Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

The effect of lifestyle change on autonomic nervous system dysfunction in patients witmetabolic syndrome

Ali Birant[a,*], Guliz Kozdag[b], Dilek Ural[b], Aysen Agacdiken Agir[b]

[a] *University of Health Sciences, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Deapertment of Cardiology, Istanbul, Türkiye*
[b] *Kocaeli University, Faculty of Medicine, Department of Cardiology, Kocaeli, Türkiye*

ARTICLE INFO

Keywords:
Metabolic syndrome
Heart rate variability
Autonomic neuropathy

Received: Jul 04, 2022
Accepted: Apr 07, 2023
Available Online: 28.04.2023

DOI:
10.5455/annalsmedres.2022.04.150

Abstract

Aim: In this study, it was aimed to examine the effects of metabolic syndrome, which affects many organs, on the autonomic nervous system and to observe the changes after treatment.

Materials and Methods: Heart rate variability values of 101 metabolic syndrome patients who were treated at the Kocaeli University Cardiology Outpatient Clinic included in the study. All patients were offered lifestyle change suggestions in addition to their medical treatments. At the end of three months, the heart rate variability parameters of the patients were re-evaluated.

Results: Heart rate variability values were found to be significantly lower in metabolic syndrome patients compared to the control group. It was observed that the heart rate variability values improved significantly in half of the patients who applied the given treatment with lifestyle changes. A decrease in heart rate change parameters was found in the group that did not implement lifestyle changes compared to the beginning of the study.

Conclusion: Autonomic nervous system functions evaluated by heart rate variability decreased in patients with metabolic syndrome, and the treatment and lifestyle changes had a positive effect on these parameters.

Introduction

Metabolic syndrome (MetS) is an important public health problem today, consisting of the sum of cardiovascular risk markers rather than a disease. It is an important situation that affects the whole world, especially due to the increase in sedentary lifestyle and unhealthy, calorie-rich diet [1]. Metabolic syndrome consists of interrelated markers that increase the risk of cardiovascular disease, stroke, heart failure and DM.

Several systematic reviews proposed that autonomic nervous system disorder may play a role in the development of MetS [2,3]. Many studies have shown increased morbidity, and cardiovascular and all-cause mortality associated with cardiac autonomic neuropathy (CAN). The CAN is linked to myocardial ischemia, cardiovascular events, and cardiac mortality [4,5]. Besides, CAN is also associated with more severe heart failure symptoms in patients with diabetes [6,7]. Heart rate variability (HRV) is one of the reliable and noninvasive parameters for evaluating autonomic control of the cardiovascular system in patients. These tests are used to evaluate the prognosis and treatment of many different diseases. We aimed to evaluate autonomic nervous system functions with HRV parameters in patients with MetS and re-evaluate autonomic nervous system functions in the third month after medical treatment and lifestyle change recommendations.

Materials and Methods

Study design

We conducted a clinical cohort study. This study has been prepared in accordance with the Declaration of Helsinki.

Necessary approval documents were obtained from the local ethics committee to which the study was affiliated. Ethical approval was obtained from Kocaeli University Clinical Research Ethics Committee. (Date: 10.04.2006, IRB number: AEK 89/5).

*Corresponding author:
Email address: ali_birant@yahoo.com (Ali Birant)

