInterval(ms)	804.79±73.29	776.74±90.25	831.69±92.02
	(700-997.20)	(653.60-963.10)	(608.2-1032)
SDRR(ms)	25.05±5.16***	21.51±4.24***	59.30±19.05
	(18.15-34.55)	(12.68-30.94)	(35.85-111.7)
CVRR	0.032±0.008***	0.028±0.006***	0.073±0.026
	(0.020-0.045)	(0.019-0.043)	(0.039-0.154)
SD rate(beats/min))	2.39±0.77***	2.20±0.55***	5.10±1.85
	(1.22-3.86)	(1.39-3.51)	(2.36-10.33)
SDSD(ms)	18.81±5.66***	15.02±4.35***	66.25±28.06
	(10.61-30.50)	(7.50-23.81)	(37.61-148.8)
RMSSD(ms)	18.78±5.65***	15.00±4.34***	66.16±28.02
	(10.61-30.46)	(7.50-23.77)	(37.56-148.6)
pRR50(%)	1.52±2.18***	0.70±1.00***	37.07±17.02
	(0.00-6.15)	(0.00-3.71)	(2.26-70.77)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by one-way ANOVA followed by post-hoc Bonferroni test. 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; level, N- Total number of subjects; n- Number of subjects in each group.*This depicts control vs hypothyroid group, ***p<0.001.

Table III : Time domain parameters in different groups (N=70)

Variables	Hypothyroid(n=40)		Control(n=30)
	Normal Ca (n=21)	Low Ca(n=19)	
Mean heart rate(beats/min)	77.34±6.20	76.93±9.58	73.43±8.55
	(62.86-89.72)	(60.19-91.86)	(58.25-99.37)
Mean R-R Interval(ms)	781.89±65.62	793.19±102.56	831.69±92.02
	(669.4-955.00)	(653.60-997.20)	(608.2-1032)
SDRR(ms)	24.90±4.56***	20.55±4.23***	59.30±19.05
	(18.15-34.55)	(12.68-30.94)	(35.85-111.7)
CVRR	0.032±0.007***	0.026±0.006***	0.073±0.026
	(0.023-0.045)	(0.019-0.043)	(0.039-0.154)
SD rate(beats/min)	2.49±0.65***	2.03±0.55***	5.10±1.85
	(1.438-3.86)	(1.22-3.51)	(2.357-10.33)
SDSD(ms)	18.29±5.07***	4.41±4.58***	66.25±28.06
	(10.61-30.50)	1(7.50-23.81)	(37.61-148.8)
RMSSD(ms)	18.26±5.06***	14.39±4.57***	66.16±28.02
	(10.61-30.46)	(7.50-23.77)	(37.56-148.6)
pRR50(%)	1.53±1.95***	0.43±0.75***	37.07±17.02
	(0.00-6.15)	(0.00-2.65)	(2.26-70.77)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by one-way ANOVA followed by Bonferroni test post-hoc. 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.*This depicts control vs hypothyroid group, ***p<0.001

Table IV : Time domain parameters in different groups (N=70)

Variables	Hypothyroid(n=40)		Control (n=30)
	Normal Mg (n=19)	High Mg (n=21)	
Mean heart rate(beats/min)	78.67±7.60	75.76±8.08	73.43±8.55
	(65.25-91.86)	(60.19-89.72)	(58.25-99.37)
Mean R-RInterval(ms)	770.66±76.17	802.28±90.33	831.69±92.02
	(653.60-919.90)	(669.40-997.20)	(608.2-1032)
SDRR(ms)	21.64±4.93***	23.92±4.64***	59.30±19.05
	(12.68-31.63)	(16.37-34.55)	(35.85-111.7)
CVRR	0.028±0.01***	0.030±0.01***	0.073±0.03
	(0.02-0.05)	(0.02-0.04)	(0.039-0.154)
SD rate(beats/min))	2.22±0.60***	2.32±0.69***	5.10±1.85
	(1.39-3.86)	(1.22-3.77)	(2.357-10.33)
SDSD(ms)	14.33±4.27***	18.35±5.26***	66.25±28.06
	(7.50-23.81)	(8.36-30.50)	(37.61-148.8)
RMSSD(ms)	14.31±4.26***	18.33±5.25***	66.16±28.02
	(7.50-23.77)	(8.35-30.46)	(37.56-148.6)
pRR50(%)	0.66±1.11***	1.32±1.88***	37.07±17.02
	(0.00-3.71)	(0.00-6.15)	(2.26-70.77)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by One-way ANOVA followed by post-hoc Bonferroni test. 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.*This depicts control vs hypothyroid group, ***p<0.001.

