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Original Article

The impact of glycemic control on heart rate variability in patients with type 2 Diabetes Mellitus and the potential for prediction

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Abstract

The objective was to ascertain whether glycemic control impacts heart rate variability in patients with type 2 diabetes and determine whether alterations in heart rate variability can be anticipated through continuous glucose monitoring data analysis. A total of 53 adult patients with type 2 diabetes (T2DM) and a glycosylated level (HbA1c) of ≤10% were examined. The study was based on the synchronous recording of heart rate variability and continuous glucose monitoring (CGM) before and six months after the modification of glucose-lowering therapy. Correlation, logistic regression, and receiver operating characteristic (ROC) analyses were employed. Following a six-month period, patients exhibited a notable reduction in HbA1c, time above range, time below range, glycemic variability, and a decline in the frequency of hypoglycemic episodes. The presence of hypoglycemia before the modification of glucose-lowering therapy was identified as a prognostic factor for predicting HRV improvement. The study's findings suggest enhanced glycemic control is associated with increased absolute all-time and frequency domain characteristics of HRV. A mathematical model for HRV prediction based on CGM parameters for T2DM was developed, exhibiting a sensitivity of 60.0% and a specificity of 83.33%.

Keywords: diabetes mellitus, heart rate variability, continuous glucose monitoring, hypoglycemia, diabetes, prediction.

Introduction

The regulation of the heart rate is the result of the rhythmic activity of automatic cells in the sinus node, as well as the influence of the autonomic and central nervous system's humoral and reflex interactions [1, 2] Changes in the cardiac cycle from contraction to contraction reflect the balance between sympathetic and parasympathetic influences on the heart. Heart rate variability (HRV) assesses the differences in beat-to-beat time intervals during the cardiac cycle. It is a valuable tool for evaluating neurocardiac physiology's state and various factors' influence on heart rhythm [3, 4]. A high HRV reflects the body's high adaptive capabilities [5]. However, it is important to note that HRV tends to decrease with age due to an age-related decline in autonomic nervous system activity [6].

A meta-analysis of 28 cohort studies comprising a total of 3094 participants demonstrated that a reduction in HRV was associated with an elevated risk of all-cause mortality and cardiovascular events. The pathophysiological mechanisms by which low HRV increases cardiovascular risk are related to secondary sympathetic dominance due to reduced parasympathetic activity [7]. Other studies have also found that low HRV values are associated with cardiac events such as myocardial infarction, progressive atherosclerosis, heart failure, coronary heart disease and sudden death, as well as diabetes mellitus, acute and chronic stress, and metabolic syndrome [8–11].

HRV reduction in diabetic patients is associated with the preclinical manifestations of diabetic autonomic neuropathy (DAN) resulting from lesions of both sympathetic and parasympathetic nerve fibers [12].

The clinical manifestations of diabetic autonomic neuropathy (DAN) are highly variable and contingent upon the affected target system. DAN may present with a range of signs and symptoms, including cardiovascular, gastrointestinal, urogenital, and other autonomic dysfunctions [13, 14]. The efficacy of tight glycemic control in the prevention of cardiovascular autonomic neuropathy (CAN) occurrence and progression has been substantiated by the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) studies in patients with type 1 diabetes mellitus [15]. Concurrently, the Steno-2 study demonstrated that in patients with type 2 diabetes mellitus (T2DM), CAN was more strongly correlated with conventional cardiovascular risk factors, including hypertension, smoking, dyslipidemia and obesity. Furthermore, a comprehensive impact on these factors was observed to reduce the manifestation of CAN, while the positive effect of intensifying glycemic control was not proven [16].

The development of continuous glucose monitoring (CGM) systems and their integration into clinical practice provides a unique opportunity to comprehensively investigate the relationship between glycemia and HRV in diabetic patients. This assessment of glycemic control offers a significant advantage over the determination of glycosylated hemoglobin levels and self-monitoring of blood glucose, which provide limited information [17, 18].

Clearly, early detection and prevention of the progression of autonomic dysfunction is important in the management of T2DM patients to prevent the progression of chronic diabetic complications and premature death.

The objective was to ascertain whether glycemic control impacts heart rate variability in patients with type 2 diabetes and determine whether alterations in heart rate variability can be anticipated through continuous glucose monitoring data analysis.

