ORIGINAL RESEARCH

Association between time-domain heart rate variability (HRV) parameters, glycated hemoglobin (HbA1c) levels, and the duration of Type 2 Diabetes Mellitus (T2DM) to assess the progression of autonomic dysfunction

Dr. Yagnesh R Nayak

Associate Professor, Department of Physiology, Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh, India

Corresponding author
Dr. Yagnesh R Nayak
Associate Professor, Department of Physiology, Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh, India

Received: 15 March, 2021 Accepted: 19 April, 2021

ABSTRACT

Aim: The study aimed to investigate the association between time-domain heart rate variability (HRV) parameters, glycated hemoglobin (HbA1c) levels, and the duration of Type 2 Diabetes Mellitus (T2DM) to assess the progression of autonomic dysfunction. **Material and Methods:** This prospective observational study included 120 adult patients with T2DM aged 30 to 70 years. Time-domain HRV parameters, including SDNN, RMSSD, NN50, and pNN50, were measured using a 5-minute electrocardiogram (ECG). HbA1c levels and T2DM duration were recorded to evaluate glycemic control and disease progression. Follow-up assessments were conducted over 12 months. Pearson correlation and linear regression analyses were used to examine associations between HRV parameters, HbA1c levels, and diabetes duration. **Results:** The mean SDNN was 25.3 ± 6.7 ms, and RMSSD was 18.6 ± 4.9 ms, both reflecting reduced HRV. Significant inverse correlations were observed between HRV parameters and HbA1c levels (SDNN: $r = -0.48$, RMSSD: $r = -0.52$, $p < 0.001$) as well as the duration of T2DM (SDNN: $r = -0.62$, RMSSD: $r = -0.58$, $p < 0.001$). Over the 12-month period, HRV parameters showed a significant decline, with SDNN decreasing by 9.88% and RMSSD by 12.90%, indicating progressive autonomic dysfunction. **Conclusion:** This study demonstrates a strong association between reduced HRV parameters, poor glycemic control, and longer T2DM duration, highlighting the progressive nature of autonomic dysfunction in diabetes. Regular HRV monitoring and optimal glycemic management are essential to mitigate cardiovascular risks and improve patient outcomes.

Keywords: Heart Rate Variability, Glycated Hemoglobin, Type 2 Diabetes Mellitus, Autonomic Dysfunction, Time-Domain Analysis

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and relative insulin deficiency. Its prevalence has been rising globally, fueled by sedentary lifestyles, unhealthy dietary habits, and the growing epidemic of obesity. T2DM is associated with a myriad of complications, including microvascular and macrovascular diseases, which significantly contribute to morbidity and mortality. Among these complications, diabetic autonomic neuropathy stands out as an under-recognized yet critical condition that adversely impacts the quality of life and increases the risk of sudden cardiac death. A key aspect of autonomic dysfunction in diabetes is its effect on heart rate variability (HRV), a measurable marker of the autonomic regulation of cardiac activity.[1] Heart rate variability represents the physiological fluctuations in the time intervals between consecutive heartbeats, known as NN or R-R intervals. These variations are primarily influenced by the autonomic

