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Relationship between changes in heart rate variability indices and blood glucose control in Type 2 Diabetes Mellitus

Relación entre los cambios en los índices de variabilidad de la frecuencia cardíaca y el control de la glucosa en sangre en la diabetes mellitus tipo 2

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Abstract

Diabetes mellitus (DM) is one of the most common health problems in the community. DM is associated with pathologic changes in the cardiovascular system due to alterations in the autonomic nervous system (ANS). Dysfunction of the cardiovascular ANS can lead to fatal arrhythmias and sudden death. The aim of this study was to investigate the relationship between changes in heart rate variability (HRV) indices and blood glucose control status in patients with type 2 DM. Patients with type 2 DM who presented to our university Diabetes Clinic were eligible to be included. Fasting blood glucose (FBG), 2-hour postprandial blood glucose test (2PPG), and hemoglobin A1C (HbA1C) were measured. According to the HbA1C the patients were categorized as euglycemia (HbA1C <7%) and poorly controlled DM (HbA1C >7%). HRV indices were determined by 24-hour Holter monitoring. There were 41 patients with euglycemia and 39 patients whose blood glucose was poorly controlled. pNN, SDANN, and SDNN indices were significantly higher in the euglycemia group than in the group with poorly controlled glucose. There was significant and inverse correlation between pNN, SDANN, and SDNN with serum levels of HbA1C. However, no significant correlation was observed between FBS and 2PPG with HRV indices. HRV indices were significantly lower in diabetic patients with poorly controlled blood glucose when compared to diabetics with good control of blood glucose. These findings reflect dysfunction of the ANS in patients with poorly controlled blood glucose.

Keywords: Diabetes mellitus; autonomic nervous system; heart rate variability (HRV); hemoglobin A1C.

Resumen

La diabetes mellitus (DM) es uno de los problemas de salud más comunes en la comunidad. La DM se asocia con cambios patológicos en el sistema cardiovascular debido a alteraciones en el sistema nervioso autónomo (SNA). La disfunción de la ANS cardiovascular puede llevar a arritmias fatales y muerte súbita. El objetivo de este estudio fue investigar la relación entre los cambios en los índices de variabilidad de la frecuencia cardíaca (HRV) y el estado de control de la glucosa en sangre en pacientes con DM tipo 2. Los pacientes con DM tipo 2 que acudieron a nuestra Clínica de Diabetes de la universidad fueron elegibles para ser incluidos. Se midieron la glucemia en ayunas (FBG), la prueba posprandial de glucosa en sangre durante 2 horas (2PPG) y la hemoglobina A1C (HbA1C). Según la HbA1C, los pacientes se clasificaron como euglucemia (HbA1C <7%) y DM mal controlada (HbA1C >7%). Los índices de HRV se determinaron mediante un monitoreo Holter de 24 horas. Hubo 41 pacientes con euglucemia y 39 pacientes cuya glucemia estaba mal controlada. Los índices pNN, SDANN y SDNN fueron significativamente más altos en el grupo con euglucemia que en el grupo con glucosa mal controlada. Hubo una correlación significativa e inversa entre pNN, SDANN y SDNN con los niveles séricos de HbA1C. Sin embargo, no se observó una correlación significativa entre FBS y 2PPG con índices HRV. Los índices de HRV fueron significativamente más bajos en los pacientes diabéticos con glucemia mal controlada en comparación con los diabéticos con buen control de la glucemia. Estos hallazgos reflejan una disfunción de la ANS en las pacientes con glucosa en sangre mal controlada.

Palabras clave: Diabetes mellitus; Sistema nervioso autónomo; variabilidad de la frecuencia cardíaca (VFC); hemoglobina a1c.

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share hyperglycemia in their phenotype¹. The metabolic imbalances seen in DM can result in pathophysiologic changes in several parts of the body. These changes are responsible for most morbid states seen in diabetics in a way that DM is known as the leading cause of end-stage renal disease (ESRD), non-traumatic amputations of the lower extremities, cardiovascular diseases and blindness in adults². As the prevalence of DM is increasing worldwide, DM will continue to be a major cause for morbidity and mortality.

Diabetic neuropathy is seen in about 50% of people with long-term types 1 and 2 DM. This disorder can manifest as polyneuropathy, mononeuropathy, or autonomic neuropathy. DM-related autonomic neuropathy can affect several organs including cardiovascular, digestive, genitourinary systems. Autonomic neuropathy that affects the cardiovascular system causes tachycardia at rest and orthostatic hypotension³. Autonomic neuropathy may be due to the involvement of the sinus node regulation which results in decreased heart-rate variability (HRV). The decreased HRV can predispose the patient to fatal arrhythmias. Autonomic neuropathy, characterized by a massive neurological degeneration, affects the small neural fibers of the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS)⁴.