Material and methods

The study was conducted at the Endocrinology Department of the University Clinic in Dnipro, Ukraine, between 2022 and 2023. Our study was carried out in accordance with the ethical principles set out in the Declaration of Helsinki on ethical principles for medical research involving human subjects. The study protocol was approved by the Bioethics Committee of the Dnipro State Medical University (approval number: 1, 10/Feb/2020).

Inclusion criteria: previous diagnosis of T2DM, age ≥18 years, HbA1c ≤10%, stable glucose-lowering treatment during the past 3 months, voluntary written informed consent.

Exclusion criteria: diabetic proliferative retinopathy; chronic kidney disease stage 3, 4, 5; heart failure C, D according to the American College of Cardiology and American Heart Association (ACC/AHA) classification; congenital and acquired heart defects; atrial fibrillation; history of myocardial infarction, myocarditis, cardiomyopathy; electrolyte imbalance; exacerbation of concomitant chronic diseases and conditions; acute somatic events; thyroid dysfunction; and pregnancy.

Biochemical measurement parameters

HbA1c was estimated by immunoturbidimetry using an automatic biochemical analyzer SAPPHIRE 400 (Tokyo Boeki, Japan).

Instrumental research methods

Continuous glucose monitoring (CGM) was conducted utilizing the Guardian™ Connect system (Medtronic, USA). The time above range (TAR), time below range (TBR), time in range (TIR), and glycemic variability (%CV) were subjected to analysis. The glucose profiles were processed using the CareLink™ software. The range of glucose measurement by this method is from 2.2 to 22.2 mmol/l. A hypoglycemic episode was defined as a reading of less than 3.9 mmol/l [19].

Concurrently with the CGM, the 24-hour registration of electrocardiogram (ECG) with the Holter method was carried out. We used the SDM23 Holter monitoring device (manufacturer: X-Techno Ukraine) and three modified leads: MV4, Y, and MV6. The analysis of HRV parameters was conducted using ARNIKA software, version 8.3.9.

Analysis of HRV time domain measures included standard deviation of all normal-to-normal (RR) intervals (SDNN) in ms, square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) in ms, percentage of the difference between adjacent RR intervals that were greater than 50 ms for the period of analysis (PNN50). Frequency domain analysis of HRV was performed by determining the spectral power at three frequencies: high frequency (HF) – 0.15–0.4 Hz, low frequency (LF) – 0.04–0.15 Hz, very low frequency (VLF) – 0.003–0.04 Hz, together with the total power (TP) expressed in ms2 and the ratio between low and high frequency (LF/HF ratio) [1].

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We modified glucose-lowering therapy in patients according to the guidelines of the American Diabetes Association (ADA) [19].

HbA1c level and instrumental examination were repeated in 6 months.

Statistical analysis

Microsoft Excel software (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 software (StatSoftInc., serial number AGAR909E-415822FA) were used to analyze the results. The median and interquartile range (25th and 75th percentiles) were employed to describe quantitative data, whereas relative values were used for qualitative features. Correlation analysis was conducted by calculating Spearman's rank correlation coefficients (rs). Receiver operating characteristic (ROC) analysis was performed to assess the characteristics' prognostic ability and prediction accuracy according to the logistic equation. The value of the significance level $p<0.05$ (5%) was considered statistically significant.

Results

In accordance with the established inclusion and exclusion criteria, 53 patients were selected for the study. The patients were required to modify their glucose-lowering therapy to achieve compensation for T2DM. The gender distribution was as follows: men (n=29, 54.7%) and women (n=24, 45.3%). The mean age of the patients was 57.0 (51.0; 64.0) years. The average T2DM duration was 9.0 (5.0–14.0) years.

Glucose-lowering therapy for patients at baseline included: biguanides (metformin), sulfonylureas (gliclazide, glimepiride), thiazolidinediones (pioglitazone), dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 analogs (liraglutide), sodium-glucose cotransporter-2 (SGLT2) inhibitors (dapagliflozin), long-acting insulin analogs (glargine, degludec, levemir), intermediate-acting insulin (insulin human recombinant).

Table 1 shows glucosemic parameters, HRV, and laboratory examinations in T2DM patients at baseline and 6 months after modification of glucose-lowering therapy.

