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The relationship between Cardiac Autonomic Dysfunction and Glycemic Variability in Pediatric Patients with Type 1 Diabetes Mellitus

Münevver Yılmaz[1]*, Dolunay Gürses[1], Selda Ayça Altıncık[2], Bayram Özhan[2]

1 Department of Pediatric Cardiology, Faculty of Medicine, Pamukkale University Denizli, TR
2 Department of Pediatric Endocrinology, Faculty of Medicine, Pamukkale University Denizli, TR

*** Corresponding Author:** Münevver Yılmaz **E-mail:** munevveryl@yahoo.com

ABSTRACT

Objective: Objective: Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of cardiovascular autonomic control in patients with diabetes mellitus (DM) after excluding other causes. This study aims to investigate the relationship between glycemic variability and CAN in pediatric patients with type 1 DM

Material and Methods: The study population consisted of children aged 8-18 who were being followed up with the diagnosis of type 1 DM. The diagnosis of CAN was made based on the heart rate variability indices and the results of the cardiovascular reflex tests..

Results: The study included 21 pediatric patients with type 1 diabetes mellitus (DM), consisting of 6 males and 15 females, with a median age of 13.94 years. Among them, 5 (23.8%) had early involvement, and 4 (19%) had definitive cardiovascular autonomic neuropathy (CAN). Patients with definitive CAN were significantly older and had a longer disease duration than those without CAN ($p<0.05$). Additionally, patients with definitive CAN had significantly higher hemoglobin A1c (HbA1c) levels ($p<0.05$). The time in the target blood glucose range (TIR) was significantly lower, while the time above the target blood glucose range (TAR) was significantly higher in patients with definitive CAN than in other patients ($p<0.05$). The standard deviation (SD) was also higher in patients with definitive CAN, but not significantly so ($p>0.05$).

Conclusion: The study's findings indicated that TIR, which is one of the glycemic variability parameters, was significantly lower and TAR was considerably higher in children with definitive CAN, and SD was higher, albeit not significantly, in children with definitive CAN. Nevertheless, large-scale, prospective cohort studies are needed to fully elucidate the relationship between CAN and glycemic variability in pediatric type 1 DM patients.

Keywords: Cardiovascular autonomic neuropathy, Glycemic variability, Type 1 diabetes mellitus, Children

INTRODUCTION

Cardiovascular autonomic neuropathy (CAN) is the most serious yet, at the same time, the most overlooked complication of diabetes mellitus (DM). CAN is defined as the impairment of cardiovascular autonomic control in patients with DM after excluding other causes. DM patients with CAN can have tachycardia at rest and decreased exercise tolerance (1-3). In adult diabetic patients, CAN may result in severe cardiac morbidities, including life-threatening arrhythmias, silent myocardial ischemia, and sudden cardiac death (4,5). In addition to the cardiovascular system, autonomic neuropathy in diabetes also impairs various bodily functions, including thermoregulation, pupillomotor function, respiratory, gastrointestinal, and urogenital systems. This multisystem involvement can have a significant impact on the quality of life of affected individuals, contributing to reduced physical and psychological well-being (2,6).

The diagnosis of CAN is commonly based on the heart rate variability (HRV) indices and the results of the cardiovascular reflex tests. Cardiovascular reflex tests evaluate changes in heart rate and blood pressure against different stimuli. It has also been reported that HRV helped detect CAN at an early stage (3,6,7).

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The prevalence of CAN in adult DM patients reported in the literature varies greatly. In parallel, the prevalence of CAN in adult type 1 DM patients has been reported between 2% and 91% (3-5,8). Slightly lower CAN prevalence was reported in children and adolescents with type 1 DM. Additionally, the studies in which CAN diagnosis was made based on the results of cardiovascular reflex tests reported the prevalence of CAN between 4% and 75%, and the studies in which CAN diagnosis was made based on HRV indices reported the prevalence of CAN between 8% and 50%. The prevalence of symptomatic CAN in pediatric type 1 DM patients remains unknown (6,8,9).