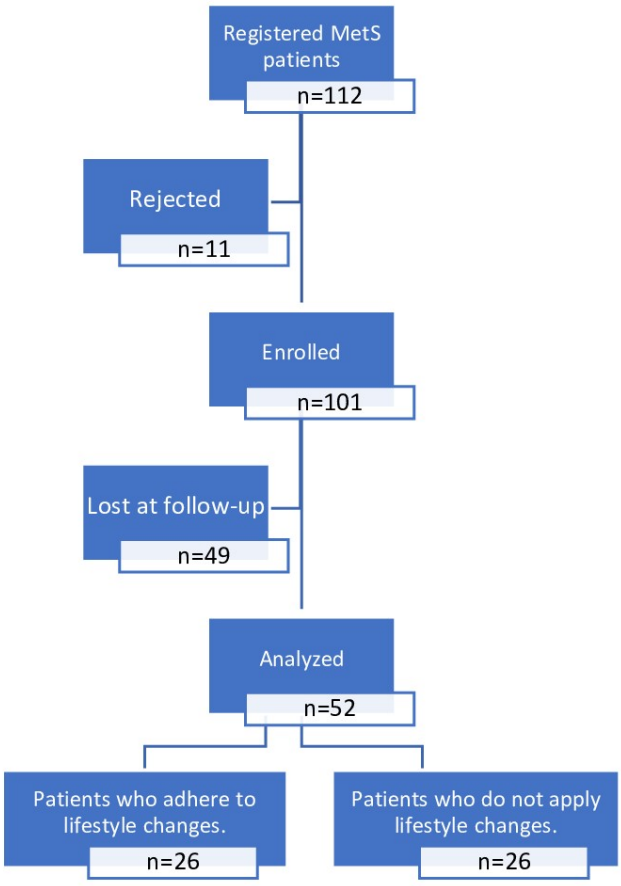

Figure 1. Participant flow diagram.

Settings

The study was conducted at the cardiology outpatient clinic in Kocaeli University hospital, located in a city with around 1 million inhabitants.

Participants

The participants of the study were our clinical cohort with established MetS diagnosis. A total of 112 MetS patients were under follow-up at the research hospital (Figure 1). Eleven patients refused to participate in the study. One hundred and one metabolic syndrome patients gave informed consent to participate in the study. Those with known coronary artery disease, those with another systemic disease requiring treatment, those who took insulin, patients with atrial fibrillation, and patients who received lipid-lowering treatment in the last six weeks were excluded. All patients underwent a detailed echocardiographic examination. All metabolic syndrome patients were advised to make lifestyle changes. These changes were consisted of a healthy diet, regular exercise and reaching a healthy weight.

Variables

The primary endpoint of the study was HRV. The following HRV parameters were measured: the standard deviation of the average of RR intervals (SDNN), the standard deviation of the average RR interval in all 5-min recordings (SDANN), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD), the mean of the standard deviations of the RR intervals for all 5-min recordings (SDNN index) and the total number of RR intervals divided by the height of the histogram of all RR intervals on a discrete scale (triangular index).

Data sources/measurement

All patients' body mass index (BMI) was calculated and the appropriate diet was organized taking into account waist circumference (WC). All patients were offered an exercise program. After three months, 52 patients who had been treated were called for a check-up and physical and laboratory examinations were performed again. Patients were again given 24-hour ECG Holter examinations. At the end of the study, patients were informed about their medical condition and their treatment was continued within the current guidelines. The presence of hypertension indicates a prolonged increase in arterial blood pressure above certain values. These values were defined as systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg while the patient was lying supine [8]. The definition of CHF was made by current guidelines and diabetes mellitus (DM) was defined as a fasting serum glucose level $\geq$ 126 mg/dL, glycated hemoglobin level $\geq$ 6.5%, or a history of hypoglycemic medication(s) [9,10]. Coronary artery disease (CAD) was defined as significant stenosis [>50%] in at least one epicardial artery [11]. Body mass index (BMI) was obtained from body weight in kilograms divided by the height in meters squared (kg/m^2). According to the guidelines the presence of chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2 [12]. The 5 risk factors for metabolic syndrome are:: (1) fasting glucose $\geq$100 mg/dL (or receiving drug therapy for hyperglycemia); (2) blood pressure $\geq$130/85 mm Hg (or receiving drug therapy for hypertension); (3) triglycerides $\geq$150 mg/dL (or receiving drug therapy for hypertriglyceridemia); (4) HDL-C $<$ 40 mg/dL in men or $<$ 50 mg/dL in women (or receiving drug therapy for reduced HDL-C); (5) WC $\geq$ 102 cm in men or $\geq$ 88 cm in women; if Asian, $\geq$ 90 cm in men or $\geq$ 80 cm in women [13]. Patients with three of the five factors are defined as having metabolic syndrome. Diabetes patients included in the study were treated to control their blood sugar levels. Treatment of hyperlipidemia and hypertension of each patient has been organized under current guidelines.

