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Original Article

Evaluation of Cardiovascular Autonomic Neuropathy in Patients with Hypertensive Type 2 Diabetes Mellitus

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ABSTRACT

Background: A non-invasive test called heart rate variability (HRV) and heart rate turbulence (HRT) uses sinus node rates and the sinus node rates' deceleration after premature contractions of the heart to identify cardiovascular autonomic dysfunction. The incidence of type 2 diabetes mellitus (DM), which continues to be the most significant health issue, is rising. Combining DM and hypertension raises the risk of heart disease. Our goal was to assess the impact of HRV and HRT analyses on cardiac autonomic functioning in diabetic patients who have hypertension.

Methods: A total of 108 DM patients, 50 normotensives, and 58 hypertensives were involved in this cross-sectional study. Outpatients had 24-hour Holter monitoring, and all recordings were evaluated and cleared of artifacts afterwards. After that, HRT and HRV analyses were performed.

Results: Age, gender, and comorbidity were similar across the study groups. The HRV parameters of SDNN (103.7±2.5, 113.6±1.68, p=0.002), and SDANN (95.1±2.3, 103.2±2.1, p=0.014) were significantly lower in the hypertensive DM group. The HRT values did not significantly differ between the two groups.

Conclusions: In our study, asymptomatic hypertensive DM patients showed a significant decline in HRV parameters. Patients who have both diabetes and hypertension are more likely to exhibit autonomic dysfunction, as seen by HRV. As a result, these people need to be monitored more carefully for cardiovascular diseases.

Keywords: Diabetes Mellitus, hypertension, autonomic dysfunction, heart rate variability, heart rate turbulence

INTRODUCTION

Considering the high rates of mortality and morbidity, type 2 diabetes mellitus (T2DM) is still a major global health concern. Its incidence has been increasing dramatically over time. Particularly, DM nearly doubles the risk of cardiovascular mortality. It has a direct correlation with a higher risk of peripheral artery disease, myocardial infarction, heart failure, stroke, and coronary heart disease (1). Having DM and hypertension (HT) increases the risk of cardiovascular heart disease (CVD) (2).

Previous research has demonstrated that diabetic hypertensives are at increased cardiovascular risk than normotensive diabetics despite maintaining good glycemic and blood pressure control (3). Both conditions provide serious cardiovascular problems, which are one of the main causes of death throughout. Therefore, HT and DM prevention and aggravation pose major concerns (4).

One of the most significant DM consequences, cardiovascular autonomic dysfunction (AD), is frequently overlooked by healthcare professionals (5). Patients with DM can have several clinical manifestations of AD. It is common to see diurnal heart rate variability, resting tachycardia, and diminished reflex responsiveness. Additionally, there are left ventricular dysfunction, ischemia, painless myocardial infarction, and sympathovagal blood pressure imbalance. Another theory is that sudden mortality in diabetes individuals is brought on by QT-interval prolongation, which is linked to the imbalance between parasympathetic and

sympathetic innervation (6). Several methods, including heart rate variability (HRV) and heart rate turbulence (HRT), can be used to evaluate AD (7). Previous studies have demonstrated reduced HRV and deterioration of HRT to predict increased cardiac mortality (8,9). HRV and HRT are frequently used to diagnose AD and potentially identify patients who pose a risk. It is noteworthy that hypertensive DM patients experience a higher frequency of cardiovascular events, and these patients need to undergo an extensive evaluation of AD. Evaluation of the relationship of the two major risk factors for CV mortality, hypertension and diabetes, is an important issue. In this work, we sought to determine the impact of HRV and HRT analysis on cardiac autonomic functions in relation to the presence of hypertension in diabetic individuals.