The pathogenesis of CAN has yet to be elucidated. However, hyperglycemia has been implicated in some studies, which is the reason CAN therapy is based on achieving reasonable metabolic control (2,3,6,9). Hemoglobin A1c (HbA1c) is an indicator of metabolic control in patients with diabetes. Nevertheless, it does not reflect the fluctuations in blood sugar levels, i.e., the glycemic variability. Emerging evidence suggests that increased glycemic variability, independent of HbA1c, may play an essential role in the development of micro- and macrovascular complications of diabetes, including CAN (10-13). Glycemic variability encompasses different parameters, such as the fluctuations observed in glucose levels during the day and during the same time frame on different days, increases observed in glucose levels during the day, and hypoglycemic periods (10,11).

While some studies on the relationship between glycemic variability and CAN in adults found a significant association between glycemic variability and CAN, others did not (11-16). Nonetheless, to the best of our knowledge, no studies have yet investigated the association between glycemic variability and cardiovascular autonomic neuropathy (CAN) specifically in the pediatric population.. In this context, the objective of this study is to investigate the relationship between glycemic variability and CAN in pediatric patients with type 1 DM.

MATERIAL and METHODs

The study population consisted of children aged 8-18 years who were being followed up with the diagnosis of type 1 DM in Pamukkale University Medical Faculty Hospital. Patients with advanced (grade III or grade IV) retinopathy, underlying chronic neurological or pulmonary disease, heart disease and/or conduction disorder, and an additional disease that may potentially cause problems during the performance of cardiovascular reflex test maneuvers were excluded from the study. In addition, those who stopped using the sensors for any reason or whose continuous glucose monitoring system (CGMS) data were below 80% for technical reasons were excluded from the study due to insufficient data. All patients were subjected to detailed physical examinations. Patients' anamneses were taken, heights and weights were measured, and body mass index (BMI) values were calculated. Patients' HbA1c levels measured in the last year were obtained from their medical records.

The patients used the continuous glucose monitoring system (CGMS), a subcutaneous glucose sensor (Medtronic-IPRO2), for seven days. Among the glucose indices calculated by CGMS, time in the target blood glucose range (70-180 mg/dl) (TIR), time above the target blood glucose range (>180 mg/dl) (TAR), time below the target blood glucose range (<70 mg/dl) (TBR), coefficient of variance (CV) and standard deviation (SD) indices were collected as the research data. The coefficient of variation (CV%) is a statistical measure of spread that reflects glycemic variability. CV% is calculated by dividing the standard deviation by the mean value followed by multiplying the quotient by 100. In clinical practice, CV values of ≤ 36% are targeted (10).

Five cardiovascular reflex tests were performed on all patients. Resting electrocardiographic (ECG) recordings of the patients were taken while they were lying on the bed in the supine position in a quiet room using an ECG device equipped with a digital monitor. To obtain blood pressure measurements, both arms of the patient were assessed after a 5-minute rest period in a quiet environment, both at baseline and during the specified maneuver. Patients' blood pressure was also measured within the scope of the blood pressure response to standing (orthostatic hypotension, OH) test after 3 minutes of standing, following resting in a comfortable supine position for 5 minutes. A decrease of ≥ 20 mmHg in systolic blood pressure and ≥ 10 mmHg in diastolic blood pressure was defined as OH. Additionally, in the blood pressure response to the hand grip (isometric exercise) test, a ≥ 16 mmHg increase in the blood pressure was defined as normal, 11–15 mmHg as borderline, and ≤ 10 mmHg as pathological. Heart rate response to standing up (30/15 ratio), heart rate response to deep breathing and heart rate response to the Valsalva maneuver (Valsalva ratio) tests were performed. The results were evaluated according to the age group of the patients (1,17).