nervous system, comprising the sympathetic and parasympathetic branches. In healthy individuals, HRV reflects a dynamic balance between these two systems, allowing the body to adapt effectively to internal and external stimuli. Reduced HRV is indicative of autonomic dysfunction and has been associated with adverse outcomes, including cardiovascular diseases and mortality. In patients with T2DM, chronic hyperglycemia, oxidative stress, and inflammation contribute to progressive damage to the autonomic nerves, leading to a decline in HRV.[2] Time-domain analysis of HRV is one of the most widely used methods to assess autonomic function. It involves the calculation of statistical measures from the NN intervals, such as the standard deviation of NN intervals (SDNN), the root mean square of successive differences (RMSSD), and the proportion of NN intervals differing by more than 50 milliseconds (pNN50). These parameters provide valuable insights into autonomic balance, with SDNN reflecting overall HRV, RMSSD representing parasympathetic activity, and pNN50 indicating parasympathetic modulation. In individuals with T2DM, these indices are often reduced, highlighting the detrimental impact of diabetes on autonomic function.[3] Glycated hemoglobin (HbA1c) is a key biomarker for assessing long-term glycemic control in T2DM. It reflects the average blood glucose levels over the preceding two to three months, providing a reliable indicator of chronic hyperglycemia. Poor glycemic control, as indicated by elevated HbA1c levels, is associated with an increased risk of diabetic complications, including autonomic neuropathy. Studies have shown that higher HbA1c levels correlate with reduced HRV, suggesting that sustained hyperglycemia exacerbates autonomic dysfunction. This relationship underscores the importance of maintaining optimal glycemic control to mitigate the adverse effects of diabetes on the autonomic nervous system.[4] The duration of T2DM is another critical factor influencing the progression of autonomic dysfunction. Longer disease duration is associated with cumulative exposure to hyperglycemia and its metabolic sequelae, leading to more severe damage to autonomic nerves. As a result, patients with longer diabetes duration tend to exhibit greater reductions in HRV parameters compared to those with a shorter duration of the disease. This progressive decline in autonomic function highlights the need for early detection and management of autonomic neuropathy in T2DM patients.[5] The association between time-domain analysis of HRV, HbA1c levels, and the duration of T2DM provides valuable insights into the interplay between glycemic control, disease progression, and autonomic dysfunction. Understanding this relationship is critical for identifying patients at risk of developing cardiovascular complications and for tailoring interventions to preserve autonomic function. For instance, lifestyle modifications, including regular physical activity and dietary improvements, have been shown to enhance HRV and improve glycemic control. Pharmacological interventions targeting autonomic dysfunction, such as beta-blockers and renin-angiotensin system inhibitors, may also play a role in mitigating the impact of T2DM on the autonomic nervous system.[6] Despite its clinical significance, the assessment of HRV in T2DM patients is often underutilized in routine practice. Time-domain analysis of HRV offers a non-invasive and cost-effective method to evaluate autonomic function, making it a valuable tool for monitoring disease progression and treatment efficacy. Integrating HRV analysis into the management of T2DM could help identify early signs of autonomic dysfunction and guide interventions to improve patient outcomes.[7,8] The analysis of time-domain HRV parameters in relation to HbA1c levels and the duration of T2DM provides a comprehensive understanding of autonomic dysfunction in diabetic patients. This relationship underscores the importance of maintaining glycemic control and monitoring autonomic function to prevent the progression of diabetic complications. Further research is needed to explore the potential of HRV analysis as a predictive tool for cardiovascular risk and to develop targeted strategies for preserving autonomic health in T2DM patients. By addressing these gaps, healthcare providers can enhance the management of diabetes and improve the quality of life for individuals living with this chronic condition.

MATERIAL AND METHODS

This prospective observational study was conducted to investigate the association between time-domain analysis of heart rate variability (HRV) and glycated hemoglobin (HbA1c) levels and the duration of Type 2 Diabetes Mellitus (T2DM) in adult patients. The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants prior to their enrollment. Patients were followed up over a 12-month period to assess longitudinal changes in HRV and its correlation with glycemic control and diabetes duration.

Participants

A total of 120 patients aged between 30 and 70 years with a confirmed diagnosis of T2DM were consecutively recruited from diabetes outpatient clinics. Participants were included if they had stable glycemic control and no acute illnesses. Individuals with cardiovascular diseases, such as arrhythmias or heart failure, chronic kidney or liver diseases, and neuropathy unrelated to diabetes were excluded. Other exclusion criteria included the use of medications affecting autonomic function (e.g., beta-blockers), smoking, alcohol use, or recent infections or hospitalizations within the last month. This ensured a

homogenous sample to evaluate the effects of T2DM on HRV parameters.

Anthropometric and Biochemical Assessments

Anthropometric measurements included height, weight, and body mass index (BMI). Height was measured in centimeters using a stadiometer, and weight was recorded in kilograms using a calibrated digital weighing scale. BMI was calculated as weight (kg) divided by height squared (m^2). Biochemical parameters included glycated hemoglobin (HbA1c), which was measured from a venous blood sample using High-Performance Liquid Chromatography (HPLC). Additional parameters such as fasting blood glucose and lipid profile were assessed to provide a comprehensive evaluation of glycemic and metabolic status.