The modification of glucose-lowering therapy improved glycemic control, as evidenced by a significant decrease in HbA1c, a reduction in the frequency of hypoglycemic episodes, and a decrease in glycemic variability at the second examination.

The dynamics of HRV in T2DM patients 6 months after modification of glucose-lowering therapy showed statistically significant positive changes. There was an increase in all time and frequency domain characteristics of HRV (SDNN, RMSSD, PNN50, TP, VLF, LF, HF) and a decrease in the LF/HF ratio.

To determine the factors influencing the improvement in HRV dynamics, a group of patients was identified who showed positive changes in more than 65% of the analyzed daily HRV values. A total of 17 patients (32.1%) had these changes. An analysis of the HRV increase in T2DM patients about the presence of hypoglycemia showed that hypoglycemia was present in 100% of cases at the first examination.

To determine the factors influencing HRV, correlation analysis was conducted, revealing statistically significant associations with HRV improvement: with

Table 1: Glycemic parameters, HRV, and laboratory tests in T2DM patients (median and interquartile range Me (25th; 75th percentile).

Indicators	At baseline	After modification of glucose-lowering therapy
HbA1c (%)	8.1 (6.6; 9.7)	7.1 (6.6; 8.4)*
TAR (%)	39.0 (19; 41.0)	27.0 (15; 34.0)*
TBR (%)	6.0 (3.0; 9.0)	2.0 (0.0; 6.0)*
TIR (%)	49.0 (39; 64.0)	69.0 (61; 83.0)*
%CV	37.7 (22.4; 58.6)	25.6 (20.8; 38.2)*
Frequency of hypoglycemic episodes (%)	32.1	3.8*
SDNN (мс)	110 (91; 127)	116 (99; 135)*
RMSSD (мс)	28 (17; 43)	36 (26; 45)*
pNN50 (%)	2 (1; 6)	3 (2; 7)*

Table 1: Continued.

Indicators	At baseline	After modification of glucose-lowering therapy
TP (мс²)	4107 (2269; 6308)	4962 (2984; 6672)*
VLF (мс²)	2981 (1658; 4259)	3225 (1965; 4799)*
LF (мс²)	884 (398; 1425)	966 (542; 1395)*
HF (мс²)	160 (76; 801)	373 (232; 791)*
LF/HF	4.9 (2.5; 6.2)	2.6 (1.4; 4.8)*

Note: * – p<0.05 compared to the result at the beginning of the study.

the presence of hypoglycemia at the first examination (r_s=0.43; p=0.004); with changes in %CV (r_s=-0.36; p=0.042); with changes in HbA1c (r_s=-0.34; p=0.014); and with TIR (r_s=0.31; p=0.046).

Multiple logistic regression analysis was performed to estimate the probability of HRV improvement. We used the logistic regression equation, which assumes that the positive effect is related to the level of the studied factors according to formula (1):

$$y = \exp (b_0 + b_{1\text{-}n} \times x_{1\text{-}n}) / [1 + \exp (b_0 + b_{1\text{-}n} \times x_{1\text{-}n})], \quad (1)$$

were y – is the outcome (probability of HRV improvement); b_0 – is a coefficient indicating the value of the outcome when the predictor is 0; $b_{1\text{-}n}$ – regression coefficients indicating how much, on average, the logarithm of the probability of developing a positive effect changes when the independent variable changes by one unit of its measurement; $x_{1\text{-}n}$ – predictor variables, indicators of each individual patient for whom the prognosis is calculated.

For the defined predictors, the indicator is entered in the obtained values of the measurement units for the presence of hypoglycemia in binary (0 – no hypoglycemia, 1 – hypoglycemia is present).

The obtained result of equation (1) varies from 1 (improvement in HRV) to 0 (no improvement in HRV).

The equation developed to predict HRV in these patients was reduced to a simple logistic regression model, as only one statistically significant predictor was