Measurement of heart rate variability

All subjects underwent resting ECG and 24-hour ambulatory continuous electrocardiographic monitoring. Patients who were found to have atrial fibrillation, atrial tachycardia or other serious rhythm problems in the inserted holters or who could not have adequate records were excluded from the study. All recordings were also examined visually and artifacts were deleted manually. HRV was analyzed using the HRV analysis module in the Cardio Navigator Holter system (Del Mar Reynolds Medical Ltd, UK). The measured HRV domains were SDNN, SDANN, RMSSD, SDNN index and triangular index. All registered patients and control groups were warned not to take drugs, caffeine, cola and similar beverages that could affect their

heartbeat and speed, and not to engage in heavy sports activities. They were advised to do their normal daily activities. The spectral analysis of HRV parameters was not performed because of non-stationary conditions during the 24-h period.

Study size

All patients under follow-up were invited to participate without sampling.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Results are presented as mean ± SD, median-interquartil range (IQR) or as percentages and numbers for categorical data. The Shapiro-Wilk normality test was used for all variables. A Chi-square test was employed to compare categorical variables between the groups. The Student's t-test was used if the independent variables were normally distributed, and the Mann-Whitney U test was used if they were not normally distributed. The effect of treatment and lifestyle changes on dependent variables was evaluated by paired samples t-test if the variables were normally distributed, and Wilcoxon Signed Rank if they were not normally distributed. P values below 0.05 were considered statistically significant.

Results

The baseline descriptive characteristics of the participants are shown in Table 1. There were no differences between the patient group and healthy control groups in terms of age, gender, and height. The weight and BMI indices were found to be higher in the patient group than in the control group. As expected, blood pressure values were higher in the Met S group, while glucose values and lipid measurements were found to be significantly impaired compared to the control group.

In unadjusted analyses, significantly lower heart rate variabilities were observed in with MetS. SDNN, SDANN, and triangular index differences were statistically significant (Table 2).

HRV findings in the third month of the study

When all patients are examined, some improvements in HRV findings are detected at the third month, but these are not significant (Table 3).

Although every patient was advised to exercise and diet, only half of the patients followed these recommendations. In patients who did not perform lifestyle changes, a decrease in all HRV parameters was detected, while this decrease in SDNN and SDANN parameters was significant (Table 4 and 5). Although it was not statistically significant, female patients followed lifestyle change recommendations more. At the beginning of the study, there was no difference between the HRV parameters of patients who made lifestyle changes and those who did not. In the third month measurements, HRV parameters were found to be better in the group that implemented lifestyle changes than in the group that did not, while the difference in SDNN and SDANN parameters was statistically significant (Table 6).

Table 1. Demographic, clinical, and laboratory data for metabolic syndrome patients and controls.

Characteristic	Metabolic Syndrome	Controls	Test	p
	(n = 101)	(n=36)	Value	
Age – Mean	52 ± 8	51 ± 8	-0.941	0.348*
Male,n	36 (% 35.6)	18 (%50)	2.291	0.130 µ
Female,n	65 (% 64.4)	18 (%50)		
Height (cm)	161 ± 8	165 ± 8	2.007	**0.047***
Weight (kg)	87 ± 16	69 ± 10	-6.177	**< 0.001***
BMI – mean (kg/m^2)	33,44 ± 6,72	25,51 ± 3,24	-6.786	**< 0.001***
WC (cm)	105 ± 12	86 ± 9	-9.973	**< 0.001***
Smoking (yes), n (%)	26 (% 25)	6 (%17)	1.221	0.269 µ
Family history, CVD n (%)	45 (%45)	7 (%19)	7.106	**0.008 µ**
Fasting glucose (mg/dl)	116 ± 27	95 ± 7	-4.453	**< 0.001***
HgbA1C (%)	6.0 ± 0.8	5.3 ± 0.5	-4.257	**< 0.001***
TG (mg/dl)	209 ± 96	95 ± 35	-7.498	**< 0.001***
HDL-Cholesterol (mg/dl)	44 ± 9	50 ± 13	3.010	**0.005***
Systolic BP (mmHg)	152 ± 28	110 ± 13	-8.612	**< 0.001***
Diastolic BP (mmHg)	92 ± 13	73 ± 11	-7.974	**< 0.001***
İnsülin (U/mL)	16.4 ± 17.8	8.17 ± 5.37	-2.693	**< 0.001***
HOMA	4.74 ± 4.54	1.91 ± 1.25	-3.632	**< 0.001***

Values are expressed as mean ± SD or percentage. BMI, body mass index; WC, waist circumference; CVD, cardiovascular disease; TG, triglyceride. *:Independent samples t-test, µ: Chi-square.