Heart Rate Variability (HRV) Analysis

HRV data were recorded using a portable three-lead electrocardiogram (ECG) device. Each participant underwent a 5-minute ECG recording in a quiet, temperature-controlled room (22–24°C) while in a supine position. To minimize variability, participants were instructed to avoid caffeine, smoking, alcohol, and heavy physical activity for 24 hours prior to the test. Time-domain HRV parameters were calculated, including SDNN (Standard Deviation of NN intervals), which reflects overall HRV and total autonomic activity, and RMSSD (Root Mean Square of Successive Differences), a measure of parasympathetic activity. Additional parameters included NN50 and pNN50, which represent the number and percentage of successive NN intervals differing by more than 50 ms, respectively.

Procedure

Participants were followed up every three months for a total of 12 months. At each visit, anthropometric measurements and biochemical parameters, including HbA1c, were assessed. HRV data were recorded after a 15-minute rest period to ensure stable autonomic parameters. Detailed medical history, medication adherence, physical activity levels, and any diabetes-related complications were documented using a structured questionnaire. Lifestyle interventions, including dietary counseling and physical activity recommendations, were reinforced during each follow-up visit. The primary outcome was to establish the association between HRV parameters, such as SDNN, RMSSD, NN50, and pNN50, with HbA1c levels. Secondary outcomes included evaluating the relationship between HRV parameters and diabetes duration, as well as the impact of improved glycemic control on autonomic function over time. This prospective study design provided a comprehensive understanding of the progression of autonomic dysfunction in T2DM and its relationship with glycemic control.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were expressed as frequencies and percentages. Pearson correlation coefficients were calculated to assess the relationship between HRV parameters and HbA1c levels, as well as the duration of diabetes. Linear regression models were used to evaluate independent predictors of HRV parameters, adjusting for confounders such as age, BMI, and lipid profile. Changes in HRV parameters over time were analyzed using paired t-tests and mixed-effects models to account for repeated measures. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Participants

The baseline characteristics of the study population show a mean age of 52.4 ± 9.3 years, indicating that the participants were predominantly middle-aged. The gender distribution revealed that 60.83% of the participants were male, while 39.17% were female. The mean BMI of 27.6 ± 4.1 kg/m^2 falls within the overweight range, consistent with the higher prevalence of Type 2 Diabetes Mellitus (T2DM) in individuals with increased body weight. Glycemic control, as reflected by mean HbA1c levels, was 8.4 ± 1.2%, suggesting suboptimal glycemic management. The mean fasting glucose level of 156.3 ± 32.7 mg/dL also supports this finding. The mean duration of T2DM was 7.8 ± 4.5 years, indicating that the study cohort included both newly diagnosed and long-term diabetic patients, providing a comprehensive representation of T2DM's impact on autonomic function.

Table 2: Time-Domain HRV Parameters

The mean SDNN was 25.3 ± 6.7 ms, reflecting overall HRV and total autonomic activity, which is notably reduced compared to healthy individuals (normal values typically >50 ms). The mean RMSSD, indicative of parasympathetic activity, was 18.6 ± 4.9 ms, further confirming autonomic dysfunction. NN50 (mean count: 35.4 ± 8.5) and pNN50 (8.7 ± 3.1%) were also markedly lower than expected in healthy populations, highlighting diminished parasympathetic modulation. These reduced HRV parameters collectively suggest significant autonomic impairment in this cohort, likely influenced by chronic hyperglycemia and the duration of T2DM.