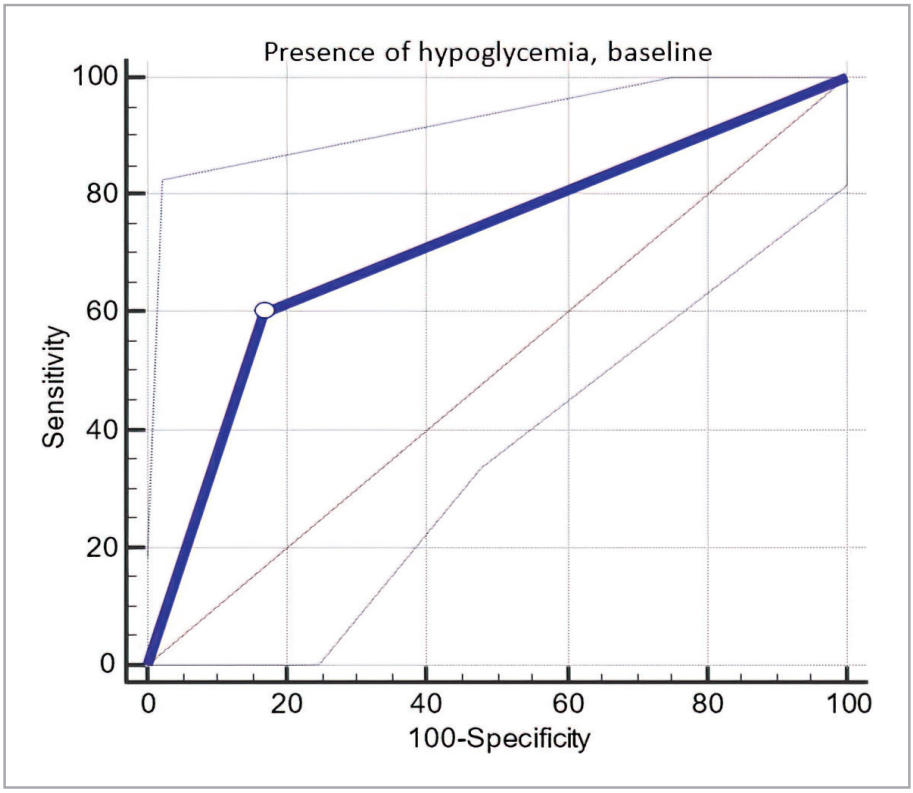

Figure 1: ROC curve for prediction of HRV in T2DM patients according to logistic regression analysis.

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identified—the presence of hypoglycemia at baseline, with a sensitivity of 60.0% and a specificity of 83.33%.

$$PI = \exp(-0.406 + 2.015 \times x1) / [1 + \exp(-0.406 + 2.015 \times x1)] \quad (2)$$

where PI – prognosis of HRV improvement in T2DM patients; -0,406 – free term of the regression model; x1 – presence of hypoglycemia before correction of sugar-lowering therapy (0 – absent, 1 – present).

The percentage of accurate forecasts of the patient's prognosis was 69.77%. This demonstrates a satisfactory level of alignment between the observed distribution and the one the logistic regression equation predicted. The assessment of the logistic regression equation using the chi-square value indicated its suitability ($p<0.01$).

The prognostic model demonstrated favorable operating characteristics, as indicated by the shape of the ROC curve and the area under the curve (AUC). The AUC was 0.717 (95% CI 0.559–0.843; p=0.001) (Figure 1).

The cut-off point (>0.4) on the ROC curve for HRV prediction in T2DM patients allows us to establish a prediction criterion based on the equation's result. If the calculated probability is less than or equal to 0.4, it can be assumed that the event will not occur (no improvement); otherwise (probability greater than 0.4), HRV improvement in T2DM patients is predicted (Figure 2).

Discussion

We provide clinical examples to demonstrate the mathematical model's application in practice.

Example 1:

Patient M., 55 years old, with T2DM for 16 years. Glucose-lowering therapy: metformin + intermediate-acting insulin. A hypoglycemic episode (x1) with a glycemic level of 3.6 mmol/L was recorded at the first examination. At baseline, HbA1c was 8.9%, and 6 months after modification of glucose-lowering therapy, HbA1c was 7.4%, with no hypoglycemic episodes recorded.

The resulting presence of hypoglycemia at the first examination was substituted into the logistic equation (2):

$$PI = \exp(-0.406 + 2.015 \times x1) / [1 + \exp(-0.406 + 2.015 \times x1)]$$

where PI – prognosis of HRV improvement in patients with T2DM.