METHODS

This cross-sectional study included 108 outpatients with T2DM in total, 50 of them had normotensive blood pressure and 58 had hypertension. These patients were those who visited the outpatient clinic on a regular basis for routine care but hadn't developed any symptoms at the time. This study was conducted at the Afyonkarahisar State Hospital and the Afyonkarahisar Health Sciences University between July 1, 2019, and March 1, 2020. Using admittance numbers that were specific to each patient, we were able to obtain epidemiological, demographic, clinical, and laboratory data from the medical records of the patients. All participant laboratory findings have been collected from patient files, and blood samples tested after a 12-hour fasting period. All participants completed an informed consent form; the study was carried out in accordance with the Declaration of Helsinki; and it was authorized by the institutional local ethics committee (Number: 2019/213).

All patients completed a 24-hour course of Holter monitoring using Reynolds Medical's Pathfinder Holter Software Version 8.255, after which all Holter recordings were analyzed. A computer program (HRT View, Version 0,60-0,1 Software Program, Munich, Germany) automatically calculated the HRT parameters, turbulence onset (TO), and turbulence slope (TS). Before analysis, each contraction that the software determined to be a premature ventricular contraction was visually assessed, and artifacts were removed from the research. HRT was determined using the turbulence onset (TO) and turbulence slope (TS) parameters. The degree of early sinus rate acceleration that followed premature ventricular contraction was referred to as T0. The time constant (TS), which was measured in milliseconds per contraction, was defined as the rate of deceleration after the early sinus rate acceleration. The highest positive regression slope across any five consecutive sinus rhythm RR intervals, out of the RR interval of the first 15 sinus rhythms following premature ventricular contraction, was used to compute the target slope (TS). According to advice given by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, an HRV analysis was conducted (10). The time-domain method was used in the measurement of HRV. SDNN (estimates total HRV, Standart deviation of NN intervals), SDANN (standart deviation of the averages of normal to normal intervals in all 5-minute segments of the entire recording, estimates 24hr. components of HRV), pNN50 (percentage of successive RR intervals that differ by more than 50 ms, estimates short-term components of HRV), RMSSD (root mean square of successive RR interval differences, estimates short-term components of HRV), Tİ (triangular index, total number of all normal to normal intervals divided by the height of the histogram of all normal to normal intervals measured on a discrete scale with bins of 7.8125 ms) values were obtained.

Definitions

Patients with a history of oral anti-diabetic and/or insulin therapy, fasting blood sugar measurements ≥126 mg/dL at least twice, hemoglobin A1C levels ≥ 6.5%, a 2-hour plasma glucose value above 200 mg/dL following a 75-gram oral glucose tolerance test, and/or a random plasma glucose analysis above 200 mg/dL in a patient with classic hyperglycemia symptoms were all considered to have diabetes mellitus (DM) (11,12). Patients who were previously on antihypertensive therapy or those with blood pressures measured at least twice ≥ 140/90 mmHg, and who had an ABPM measurement average above 140/90 mmHg were considered hypertensive, but newly diagnosed patients (within the last 1 months) were not included in the study (13). Also, patients who had critical coronary stenosis, and patients undergoing percutaneous transluminal coronary angioplasty or stenting, and those who had undergone coronary bypass surgery were defined as having CAD (14). The presence of kidney damage or an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2, persisting for 3 months or more, were considered chronic kidney disease (CKD) (15). The term chronic obstructive pulmonary disease (COPD) refers to spirometry-based evidence of lung airflow limitation. Smokers were defined as patients who had used tobacco products within the previous month.

Exclusion Criteria

Patients with hormonal disorders (such as thyroid dysfunction), Type 1 DM, pregnancy, those under the age of 18 and over the age of 65, atrial fibrillation, heart failure, autonomic nervous system disorders, neurological diseases, major infections and those on antiarrhythmic medications were excluded.

STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS software version 23.0. determine the normal distribution of variables. Normally distributed variables were expressed as mean and standard deviation and non-parametric variables as median and interquartile. Nonparametric data were compared using Mann–Whitney U test and Parametric data with T-test. Also, a Chi-square test was used to compare ordinal and categorical variables. A P-value <0.05 was considered statistically significant.