Table 2. HRV findings at the beginning of the study in the MS and control groups.

	Metabolic S.	Control	Test value	p
Average RR range (msn)	801 ± 111	820 ± 82	0.944	0.347*
SDNN (msn)	128 ± 31	143 ± 28	2.546	**0.012***
SDNNi(msn)	49 ± 17	53 ± 10	1.565	0.121*
SDANN (msn)	115 ± 30	131 ± 30	2.769	**0.006***
RMSSD (msn) Median (IQR)	23 (16-31)	26 (21.25-31.75)	1388	0.097**
Triangular index	35 ± 10	38 ± 6	2.029	0.045*

Parametric values are stated as mean ± standard deviation, non parametric values are stated as median, interquartil range (IQR). *:Independent sample t-test, **: Mann Whitney-U test.

Discussion

In this study, it was shown that autonomic nervous system functions assessed with HRV, decreased in patients with MetS and that lifestyle changes had a positive effect on HRV parameters.

Basal measurements showed a decrease in all HRV parameters in MS patients compared to the control group, the difference between SDNN, SDANN, and the triangular in-

Table 3. Basal and third month HRV findings of metabolic syndrome patients.

	Baseline	3-Months	Test value	p
Average RR range (msn)	806 ± 113	809 ± 99	-0.246	0.807*
SDNN (msn)	126 ± 30	128 ± 33	-0.718	0.476*
SDNNi(msn)	48 ± 17	48 ± 16	-0.059	0.953*
SDANN (msn)	112 ± 28	115 ± 31	-1.294	0.201*
RMSSD (msn) Median (IQR)	23 (16-31.5)	22 (17-31.75)	-0.873	0.383**
Triangular index	33 ± 10	34 ± 10	-1.851	0.070*

Parametric values are stated as mean ± standard deviation, non parametric values are stated as median, interquartil range (IQR). *: Paired-samples T test, **: Wilcoxon's Signed Rank test.

Table 4. Basal and third month HRV findings of patients who did not make lifestyle changes.

	Baseline	3-Months	Test value	p
Average RR range (msn)	804 ± 92	811 ± 78	-0.642	0.527*
SDNN (msn)	127 ± 20	116 ± 20	2.515	**0.019***
SDNNi(msn) Median (IQR)	49 (36-57)	46 (36.5-51)	1.432	0.152**
SDANN (msn)	113 ± 19	105 ± 21	2.136	**0.043***
RMSSD (msn) Median (IQR)	23.5 (16.8-30.5)	20.5 (17-26.5)	1.206	0.228**
Triangular index	32 ± 7	32 ± 7	0.108	0.915*

Parametric values are stated as mean ± standard deviation, non parametric values are stated as median, interquartil range (IQR).*:Paired-samples t-test **: Wilcoxon's Signed Rank test.

Table 5. Basal and third month HRV findings of patients who make lifestyle changes.

	Baseline	3-Months	Test value	p
Average RR range (msn) Median (IQR)	774 (722.5-857.8)	806 (729.5-871)	-0.165	0.869**
SDNN (msn)	124 ± 38	140 ± 38	-6.260	**< 0.001***
SDNNi(msn)	48 ± 19	51 ± 18	-2.982	**0.007***
SDANN (msn)	111 ± 35	125 ± 37	-4.643	**< 0.001***
RMSSD (msn) Median (IQR)	22.5 (15-41.3)	22.5 (17-46.3)	-2,335	**0.020****
Triangular index	33 ± 13	37 ± 12	-2.939	**0.004***

Parametric values are stated as mean ± standard deviation, non-parametric values are stated as median, interquartil range (IQR). *: Paired-samples t-test, **: Wilcoxon's Signed Rank test.

dex was statistically significant. Autonomic neuropathy, especially cardiac neuropathy, is an important indicator of cardiovascular death and myocardial infarction [14-16]. Many previous studies have shown that HRV parameters

Table 6. Demographic and HRV data according to lifestyle change adaptation.