Table V : Correlations of time domain HRV measures with serum Zinc,Calcium and Magnesium levels in hypothyroid patients. (n=40)

Variables	Zn		Ca		Mg	
	r value	p value	r value	p value	r value	p value
Mean heart rate(beats/min)	-0.299	0.061	-0.206	0.202	-0.256	0.111
Mean R-RInterval(ms)	0.273	0.088	0.154	0.342	0.258	0.109
SDRR(ms)	0.191	0.239	0.386	0.014	0.193	0.233
CVRR	0.066	0.687	0.288	0.072	0.083	0.611
SDrate(beats/min))	-0.071	0.665	0.160	0.324	-0.018	0.911
SDSD(ms)	0.501	0.001	0.526	0.000	0.193	0.233
RMSSD(ms)	0.501	0.001	0.526	0.000	0.476	0.002
pRR50(%)	0.424	0.006	0.421	0.007	0.333	0.036

Statistical analysis was done by Pearson's correlation coefficient (r) test; Group A- Study group; n- Number of subjects, 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

Discussion

In this study, the higher DBP found in female hypothyroid patients supports previous reports which was related to diastolic hypertension with possible sympathetic hyperactivity.[16-17] We also found a lower value of SDRR, CVRR, RMSSD and pRR50% in our female hypothyroid patients irrespective of mineral levels suggesting parasympathetic hypoactivity in these hypothyroid patients. Earlier investigators also reported similar results of parasympathetic deficit with upper hand of sympathetic tone[1]in thyroid hormone deficient.[18,21] The results of several mineral status of hypothyroid patients showed both serum Zn and Cal were either deficient or normal and Mg was either normal or elevated presenting a mixed pattern of mineral profile. It is also noteworthy that influence of these minerals on autonomic dysfunction in hypothyroid was not apparent. Further correlation analysis explored the significant positive correlation of SDSD, RMSSD, pRR50%with serum Zn, Ca and Mg and SDRR with only Ca level were found in hypothyroid patients. These findings suggested association of lower parasympathetic activity with serum Zn, Cal and Mg in hypothyroid patients which was also supported by other researchers.[22,-24]So, it is obvious that hypothyroid patients are affected with autonomic dysfunction characterized by parasympathetic hypo-activity which was associated with trends of lower serum Zn and Ca but high Mg level in this particular group of patients. Literature review considered autonomic disturbances in hypothyroidism might be related to a high level of plasma adrenaline with a post-receptor sensitization,[25] decreased chronotropic response to beta-adrenergic stimulation or adrenergic sensitivity[10] and increased thyrotropin-releasing hormone (TRH). TRH directly influences the sympathetic outflow and norepinephrine release from the sympathetic nerve ending is increased. [9] On the other side, thyroid hormones regulate the mineral pool in the body by affecting mineral mobilization into the blood and also by influencing renal hemodynamics, GFR and renal clearance.[15] Thyroid hormones alter Zn, Ca and Mg reabsorption directly by influencing the glomerular filtration rate and renal blood flow.[26]There is no clear evidence for the

relationship between serum Ca, Mg, and Zn and cardiac autonomic dysfunction, in spite of that numerous hypothesized explanations have been suggested.[24,27-30-]Alteration of serum Zn, Ca and Mg level may be considered as potent risk factor for CVD events in hypothyroid patients.

Conclusions

The results of this study concluded that cardiac autonomic nerve dysfunction characterized by parasympathetic hypo-activity was associated with hypothyroidism. Furthermore, lower trend of Zn,Ca and higher trend of Mg were associated with autonomic dysfunction with parasympathetic hypo-activity in female hypothyroid patients.

Ethical aspects

The ethical aspects of the study following the Helsinki declaration involving human and technical aspects of the study were approved by the Institutional Review Board of BSMMU (No.BSMMU/2021/7042 date 09/08/21)

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Conflict of interest

Authors declare no conflict of interest.

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