RESULTS

The average age of the hypertensive group was 53.5±0.83 and of the normotensive group 54.1±0.76. There was no significant difference between the groups in terms of their gender, smoking status, have a chronic disease or BMI values. Among the groups included in the study, the total cholesterol value was significantly higher and HDL cholesterol was significantly lower in the hypertensive T2DM group (p=0.033, p=0.006, respectively). The drug use, laboratory results, and all variable of patients were shown in **Table 1**.

The HRV parameters of SDNN (103.7±2.5, 113.6±1.68, p=0.002), SDANN (95.1±2.3, 103.2±2.1, p=0.014) were significantly lower in the hypertensive T2DM group. The other HRV and HRT parameters did not differ between the two groups (**Table 2**).

Additionally, a correlation analysis study was carried out to see how HRV and HRT parameters related to other variables, but no significant correlations were identified.

DISCUSSION

Disorders of autonomic balance developing in diabetic patients in the form of a marked decrease in parasympathetic tone and a relative increase in sympathetic tone are among the known features of diabetes. Particularly, hyperglycemia and hyperinsulinemia raise sympathetic tone in the cerebral canters that regulate the autonomic nervous system. In diabetics, the onset of cardiac autonomic neuropathy, which can result in arrhythmia, silent infarction, and sudden death, is a poor prognostic predictor. In our investigation, patients with diabetes and hypertension underwent combined HRV and HRT analyses. The largest likelihood of autonomic dysfunction with lower HRV values was seen in subjects with both DM and HT. This group of patients can be evaluated for more frequent and earlier in terms of cardiovascular diseases. A decline in HRV indicates increased sympathetic tone and decreased parasympathetic tone. It has long been thought to have a detrimental effect on the prognosis of cardiovascular disease (16). The co-existence of DM and systemic arterial HT is very common, and some studies have evaluated this situation using time-and frequency-domain HRV analysis. In a study of Nagy et al., hypertensive patients were parted according to the presence of DM and compared with the control group, all HRV parameters of hypertensive patients were found to be lower than the control group. However, when hypertensive patients were evaluated according to the presence or absence of DM, there were no significant differences (17). A small number of diabetics may be the cause of this result. Patients were separated into 4 groups according to DM and HT in Istnes et al.'s study, and each group's performance was assessed using frequency domain analysis. The study's findings indicated that diabetes has a greater impact on HRV measures than does hypertension. Patients with diabetes and hypertension had the highest likelihood of having poor heart rate variability, according to the same study

Table 1. Baseline demographic and clinical characteristics of normotensive and hypertensive Type 2 DM patients

Variables	HT-2DM+ (n:50)	HT+T2DM+ (n:58)	P value
Women, n (%)	24 (%48)	26 (%51)	0.356*
Smoker, n (%)	13 (%26)	14 (%24.1)	0.824*
CAD, n (%)	16 (%24.1)	11 (%24.1)	0.119
CRD, n (%)	6 (%12)	10 (%17.2)	0.445
COPD, n (%)	7 (%14)	8 (%13,8)	0.975
DM duration, year	5.8±1.6	5.4±1.7	0.265
Age (years)	54.1±0.76	53.5±0.83	0.589
BMI (kg/m²)	27.8±0.19	28.3±0.28	0.734
Fasting glucose (mg/dl)	159.1±2.36	161.4±2.59	0.872
HbA1c (mg/dl)	7.84±0.81	7.89±0.12	0.788
Creatinine (mg/dl)	0.83±0.03	0.86±0.21	0.390
Hemoglobin (g/dl)	13.8±0.17	13.9±0.2	0.832
Neutrophile count (x10³/uL)	5.52±0.22	5.63±0.23	0.729
Lymphocyte count (x10³/uL)	2.09±0.09	2.15±0.09	0.657
Monocyte count (x10³/uL)	0.61±0.03	0.68±0.04	0.893
Platelet count (x10³/uL)	259.7±8.4	262.4±9.8	0.921
Total Cholesterol (mg/dl)	156.3±4.1	172.7±6.2	0.033*
Triglyceride (mg/dl)	265.9±4.5	258.3±10.9	0.545
HDL Cholesterol (mg/dl)	45.1±0.71	42.2±0.66	0.006*
LDL Cholesterol (mg/dl)	139.1±4.5	148.8±4.5	0.137
OAD, n (%) OAD+Insuline, n (%) Insuline, n (%)	38 (%76) 8 (%16) 4 (%8)	38 (%76) 8 (%16) 4 (%8)	0.830