For HRV analysis, 24-hour Holter ECG recordings of all patients were analyzed. Holter ECG recordings were manually reviewed to exclude artifacts, and those with 85% or more normal beats were included in the study.HRV parameters were determined automatically by the Holter ECG data processing software based on the normal-to-normal (NN) R intervals in beats created by the Holter ECG data processing software.HRV time measures, SDNN (standard deviation of all NN intervals over a 24-hour period in msec), PNN50 (ratio of the number of consecutive pairs of NN intervals differing by more than 50 msec (NN50) to the total number of NN intervals), and RMSSD (square root of the mean of the sum of the squares of the differences between consecutive NN intervals in msec over the 24-hour recording) parameters were measured from the existing Holter ECG records of all patients using the time-dependent automatic analysis method. We considered HRV time measure values that fell two standard deviations (SD) below the normal range for the corresponding age group as indicative of reduced HRV (18,19).

Measurement of an abnormal heart rate in a cardiovascular reflex test or a decrease in HRV and two borderline heart rate measurements in the cardiovascular reflex tests were deemed to indicate "early involvement", measurement of an abnormal heart rate in two or more cardiovascular reflex tests was deemed to indicate "definitive diagnosis", and the presence of orthostatic hypotension was deemed to indicate "severe involvement" (1,20). The non-interventional clinical research ethics committee approved the study protocol prior to the conduct of the study.

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Statistical analyses of the collected data were carried out using SPSS Statistics 18.0 (Predictive Analytics Software Statistics for Windows, Version 18.0, SPSS Inc., Chicago, IL, US, 2009) software package. Continuous variables were expressed as median (interquartile range) values, and categorical variables were expressed as numbers and percentage values. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the normal distribution characteristics of the continuous variables. Mann-Whitney U and Kruskal-Wallis analysis of variance (post hoc) tests were used in the comparisons of non-parametric independent data. The probability (p) statistics of < 0.05 indicated statistical significance.

RESULTs

The study sample consisted of 21 children who were followed up with a diagnosis of type 1 DM, were able to complete cardiovascular reflex tests, and had complete CGMS data. The median age of the sample consisting of 6 males and 15 females was 13.94 (10.49-16.87) years. The median height, weight, and BMI of the sample were 156 (144-167.25) cm, 52 (35.75-64.95) kg, and 18.8 (17.365-24.87) kg/m^2. The median duration of type 1 DM was 3.5 (2.5-6) (min. 2, max. 8) years. The results of HbA1c and glycemic variability measurements, cardiovascular reflex tests, and heart rate variability measurements are shown in **Table 1**.

Based on the results of the cardiovascular reflex tests and heart rate variability measurements, it was determined that 42.8% of the patients had CAN, of whom 5 (23.8%) had early involvement, 4 (19%) had definitive CAN, and none (0%) had severe involvement. CAN was not diagnosed in any patient at an age earlier than ten years and before two years had passed since the diagnosis of type 1 DM. There was no CAN finding in 12 (57.2%) patients. Heart rate response to standing up (30/15 ratio) test result was pathological in all four patients with definitive CAN. The blood pressure response test to the hand grip (isometric exercise) test result was pathological in 3 patients, the heart rate response to the Valsalva maneuver (Valsalva ratio) in 2 patients, and the heart rate response to deep breathing in 1 patient. The results of the heart rate response to the standing up (30/15 ratio) test and blood pressure response test to the hand grip (isometric exercise) test were pathological in one patient, each with early involvement. There was a reduction in HRV in all nine patients with the early participation, and definitive CAN.

Comparison of the demographic characteristics between pediatric type 1 DM patients with early involvement and definitive CAN and without CAN did not reveal any significant difference in terms of gender (p:0.115) and standard deviation scores (SDS) of body weight, height, and BMI (p>0.05), (Table 2). Pediatric type 1 DM patients with definitive CAN were significantly older than those without CAN (p:0.009).