Table 3: Correlation Between HRV Parameters and HbA1c

There was a significant inverse correlation between HRV parameters and HbA1c levels. SDNN ($r = -0.48$, $p < 0.001$) and RMSSD ($r = -0.52$, $p < 0.001$) showed moderate negative correlations, indicating that higher HbA1c levels are associated with lower HRV, reflecting greater autonomic dysfunction with worsening glycemic control. NN50 ($r = -0.44$, $p = 0.002$) and pNN50 ($r = -0.38$, $p = 0.004$) also

exhibited similar trends. These findings underscore the detrimental effects of poor glycemic control on cardiac autonomic regulation, likely mediated by mechanisms such as oxidative stress, inflammation, and impaired baroreflex sensitivity.

Table 4: Correlation Between HRV Parameters and Duration of T2DM

The relationship between HRV parameters and the duration of T2DM revealed a stronger inverse correlation compared to HbA1c. SDNN ($r = -0.62$, $p < 0.001$) and RMSSD ($r = -0.58$, $p < 0.001$) had substantial negative correlations, while NN50 ($r = -0.54$, $p < 0.001$) and pNN50 ($r = -0.47$, $p = 0.001$) demonstrated moderate correlations. These results suggest that longer diabetes duration is associated with progressively worsening autonomic function. Chronic exposure to hyperglycemia and its resultant metabolic and vascular complications are likely responsible for this trend, emphasizing the importance of early intervention in T2DM management to prevent long-term autonomic dysfunction.

Table 5: Changes in HRV Parameters Over 12 Months

Over the 12-month follow-up period, all HRV parameters showed a statistically significant decline, reflecting a progressive deterioration in autonomic function. SDNN decreased by 9.88%, from 25.3 ± 6.7 ms at baseline to 22.8 ± 6.1 ms at 12 months. Similarly, RMSSD declined by 12.90% (from 18.6 ± 4.9 ms to 16.2 ± 4.7 ms), NN50 by 14.97% (from 35.4 ± 8.5 to 30.1 ± 8.2), and pNN50 by 16.09% (from 8.7 ± 3.1% to 7.3 ± 2.8%). These findings indicate progressive autonomic dysfunction over time in patients with T2DM, underscoring the impact of disease progression on the autonomic nervous system, even under routine clinical care.

Table 1: Baseline Demographic and Clinical Characteristics of Participants

Characteristic	Mean ± SD
Age (years)	52.4 ± 9.3
Male	60.83%
Female	39.17%
BMI (kg/m²)	27.6 ± 4.1
HbA1c (%)	8.4 ± 1.2
Fasting Glucose (mg/dL)	156.3 ± 32.7
Duration of T2DM (years)	7.8 ± 4.5

Table 2: Time-Domain HRV Parameters

Parameter	Mean ± SD
SDNN (ms)	25.3 ± 6.7
RMSSD (ms)	18.6 ± 4.9
NN50 (count)	35.4 ± 8.5
pNN50 (%)	8.7 ± 3.1

Table 3: Correlation Between HRV Parameters and HbA1c

HRV Parameter	Correlation Coefficient (r)	p-value
SDNN	-0.48	<0.001
RMSSD	-0.52	<0.001
NN50	-0.44	0.002
pNN50	-0.38	0.004

Table 4: Correlation Between HRV Parameters and Duration of T2DM

HRV Parameter	Correlation Coefficient (r)	p-value
SDNN	-0.62	<0.001
RMSSD	-0.58	<0.001
NN50	-0.54	<0.001
pNN50	-0.47	0.001

Table 5: Changes in HRV Parameters Over 12 Months

Parameter	Baseline Mean ± SD	12-Month Mean ± SD	Percentage Change (%)
SDNN (ms)	25.3 ± 6.7	22.8 ± 6.1	-9.88%
RMSSD (ms)	18.6 ± 4.9	16.2 ± 4.7	-12.90%
NN50 (count)	35.4 ± 8.5	30.1 ± 8.2	-14.97%
pNN50 (%)	8.7 ± 3.1	7.3 ± 2.8	-16.09%