Characteristic	Adherent (n= 26)	Non-adherent (n= 26)	Test value	p
Age	53.08 ± 7.6	52.26 ± 7.5	0.395	0.695*
Sex Male Female	9 (%40.9) 17 (%54.8)	13 (%59.1) 14 (%45.2)	0.999	0.318 µ
Average RR (msn) (Baseline)	809 ± 132	802 ± 91	0.085	0.933*
Average RR (msn) (3 month)	806 ± 117	811 ± 78	-0.157	0.876*
SDNN (msn) (Baseline)	124 ± 38	127 ± 20	-0.455	0.652*
SDNN (msn) (3 month)	140 ± 38	116 ± 20	2.85	**0.007***
SDNNi (msn) (Baseline)	48 ± 19	49 ± 16	-0.551	0.584*
SDNNi(msn) (3 month)	51 ± 18	45 ± 13	1.346	0.184*
SDANN (msn) (Baseline)	111 ± 35	113 ± 19	-0.24	0.812*
SDANN (msn) (3 month)	125 ± 37	105 ± 21	2.347	**0.024***
RMSSD (msn) (Baseline) Median (IQR)	22.5 (15-41.25)	23.5 (16.75-30.5)	335.5	0.963** *
RMSSD (msn) (3 month) Median (IQR)	22.5 (17-46.25)	20.5 (17-26.5)	291.0	0.389* *
Triangular index (Baseline)	33 ± 13	32 ± 7	0.116	0.908*
Triangular index (3 month)	37 ± 12	32 ± 7	1.748	0.088*

Parametric values are stated as mean ± standard deviation, non parametric values are stated as median, interquartil range (IQR). *:Independent samples t-test,**: Mann Whitney U test, µ: Chi-square.

are impaired in patients with MetS [17-19]. In a long-term study, resting heart rate and HRV were found to be significant predictors of hyperglycemia and high blood pressure [16]. It has been shown that altered autonomic functions may be present even in patients with 1 or 2 metabolic disorders, as in subjects with 3 or more metabolic disorders [20].

We found that half of the patients who came to the check-up in the third month underwent lifestyle changes with medical treatment, and the other half did not undergo lifestyle changes despite receiving medical treatment. All of the HRV parameters of patients who did not make lifestyle changes were more impaired at the third-month controls. In particular, the negative decrease in SDNN and SDANN parameters was statistically significant.

In most studies, positive changes in HRV parameters were observed in patients undergoing lifestyle changes. It is previously reported that improvements were found in the

autonomic regulation of the heart with aerobic exercises [21]. Another study found an improvement in the recovery phase of heart rate with lifestyle intervention [22]. Lifestyle changes compared to metformin reduced the incidence of diabetes in patients at high risk of developing diabetes, as well as significantly improved HRV parameters [23]. Similar to these findings, an improvement in HRV parameters was found with individual exercise programs in patients with MetS [24]. In contrast, 24-week lifestyle changes in a study of patients with MetS without diabetes did not lead to changes in autonomic nervous system function, although there was a marked decrease in oxidative stress markers. The researchers attributed this result to the shorter duration of the study and the small sample size [25].

In our study, a statistically positive significant increase in third-month controls was found in all HRV parameters in patients undergoing lifestyle changes.

As a result of our study, we found a significant decrease in HRV parameters in patients with MetS. As found in many other studies, we found that lifestyle changes were positive on HRV parameters. Improvement of HRV parameters can be considered to have a positive effect on cardiac autonomic neuropathy, so it will have a positive effect on the cardiovascular prognosis of patients. It is necessary to investigate the positive effects of lifestyle changes on the autonomic nervous system with longer-term studies.

Limitations

This study is an observational study conducted in a single-center, and the number of cases taken into the study is quite small. Another limiting point of the study is that only time-dependent heart rate analysis was performed in HRV analysis, but the frequency-dependent analysis was not performed. But both methods are affected by the same physiological impulses, and there is a strong correlation between them. In addition, we did not examine the circadian change of heart rate and HRV in our study. The follow-up period of MetS patients enrolled in the study was as short as 3 months. There may not be an improvement in autonomic nervous system function in such a short period. In addition, only half of the patients enrolled in the study underwent lifestyle changes.