Duration of type 1 DM was significantly longer in children with definitive CAN than in both children without CAN and children with early involvement (p:0.022 and p:0.011, respectively). The most recent HbA1c level was significantly higher in pediatric type 1 DM patients with definitive CAN than in those with early involvement (p:0.014). Additionally, HbA1c levels in the last year were significantly higher in pediatric type 1 DM patients with definitive CAN than in both pediatric type 1 DM patients without CAN and with early involvement (p:0.017 and p:0.005, respectively) (**Table 2**).

Comparison of glucose variability parameters between the groups revealed significantly higher TIR and significantly lower TAR values in pediatric type 1 DM patients with definitive CAN (p:0.044 and p:0.026, respectively). SD was found as 81 (57.5-85), 68.5 (50.5-73.25), and 61 (47-73.5) in pediatric type 1 DM patients with definitive CAN, without CAN, and with early involvement, respectively. Accordingly, the SD in pediatric type 1 DM patients with definitive CAN was higher than in the other two groups, yet the difference was not statistically significant (p>0.05). There was no significant difference between the groups in other parameters (p>0.05).

When dividing the pediatric type 1 DM patients into two groups based on the presence or absence of CAN, we observed a male-to-female (M/F) ratio of 1:8 in the CAN group and 5:7 in the non-CAN group. However, there was no significant difference in gender distribution between the two groups (p:0.148). The age of pediatric type 1 DM patients with CAN was 17 (14.1-17.7) years versus 13 (9.7-14) years, significantly older than those without CAN (p:0.016). Duration of DM was 4 (3-6.25) years in patients with CAN versus 3 (2.1-5.8) years without CAN, but the difference was not significant (p:0.317). The most recent HbA1c levels and HbA1c levels in the last year; It was found in 8.5% (7.2-9.6), 8.56% (7.3-11.4) and 8.4% (7.8-9.4), 8.2% (7.8-9.1) patients with and without CAN, respectively (p:0.776 and p:0.915). In pediatric type 1 DM patients with CAN; TIR 52% (40-69), TAR 38% (27-57), TBR 1% (2-4.5), SD 64 (53-82.5), CV 38.3 (33.3-41) and in patients without CAN, TIR 62% (57.5-64), TAR 31.5% (26.5-39), TBR 3.5% (1.25-8.75), SD 68.5 (50.5-73.3), CV 41 (35.3-45.2) were found. TIR, TAR, TBR, SD, and CV were similar in pediatric type 1 DM patients with and without CAN (p:0.373, p:0.227, p:348, p:522, and 0.356, respectively).

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Table 1. Demographic, clinical and laboratory findings of the study group

Sex (male/female)	6/15
Age (years)	13.94 (8-17.89)
Weight SDS	0.61 (-2.35-1.75)
Height SDS	0.4 (-2.37-1.65)
Body mass index SDS	0.22 (-1.75-1.98)
Duration of illness (years)	3.5 (2-8)
HbA1c (%)	8.5 (6.8-15.1)
HbA1c (levels in the last year, %)	8.23 (7.03-14.8)
TIR (%)	61 (22-83)
TBR (%)	3 (0-13)
TAR (%)	34 (13-78)
SD	68 (38-86)
CV	39.02 (25,5-49.33)
Heart rate response to deep breathing (bpm)	40 (7-60)
30/15 ratio	1.3 (0,9-1.5)
Valsalva ratio	1.54 (1.04-2.08)
Blood pressure response to the hand grip (mmHg)	13 (5-20)
Blood pressure response to standing (mmHg)	5 (2-9)
SDNN	133 (60-219)
PNN50	20.5 (1-42)
RMSSD	45 (17-87)
Mean heart rate (bpm)	83.5 (62-102)
Maximum heart rate (bpm)	134.5 (108-150)
Minimum heart rate (bpm)	59.5 (48-85)

Since number of subjects are very small, data given median (min-max). HbA1c: Hemoglobin A1c SDS: Standard deviation scores TIR: Time in the target blood glucose range, TAR: Time above the target blood glucose range TBR: Time below the target blood glucose vange, SD: Standard deviation, CV: coefficient of variation, SDNN: Standard deviation of all NN intervals over a 24-hour period, PNN50: ratio of the number of consecutive pairs of NN intervals differing by more than 50 msec (NN50) to the total number of NN intervals RMSSD: Square root of the mean of the sum of the squares of the differences between consecutive N-N intervals in msec over the 24-hour recording.