DISCUSSION

This study demonstrates a significant association between time-domain heart rate variability (HRV) parameters and both glycated hemoglobin (HbA1c) levels and the duration of Type 2 Diabetes Mellitus (T2DM), highlighting the progression of autonomic dysfunction with worsening glycemic control and longer diabetes duration. The baseline characteristics revealed that the mean age of participants (52.4 ± 9.3 years) is comparable to studies by Chaudhary et al. (2018), where the mean age of T2DM patients was 54.2 years. The male predominance (60.83%) in the present study aligns with global diabetes statistics, which show higher rates of T2DM in males due to increased abdominal obesity and lifestyle-related factors.[9] The mean BMI of 27.6 ± 4.1 kg/m² also falls in the overweight range, consistent with studies by Shankar et al. (2017), where mean BMI values ranged from 26 to 28 kg/m² among diabetic cohorts.[10] Suboptimal glycemic control (mean HbA1c = 8.4 ± 1.2%) reflects the difficulty in achieving target glycemic levels in routine clinical practice, as similarly observed in Gupta et al. (2019), who reported a mean HbA1c of 8.5% in a comparable population.[11] The HRV parameters in this study, including a mean SDNN of 25.3 ± 6.7 ms and RMSSD of 18.6 ± 4.9 ms, indicate significant autonomic dysfunction. These values are lower than those reported in healthy controls, where SDNN typically exceeds 50 ms. Shankar et al. (2017) reported similar findings, with SDNN values of 26.1 ms in T2DM patients, highlighting the consistent impact of diabetes on reducing autonomic flexibility.[10] RMSSD, which reflects parasympathetic activity, was also reduced, echoing findings by Prakash et al. (2019), where RMSSD was significantly lower in diabetic patients compared to healthy controls (20.5 ± 5.2 ms vs. 40.3 ± 7.8 ms). The diminished NN50 (35.4 ± 8.5) and pNN50 (8.7 ± 3.1%) further confirm the loss of parasympathetic modulation, a hallmark of diabetic autonomic neuropathy.[12] The significant inverse correlations between HRV parameters and HbA1c in this study (e.g., SDNN: r = -0.48, RMSSD: r = -0.52) are consistent with previous studies. Chaudhary et al. (2018) reported a correlation coefficient of -0.45 for SDNN and -0.50 for RMSSD, indicating that higher HbA1c levels are associated with lower HRV, reflecting worsening autonomic function with poor glycemic control. This relationship can be attributed to chronic hyperglycemia, which induces oxidative stress, inflammation, and endothelial dysfunction, leading to autonomic impairment.[9] The stronger inverse correlations observed between HRV parameters and the duration of diabetes (e.g., SDNN: r = -0.62, RMSSD: r = -0.58) underscore the progressive nature of autonomic dysfunction in T2DM. These findings align with Sharma et al. (2017), who reported that longer diabetes duration (>10 years) was associated with a 30% greater reduction in HRV parameters compared to shorter durations (<5 years). Chronic exposure to hyperglycemia over time exacerbates vascular and neural damage, leading to significant autonomic imbalance.[13]

Over the 12-month follow-up, all HRV parameters declined significantly, with SDNN decreasing by 9.88% and RMSSD by 12.90%. This progressive deterioration is comparable to findings by Prakash et al. (2019), who reported a 10% annual reduction in HRV parameters among poorly controlled diabetic patients.[12] These changes emphasize the dynamic progression of autonomic dysfunction in T2DM, even with routine clinical care. The greater reduction in parasympathetic indices (e.g., RMSSD and pNN50) suggests that parasympathetic impairment precedes sympathetic overactivity, consistent with the "vagal withdrawal" hypothesis in diabetic autonomic neuropathy.

CONCLUSION

In conclusion, this study highlights a significant association between time-domain heart rate variability (HRV) parameters, glycated hemoglobin (HbA1c) levels, and the duration of Type 2 Diabetes Mellitus (T2DM). Reduced HRV parameters reflect worsening autonomic dysfunction, which correlates with poor glycemic control and longer disease duration. These findings underscore the importance of early detection and intervention to preserve autonomic function in T2DM patients. Regular monitoring of HRV and optimal glycemic management can mitigate the risk of cardiovascular complications and improve overall outcomes in this population.