*p<0.05 statistical significance,n: number, BMI; body mass index, CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, CRD; chronic renal disease, HbA1c; glycated haemoglobin A1c, HT; hypertension; OAD; oral anti-diabetic, T2DM; type 2 diabetes mellitus

Table 2. HRV and HRT analysis of study groups

Variables	HT-T2DM+ (n=50)	HT+T2DM+(n=58)	P value
Heart rate, beats/min	78±1.07	76±0.85	0.658
SDNN, ms	113.6±1.68	103.7±2.5	0.002*
SDNN index, ms	44.04±1.6	40.79±1.6	0.166
SDANN, ms	103.2±2.1	95.1±2.3	0.014*
RMSSD, ms	26.8±0.94	24.2±1.1	0.072
pNN50, %	19±1.1	20.4±1.4	0.456
Triangular index	30.6±1.02	29.4±1.01	0.391
Turbulence onset, %	-1.15±0.13	-0.91±0.12	0.202
Turbulence slope, ms/RR	6.35±0.45	5.64±0.42	0.238

pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals. RMSSD: Root mean square of successive RR interval differences, SDANN: Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording, SDNN: Standard deviation of the NN intervals, *p<0.05 statistical significance

(18). In another research by Bassi et al., similarly, HT + T2DM patients had a significant deterioration in HRV parameters compared to the non-HT group (19). When the literature data and our results are evaluated together, it is seen that the addition of HT to T2DM causes a significant deterioration in HRV parameters compared to the non-hypertensive group. Our results may help to explain why the cardiovascular risk is higher in this group.

Abnormal HRT parameters are detected in patients with autonomic dysfunction and impaired baroreceptor sensitivity. Abnormalities in HRT parameters are also associated with all-cause death and sudden death in patients with post- infarction and heart failure (20). HRT parameters were evaluated separately in both HT and T2DM in different studies and it was shown that there was a deterioration in HRT parameters, more prominent with the progression of the related disease, and it was also associated with cardiac autonomic nervous system dysfunction (21,22). Also, Yosuke et al. reported that HRT measurement in post-infarction DM patients can predict cardiac mortality (23). As far as we know, there is no study in the literature evaluating hypertensive diabetic patients with HRT. Our study is probably the first in which these patients were evaluated with both HRV and HRT. Although HRT values were lower in hypertensive diabetics, the difference between the groups was not significant. While there is no significant difference in HRT values, the decrease we found in HRV parameters (SDNN and SDANN) in the hypertensive diabetes group may indicate cardiac autonomic neuropathy in these patients. Likewise our findings should be scrutinized, particularly with more extensive and long-term research.

Conclusion

In summary, this study's results show that patients with both diabetes and hypertension have higher risk for decreased HRV parameters, but this distinction was not observed in HRT parameters. Early evaluation of the autonomic nerve function is hence advised in diabetic patients with hypertension. Our findings indicate that HT further deteriorates HRV in diabetics, despite the fact that a healthy group was not assessed in this study. Monitoring HRV parameters, which evaluate the regulation of the autonomic nervous system and its response to stimuli, provides insight into the autonomic nervous system of the patients, and could provide leading information for treatments targeting the autonomic nervous system in hypertensive diabetic patients. Future studies are warranted to explore if HRT parameters can be used for patients with hypertensive diabetic and how they are affected. Finally, our observations may have important contributions to the risk reduction strategies.

DECLARATIONS

Conflict of interest: The authors declare that they have no conflict of interest.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Authors contribution:

Concept and design of article: SAY, ZY; Data Collecting: SAY, ZY; Writing: SAY, ZY; Drafting and critical revision of the article: SAY. All authors read and approved the final version of the manuscript.

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