Table 2. Distribution of demographic, clinical, and laboratory characteristics according to the presence and severity of cardiovascular autonomic neuropathy

	Without CAN n:12	Early involvement n:5	Definitive CAN n:4	p (I-II)	p (I-III)	p (II-III)
Sex (Male/Female)	5/7	0/5	1/3		0.115	
Age (years)	13.12 (9.7-13.95)	15.93 (11.3-17.7)	17.2 (16.2-17.9)	0.116	**0.009**	0.245
Weight SDS	0.27 (-.15-0.96)	1.28 (-0.04-1.42)	-0.03 (-0.76-1.47)	0.087	0.703	0.286
Height SDS	0.72 (-0.97-1.31)	0.04 (-0.4-0.44)	0.64 (-0.54-1.3)	0.955	0.625	0.706
Body mass index SDS	-0.08 (0.78-0.53)	1.19 (0.21-1.6)	-0.08 (-1.67-1.79)	0.071	0.931	0.166
Duration of illness (years)	3 (2.12-5.9)	3.5 (2.25-3.75)	6.5 (5.6-7.6)	0.4	**0.022**	**0.011**
HbA1c (%)	8.4 (7.75-9.4)	7.3 (6.95-8)	9.6 (9.1-13.7)	0.174	0.77	**0.014**
HbA1c (levels in the last year, %)	8.2 (7.8-9.14)	7.37 (7.15-8.1)	11.4 (8.7-14.5)	0.401	**0.017**	**0.005**
TIR (%)	62 (57.5-64)	64 (46.5-71.5)	45 (26.3-66.3)	0.749	**0.044**	0.127
TBR (%)	3.5 (1.25-8.75)	4 (1.5-6.5)	1 (1-3.3)	0.692	0.155	0.351
TAR (%)	31.5 (26.5-39)	34 (26-46)	56 (30.3-73.5)	0.732	**0.026**	0.086
SD	68.5 (50.5-73.25)	61 (47-73.5)	81 (57.5-85)	0.667	0.198	0.152
CV	40.98 (34.35-41.05)	39.1 (30.36-43.77)	38.3 (33.1-42.5)	0.295	0.578	0.717

CAN: Cardiovascular autonomic neuropathy, HbA1c: Hemoglobin A1c SDS: Standard deviation scores TIR: Time in the target blood glucose range, TAR: Time above the target blood glucose range TBR: Time below the target blood glucose vange, SD: Standard deviation, CV: coefficient of variation, SDNN: Standard deviation of all NN intervals over a 24-hour period, PNN50: ratio of the number of consecutive pairs of NN intervals differing by more than 50 msec (NN50) to the total number of NN intervals RMSSD: Square root of the mean of the sum of the squares of the differences between consecutive N-N intervals in msec over the 24-hour recording.

DISCUSSION

Diabetic autonomic neuropathy is among the least known complications of diabetes, despite its significant negative impact on survival and quality of life in individuals with diabetes. Subclinical CAN is common in children and adolescents with type 1 DM (1,15). This study was carried out to investigate the relationship between CAN and glycemic variability in 21 children aged 8-18 years who were followed up with the diagnosis of type 1 DM for 2 to 8 years. Of these patients, 5 (23.8%) had early involvement, and 4 (19%) had definitive CAN based on the results of the cardiovascular reflex tests and HRV measurements.