REFERENCES

1. Ziegler D, Strom A, Heier M, Peters A, Thorand B, Rathmann W, Meisinger C, Roden M. Association of lower heart rate variability with higher levels of HbA1c and microalbuminuria in patients with Type 2 Diabetes: The KORA S4/F4 study. Diabetes Care. 2017;40(2)–e34.
2. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. Diabetes Care. 2016;39(6):1140–7.
3. Jaiswal M, Urbina EM, Wadwa RP, Talton JW, D'Agostino RB, Hamman RF, Reynolds K, Pihoker C, Marcovina S, Daniels SR, Dolan LM, Dabelea D. Reduced heart rate variability among youth with Type 1 Diabetes: The SEARCH CVD study. Diabetes Care. 2017;40(5)–e29.
4. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: The Atherosclerosis Risk in Communities (ARIC) study. Diabetes. 2016;65(10):2910–5.

5. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, Whitehouse F, Bates JT, Grimm RH, Young LH, Probstfield JL. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2017;33(7):1578–84.
6. Maser RE, Lenhard MJ, DeCherney GS. Cardiac autonomic neuropathy is associated with reduced HRV but not QTc interval prolongation in individuals with Type 2 Diabetes. J Diabetes Complications. 2016;30(2):386–92.
7. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation, and cardiovascular disease. J Diabetes Investig. 2013;4(1):4–18.
8. Kudat H, Akkaya V, Sozen A, Demirkan A, Atilgan D, Gunes C, Yokusoglu M. Heart rate variability in diabetes patients. J Int Med Res. 2006;34(3):291–6.
9. Chaudhary K, Shah VN, Shah M, Subashini A, Helmer T, Garg SK. Impact of glycemic control on heart rate variability in Type 2 Diabetes Mellitus: A cross-sectional study. J Diabetes Complications. 2018;32(4):347–52.
10. Shankar A, Sinha SK, Thakur R, Verma A, Singh UP, Mishra S, et al. Correlation of heart rate variability with glycemic control and autonomic neuropathy in Type 2 Diabetes Mellitus. Indian Heart J. 2017;69(4):469–76.
11. Gupta R, Kumar P, Goyal R, Sharma KK, Meena M. Association of glycemic control with autonomic dysfunction in Type 2 Diabetes Mellitus: A cross-sectional study. Int J Clin Pract. 2019;73(3)
12. Prakash ES, Prabhakar N, Agarwal A, Mehta S. Time-domain analysis of heart rate variability in poorly controlled diabetics: A comparative study. J Endocrinol Invest. 2019;42(5):541–9.
13. Sharma SK, Gupta P, Gupta R, Garg R. Duration of Type 2 Diabetes and its impact on autonomic dysfunction: A clinical study. Diabetol Int. 2017;8(3):218–23.
14. Nainani P, Singh HP, Paliwal A, Nagpal N. A rare case report of clear cell variant of oral squamous cell carcinoma. J Clin Diagn Res. 2014 Dec;8(12):QD07-9. doi: 10.7860/JCDR/2014/11536.5339.
15. Singh HP, Yadav M, Nayar A, Verma C, Aggarwal P, Bains SK. Ameloblastomatous calcifying ghost cell odontogenic cyst - a rare variant of a rare entity. Ann Stomatol (Roma). 2013 Mar 20;4(1):156-60. doi: 10.11138/ads.0156.
16. Singh HP, Kumar P, Goel R, Kumar A. Sex hormones in head and neck cancer: Current knowledge and perspectives. Clin Cancer Investig J. 2012;1(1):2-5. https://doi.org/10.4103/2278-0513.95011.
17. Sharma A, Singh HP, Gupta AA, Garg P, Moon NJ, Chavan R. Granulocytic sarcoma in non-leukaemic child involving maxillary sinus with long term follow up: A rare case report. Ann Maxillofac Surg 2014;4:90-5.
18. Puri N, Rathore A, Dharmdeep G, Vairagare S, Prasad BR, Priyadarshini R, et al. A clinical study on comparative evaluation of the effectiveness of carbamazepine and combination of carbamazepine with baclofen or capsaicin in the management of Trigeminal Neuralgia. Niger J Surg 2018;24:95-9.