DM, as a metabolic derangement, is associated with cardiovascular changes as a result of changes in the ANS. Dysfunction of the cardiovascular ANS among diabetics can cause fatal arrhythmias and sudden cardiac death⁵. Cardiovascular diseases are one of the most common diseases, and heart failure today is considered to be the major cause of mortality in industrial and semi-industrial societies. For this reason, identification of disorders in the cardiovascular system of patients with DM has an important role in the prevention of disability and morbidity and mortality consequences from cardiovascular conditions.

A reliable method to investigate the cardiovascular ANS function is the analysis of HRV (heart rate variations with intervals between successive heartbeats)⁶. The intervals between the QRS complexes known as NN (normal to normal) or RR (R to R) intervals are reference indices to investigate HRV. Although there are several non-invasive methods for investigating ANS function, HRV analysis is a simple and reliable method for evaluating sympathovagal balance at the sino-atrial (SA) node level. Given the benefits of HRV analysis, this method has been used in many disorders including diabetic neuropathy, myocardial infarction (MI) and heart failure⁷. Previous studies have shown that in one-third of diabetics, some degrees of early stages of autonomic neuropathy, which can be evalu-

ated with HRV analysis, have been documented prior to development of clinical symptoms⁴.

The severity of ANS dysfunction in DM correlates with severity and duration of DM. The autonomic disorders of diabetes is related to the severity and duration of the disease. Although several studies have been conducted on the state of glucose control in diabetic patients and its association with ANS dysfunction, contradictory findings have been noted. Therefore, further studies are required. Hence, in this study, we examined the relationship between changes in HRV indices and the status of blood glucose control in diabetic patients.

In this study, 80 patients with type 2 DM who presented to the Diabetes Clinic of our medical university were included. Exclusion criteria were the presence of other underlying conditions (such as malignancy), congenital cardiovascular disorders, major thalassemia, and history of myocardial infarction, heart failure, and arrhythmia.

To evaluate the patients' blood glucose control, fasting blood glucose (FBG), 2-hour postprandial blood glucose test (2PPG), and serum hemoglobin A1C (HbA1C) levels. A serum HbA1C level less than 7 mg/dL was considered as controlled blood glucose and euglycemia⁸.

The patients were selected from those that had undergone 24-hour Holter monitoring at the Diabetes Clinic during the preceding two years. The patients were divided into two groups. One group consisted of patients with euglycemia (HbA1C <7%) and the other group consisted of diabetics with poorly controlled blood glucose level (HbA1C >7%).

The patients underwent Holter monitoring (PADSY.5.2A, Germany) to determine HRV indices. The analysis of HRV indices were done based on time intervals. The analysis of time intervals included pNN50, SDNN, and SDANN which indicate QRS complexes in 55 msec intervals. Then, the obtained data were compared with baseline indices and the changes were analyzed. The gathered data were entered into a checklist.

Statistical analyses

The continuous variables were analyzed and compared between the two groups by the Mann-Whitney U test. The categorical variables were compared between the two study groups by the Chi-squared test. The correlation between the continuous variables was analyzed by the Spearman test. A P value of less than 5% was considered statistically significant. The statistical analyses were performed by the SPSS software (ver. 16.0).

A total number of 80 patients were included. There were 41 patients in euglycemia group and 39 patients in poorly controlled blood glucose level. In euglycemia group, there were 17 male and 24 female patients. In diabetic patients whose blood glucose levels were poorly controlled, there were 16 male and 23 female patients. The gender distribution was comparable between the two groups ($P=0.968$); Table 1.

Mean (\pm SD) DM duration in euglycemia and poorly controlled glucose groups were respectively 8.7 (\pm 4.2) and 9.2 (\pm 5.6) years. As seen in Table 1, no difference was observed between the two study groups regarding age, gender distribution, DM duration, and blood pressure (systolic and diastolic). On the other hand, FBG, HbA1C, and 2PPG were significantly higher in poorly controlled blood glucose level compared to euglycemia group.

Table 1. Demographic data of the study groups

	Poorly controlled blood glucose	Euglycemia	P value
Age, year	52 (\pm 9.2)	54 (\pm 8.7)	0.233
Gender, male	16	17	0.968
Diabetes mellitus duration, year	9.2 (\pm 5.6)	8.7 (\pm 4.6)	0.306
SBP, mmHg	140 (\pm 25)	139 (\pm 18)	0.884
DBP, mmHg	81 (\pm 13)	80 (\pm 7)	0.541
FBG, mg/dL	177 (\pm 71)	128 (\pm 27)	< 0.001
HbA1C, %	8.9 (\pm 1)	6.7 (\pm 0.3)	< 0.001
2-hour postprandial blood glucose, mg/dL	255 (\pm 81)	190 (\pm 43)	< 0.001

FBG= fasting blood glucose; SBP= systolic blood pressure; DBP= diastolic blood pressure

Mean (\pm SD) primary and secondary SDANN difference time (Δ SDANN) in euglycemia group (13 ± 1) was not different from poorly controlled glucose group (17 ± 3); $P=0.946$ (Table 2).