Disclosures and conflicts of interest

This manuscript is adapted from Ali Birant's thesis titled "Dysfunction of autonomic nervous system and the effect of treatment in metabolic syndrome patients" supervised by Guliz Kozdag. Authors report no conflicts of interest.

Ethical approval

Ethical approval was obtained from Kocaeli University Clinical Research Ethics Committee. (Date: 10.04.2006 , IRB number: AEK 89/5).

References

1. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):1–8.
2. Tentolouris N, Argyrakopoulou G, Katsilambros N. Perturbed autonomic nervous system function in metabolic syndrome. Neuromolecular Med. 2008;10(3):169–78.
3. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.
4. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabet Metab J. 2019;43(1):3–30.
5. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33(7):1578–84.
6. Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, et al. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: a systematic review and meta-analysis. Diab Vasc Dis Res. 2018;15(6):477–93.
7. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Type 2 diabetes and heart failure: characteristics and prognosis in preserved, mid-range and reduced ventricular function. Diab Vasc Dis Res. 2018;15(6):494–503.9.
8. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur. Heart J 2018 39; 3021-104.
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42:3599-3726.
10. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42:S13-S28.
11. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41:407-77.
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 1–150.
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120:1640–1645.
14. Vinik, A. I., Erbas, T., and Casellini, C. M. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J. Diabetes Investig. 2013;4(1):4–18.
15. Pop-Busui, R., Boulton, A. J., Feldman, E. L., Bril, V., Freeman, R., Malik, R. A., et al. Diabetic neuropathy: a position statement by the American diabetes association. Diabetes Care. 2017;40,136–154.
16. Wulsin LR, Horn PS, Perry JL, Massaro JM, D'Agostino RB. Autonomic Imbalance as a Predictor of Metabolic Risks, Cardiovascular Disease, Diabetes, and Mortality. J Clin Endocrinol Metab. 2015;100(6):2443-8.
17. Stein PK, Barzilay JI, Domitrovich PP, Chaves PM, Gottdiener JS, Heckbert SR, et al. The relationship of heart rate and heart rate variability to non-diabetic fasting glucose levels and the metabolic syndrome: the Cardiovascular Health Study. Diabet Med. 2007;24(8):855-63.
18. Soares-Miranda L, Sandercock G, Vale S, Santos R, Abreu S, Moreira C, et al. Metabolic syndrome, physical activity and cardiac autonomic function. Diabetes Metab Res. 2012;28(4):363-9.
19. Assoumou HGN, Pichot V, Barthelemy JC, Dauphinot V, Celle S, Gosse P, et al. Metabolic syndrome and short-term and long-term heart rate variability in elderly free of clinical cardiovascular disease: The PROOF study. Rejuvenation Research. 2010;13(6):653-63.
20. Chang CJ, Yang YC, Lu FH, Lin TS, Chen JJ, Yeh TL, et al. Altered cardiac autonomic function may precede insulin resistance in metabolic syndrome. Am J Med, 2010;123:432-438.
21. Sloan RP, Shapiro PA, DeMeersman RE, Bagiella E, Brondolo EN, McKinley PS, et al. The effect of aerobic training and cardiac autonomic regulation in young adults. Am J Public Health. 2009;99(5):921-8.

22. Ribisl PM, Gaussoin SA, Lang W, Bahnson J, Connelly SA, Horton ES, et al.; Look AHEAD Research Group. Lifestyle intervention improves heart rate recovery from exercise in adults with type 2 diabetes: results from the Look AHEAD study. J Obes. 2012; 2012:309196.
23. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME; Diabetes Prevention Program Research Group. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. Diabetes Care. 2006;29(4):914-9.
24. Stuckey MI, Kiviniemi AM, Petrella RJ. Diabetes and technology for increased activity study: the effects of exercise and technology on heart rate variability and metabolic syndrome risk factors. Front Endocrinol. 2013; 4:121.,
25. Pennathur S, Jaiswal M, Vivekanandan-Giri A, White EA, Ang L, Raffel DM, et al. Structured lifestyle intervention in patients with the metabolic syndrome mitigates oxidative stress but fails to improve measures of cardiovascular autonomic neuropathy. J Diabetes Complications. 2017; 31:1437-1443.