Comparisons between the groups created according to the presence and severity of CAN indicated that TIR, one of the metabolic control parameters, was significantly lower, whereas TAR, another metabolic control parameter, was significantly higher in pediatric type 1 DM patients with definitive CAN. SD was also higher, albeit not significantly, in pediatric type 1 DM patients with definitive CAN.

Cardiovascular reflex tests are considered the gold standard in diagnosing CAN since they are safe, non-invasive, and can be well standardized (3,8).

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HRV, used to assess cardiovascular autonomic function, can detect early changes in myocardial autonomic innervations and thus CAN at earlier stages (21). HRV measurements and cardiovascular reflex tests enable the evaluation of cardiovascular branches of the autonomic nervous system at rest and under stress conditions (10,11). Both methods have been utilized in this study.

The prevalence of CAN reported in the literature varies in children and adolescents with type 1 DM due to the differences between the tests used in diagnosing CAN. In a study evaluating 60 children with DM, 36.67% had abnormal cardiovascular reflex test results. Of these children, 54.55% had early involvement, 27.27% had definitive CAN, and 18.18% had severe CAN (1). Young et al. reported that 31% of the 79 children aged between 16 and 19 with type 1 DM had abnormal cardiac parasympathetic test results (22). In line with the literature, of the 21 pediatric type 1 DM patients, 5 (23.8%) had early involvement, and 4 (19%) had definitive CAN. In another study, Verrotti et al. found that 42.72% of the 110 children with type 1 DM had one or more abnormal cardiovascular autonomic test results. Of these children with one or more abnormal cardiovascular autonomic test results, 46.81% had early dysfunction, 38.3% had definitive dysfunction, and 14.9% had severe dysfunction. The same study concluded that the most sensitive method for detecting CAN was HRV and maximum/minimum 30:15 ratio measurements during the Valsalva maneuver (23). Similarly, in this study, the most common pathological results obtained from the heart rate response test were the Valsalva and 30/15 ratios.

The use of HRV in the early diagnosis of CAN has been a matter of debate in the literature. In a study including 1646 adolescents and young adults aged 18±4 years who had type 1 DM for 8±2 years, the prevalence of CAN, which was diagnosed based on the presence of three or more pathological HRV parameters, was found to be 12% (24). In a study that evaluated cardiac HRV in 50 asymptomatic type 1 DM patients for 24 hours, Chessa et al. found significant changes in RMSSD and PNN50 parameters (21). In a study that investigated autonomic modulation through HRV indices in children with type 1 DM, Kardelen et al. observed a decrease in HRV indices in both the time and frequency domains (25). Similarly, HRV was decreased in all type 1 DM patients with CAN included in this study.

The independent risk factors for the development of CAN include hyperglycemia/HbA1c, age, duration of diabetes, smoking, high blood pressure, and BMI (10). Inadequate glucose control, which plays an essential role in the development of CAN, also plays a role in its progression through neuronal apoptosis and axonal degeneration. Autonomic dysfunction is reportedly more frequent in relatively older pediatric type 1 DM patients who have worse glycemic control (1,22,24). A positive correlation has been reported between the prevalence of CAN and the duration of type 1 DM (1,21). The positive impact of improved glycemic control on preventing or delaying the onset of autonomic dysfunction has been demonstrated in the literature (10). Chen et al. determined that Hb1Ac and disease duration were negatively correlated with all HRV indices. Accordingly, they found that children with type 1 DM with Hb1Ac level higher than 8% and disease duration longer than 4.5 years had significantly lower HRV indexes (26). Similarly, the duration of type 1 DM was significantly longer. The most recent Hb1Ac levels and the Hb1Ac levels in the last year were significantly higher in patients with definitive CAN, who were also significantly older than other pediatric patients type 1 DM patients included in this study. Accordingly, CAN was not diagnosed in any patient at an age earlier than ten years and before two years had passed since the diagnosis of type 1 DM. This finding is compatible with the recommendations of the International Society for Pediatric and Adolescent Diabetes (ISPAD) which envisages screening children who have had diabetes for 2 to 5 years for neuropathy from the age of 11 (27).