Table 2. The difference between primary and secondary measurements of heart-rate variability indices and their comparison between the two groups

	Poorly controlled blood glucose	Euglycemia	P value
Δ SDNN	18 (\pm 4)	21 (\pm 4)	0.373
Δ SDANN	17 (\pm 3.4)	13 (\pm -1)	0.946
Δ PNN	1.5 (\pm 0.19)	2.3 (\pm -0.8)	0.167

There was significant inverse correlation between serum HbA1C and HRV indices including PNN, SDNN, and SDANN. These indices were lower in those with poor controlled blood glucose and higher HbA1C level. However, no significant association was found between FBG and 2PPG with HRV indices (Table 3).

Table 3. The correlation between fasting blood glucose (FBG), 2-hour postprandial glucose (2PPG), and HbA1c level with heart-rate variability (HRV) indices

	HbA1C, %		FBG, mg/dL		2PPG, mg/dL	
	P value	r	P value	r	P value	r
SDNN1	0.001	-0.366	0.087	-0.192	0.022	-0.257
SDNN2	0.001	-0.364	0.118	-0.176	0.018	-0.265
SADNN1	0.002	-0.341	0.207	-0.143	0.108	-0.181
SADNN2	0.003	-0.332	0.275	-0.124	0.088	-0.192
PNN1	0.013	-0.277	0.832	-0.024	0.751	-0.036
PNN2	0.005	-0.313	0.095	-0.188	0.272	-0.124

Discussion

The aim of this study was to determine the relationship between changes in HRV indices and blood glucose control status in patients with type 2 DM. Several studies have been done to investigate the status of blood glucose control in diabetics and its association with ANS dysfunction. Despite controversies, all studies indicate that the severity of ANS dysfunction correlates with severity of DM and its duration. In our study, which was performed on patients with type 2 DM, it was found that HRV indices were significantly lower among those with poorly controlled blood glucose when compared to the other group with euglycemia. This decreased state of HRV indices reflects impairment of the cardiovascular ANS, was observed over two year period of follow-up. Although the HRV indices were significantly lower in patients with poorly controlled blood glucose than in euglycemia group, the decrease over the follow-up period was not statistically significant. It seems that the severity of cardiovascular ANS dysfunction was more severe in more prolonged DM and since our follow-up was relatively short (two years), the difference did not become significant.

In a study by Faulkner et al. on patients with types 1 and 2 DM, it was reported that cardiovascular stability was poorer in patients with higher body mass index (BMI), poorer control of blood glucose, and less physical activity. It was also reported that HRV in type 2 DM group was lower than in type 1 DM⁹, which is consistent with the results of this study. In another study by Faulkner et al. including healthy subjects and patients with type 1 DM, RR changes were less prominent in diabetics than in healthy subjects. Also, an inverse correlation was detected between serum HbA1C level and sympathetic balance in diabetics¹⁰, which is comparable to our findings.

Chen et al. in their study involving 79 patients with type 1 DM showed that HbA1C level and duration of DM had inverse correlation with HRV¹¹. In the presented study,

there was only a meaningful relationship between serum HbA1c and HRV indices. This can be justified as all patients with DM included had type 2 DM with lower duration of the disease. But in other studies, mostly type 1 DM patients had been studied. In a separate study by Eller on 74 patients, serum HbA1C level and waist-hip ratio had significant inverse correlation with HRV indices¹². The results reported by Richard et al. on 88 patients showed that significant decrease in ANS function which had direct relationship with serum HbA1C level and age¹³, which is in agreement with our findings.

There are several studies which contradict the obtained findings. For example, in a large study of 684 patients with type 1 DM, cardiovascular autonomic neuropathy had significant correlation with decreased low frequency (LF) and high frequency (HF) in HRV. In addition, obesity and serum HbA1C level did not show correlation with the severity of cardiovascular autonomic neuropathy¹⁴. Koharo et al. studied type 1 DM patients and reported that HRV had a significant inverse correlation with the duration of the disease, while there was no correlation with the blood glucose control status of the patients¹⁵. In studies conducted by Hsu et al. on diabetic patients who had undergone NCV (nerve conduction velocity) and HRV investigations, age, renal function impairment, HbA1C level, and FBG had correlation with somatic neuropathy, while only systolic blood pressure had correlation with autonomic neuropathy¹⁶⁻¹⁸.

In conclusion, in patients with poor control of blood glucose status, HRV indices were significantly lower compared to those with euglycemic state. This condition which reflects cardiovascular AND dysfunction remained after two years of follow-up of the patients¹⁷. Serum HbA1C level had a significant inverse correlation with HRV indices. Disturbance in cardiovascular ANS and its relationship with the state of blood glucose control can propose conduction of further studies to explore the required interventions to decrease the related complications.

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