PI for patient M.:

$$PI = \exp(-0.406 + 2.015 \times 1) / [1 + \exp(-0.406 + 2.015 \times 1)] = 0.833$$

Thus, patient M.'s PI is more than 0.4, which is defined as the probability of a positive result, which means improvement of HRV. Six months after modifying

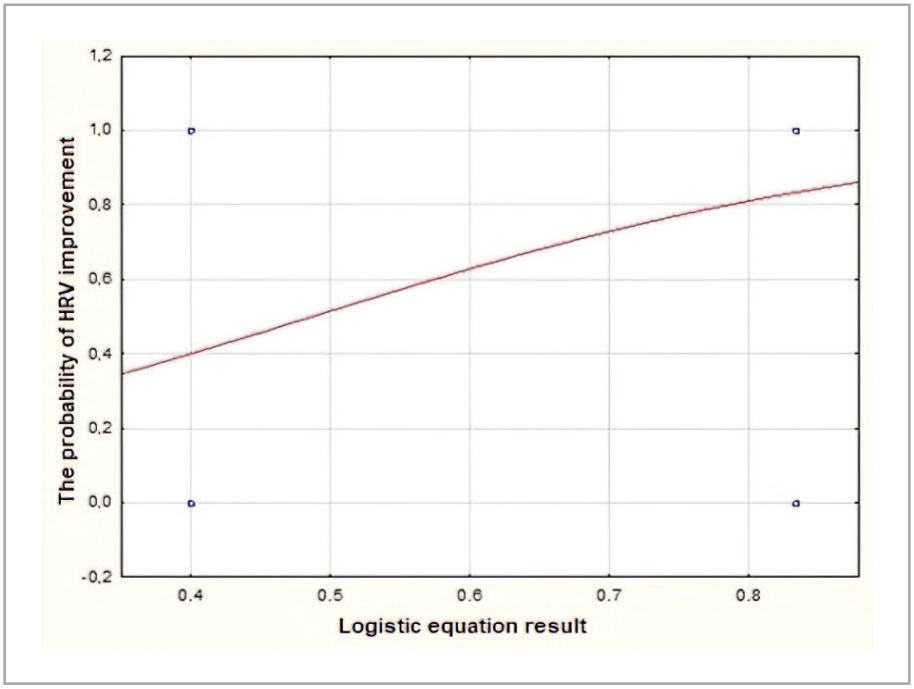

Figure 2: Dependence of the probability of HRV improvement in T2DM on the outcome calculated by the logistic equation.

glucose-lowering therapy, the patient showed an increase in SDNN, RMSSD, PNN50, TP, VLF, HF, and LF and a decrease in the LF/HF ratio.

Example 2:

Patient B, 46 years old, has had T2DM for 3 years. Glucose-lowering therapy: metformin + Sitagliptin. No hypoglycemia was detected at the first visit. At baseline, HbA1c was 8.5%. 6 months after the modification of the glucose-lowering therapy, HbA1c was 7.9%, and no hypoglycemic episodes were recorded. Substituting the data on the absence of hypoglycemia at the first visit into the above logistic equation (2) gives the PI for this patient:

$$PI = \exp(-0.406 + 2.015 \times 0) / [1 + \exp(-0.406 + 2.015 \times 0)] = 0.4.$$

The PI of patient B is therefore defined as the absence of a positive result, i.e., no increase in HRV. Six months after modification of glucose-lowering therapy, a decrease in SDNN, RMSSD, and PNN50 was obtained; TP and VLF did not change, while HF decreased, and LF and the LF/HF ratio increased. The results indicate a decreased HRV and increased sympathetic influences on cardiac activity compared to the first examination.

The logistic regression equation developed in this study enables the prediction of alterations in cardiac autonomic support in T2DM patients using a limited number of glycemic control parameters.

Conclusions

The study demonstrated that improving glycemic control in patients with type 2 diabetes mellitus was associated with an increase in heart rate variability.

The findings revealed that patients with type 2 diabetes mellitus who modified their glucose-lowering therapy exhibited a significant reduction in glycosylated hemoglobin levels, time above range, time below range, glycemic variability, and the frequency of hypoglycemic episodes. Conversely, an increase in time range was observed.

A mathematical model was developed for predicting heart rate variability in individuals with type 2 diabetes. It exhibited a sensitivity of 60.0% and a specificity of 83.33%. The area under the curve was 0.717 (p=0.001). It was determined that the sole predictor of heart rate variability growth is the presence of hypoglycemia prior to modification of glucose-lowering therapy.

Conflict of interest

The authors declare no conflict of interest.

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