Besides hyperglycemia, some researchers propose that hypoglycemia may also contribute to the development of CAN.. Studies conducted with adults have demonstrated the relationship between hypoglycemia and prolongation of the QTc interval and decreased HRV (28,29). Additionally, two studies evaluating the glycemic variability parameters used in the diagnosis of hypoglycemia found a relationship between hypoglycemia and CAN (14,15). Another study examining the relationship between hypoglycemic stress and CAN demonstrated the relationship between the area under the curve (AUC) corresponding to the low blood glucose index (LBGI) and hypoglycemia and decreased HRV. The authors of the said study argued that hypoglycemic stress might have an acute effect on modulating autonomic control by causing a sympathetic/vagal imbalance and blunting of cardiac vagal control (14).In another study, a significant increase was observed in the percentage and AUC of glucose levels below 54 mg/dL (level 2 hypoglycemia) in patients with CAN (15). In comparison, the findings of this study did not indicate any significant difference between the groups in the TBR value, which is indicative of hypoglycemia, that is, glucose levels below 70 mg/dL.

The fact that other glycemic variability parameters, such as LBGI and AUC, were not used in this study may be deemed the primary limitation of this study. New studies that include other glycemic variability parameters used in the diagnosis of hypoglycemia are needed to further address the relationship between hypoglycemia and CAN in children.

It has been speculated that the wide range of fluctuations in glucose levels might play an essential role in the development of chronic diabetes complications, including CAN, independent of HbA1c (16,30). In parallel, it has been reported that acute glycemic fluctuations can induce endothelial cell damage through the excessive formation of free oxygen radicals (31, 32). Chronic inflammation mediated by increased glucose variability has been considered a potential risk factor for developing diabetes-related complications, including CAN (33). However, the results of the studies that examined the said relationship on adults through evaluation of both glycemic variability and CAN using different parameters are contradictory. To give an example, a study evaluating 24-hour blood pressure monitoring as a marker of glycemic variability and CAN in type 1 DM patients did not find any significant relationship between glucose variability and CAN (16). Similarly, another study concluded that intraday glycemic variability derived from three-month glucose profiles did not play a significant role in the development of CAN that is diagnosed based on

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the results of three cardiovascular reflex tests (34). In contrast, a study examining the relationship between glycemic variability and HRV reported a significant negative relationship between SD and HRV (12). In parallel, SD was reportedly associated with the severity of CAN and blood pressure response to standing (13). In comparison, in this study, TIR, an indicator of glycemic control, was significantly lower, whereas TAR was significantly higher in pediatric DM 1 patients with definitive CAN. In addition, SD was higher, albeit not significantly, in pediatric DM 1 patients with definitive CAN. The orthostatic hypotension is a delayed characteristic sign of advanced neuropathy (13). The fact that SD was not found to be significantly higher in pediatric type 1 DM patients with definitive CAN might be attributed to the low number of CAN patients, and the absence of children with severe CAN in this study. Absence of the control group and the relatively small sample size are other limitations of this study. Hence, large-scale studies on the relationship between CAN and glycemic variability in children with type 1 diabetes are needed.

CONCLUSION

The results of this study demonstrated that in pediatric patients with type 1 diabetes mellitus, those with definitive cardiovascular autonomic neuropathy (CAN) exhibited significantly lower levels of time in the target blood glucose range (TIR), a parameter indicating glycemic control, and significantly higher levels of time above the target blood glucose range (TAR) compared to those without CAN. Additionally, while the standard deviation (SD) was higher in patients with definitive CAN, this difference was not statistically significant.. Further large-scale, prospective cohort studies are needed to fully elucidate the relationship between CAN and glycemic variability in children with type 1 DM.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Written consent was obtained from each patient to use their hospital data.

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