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Clinical predictors of fragmented QRS and abnormal QRS-T angle in type 2 diabetic patients without known cardiovascular diseases

Mehmet Eyüboğlu[1], Ataç Çelik[2]

[1]Department of Cardiology, Izmir Demokrasi University School of Medicine, Izmir, Türkiye
[2]Department of Cardiology, Gaziosmanpaşa University School of Medicine, Tokat, Türkiye

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ABSTRACT

Objectives: This study aims to investigate the association of clinical and glycemic parameters with fragmented QRS (fQRS) and frontal plane QRS-T (fQRS-T) angle in type 2 diabetes mellitus (DM) patients without a known cardiovascular disease (CVD).

Patients and methods: Between September 2020 and September 2021, a total of 414 consecutive type 2 DM patients (209 males, 205 females; mean age: 44.7±6.1 years; range, 33 to 61 years) without established CVD were included in this prospective study. The patients were divided into two groups according to presence or absence of fQRS on electrocardiography (ECG). Clinical and glycemic parameters of patients were compared based on fQRS, fQRS-T angle, and disease duration of DM.

Results: The frequency of fQRS on ECG was 22.9%. The glycated hemoglobin (HbA1c) levels were higher, and DM duration was longer in patients with fQRS compared to those without fQRS and in patients with fQRS-T angle >90° compared to patients with fQRS-T angle ≤90°. The frequency of fQRS and mean fQRS-T angle were significantly higher in patients with DM duration ≥10 years compared to those with DM duration <10 years. Multivariate analysis revealed that HbA1c and DM duration were independent predictors of both presence of fQRS on ECG ($p<0.001$ for both) and fQRS-T angle >90° ($p<0.001$ for both).

Conclusion: The fQRS and fQRS-T angle may predict hyperglycemic status and subclinical cardiovascular involvement in type 2 DM patients without known CVDs.

Keywords: Diabetes mellitus, diabetic cardiomyopathy, electrocardiography, fragmented QRS, frontal plane QRS-T angle.

Diabetes mellitus (DM) is a major risk factor for cardiovascular diseases (CVDs), and atherosclerotic CVD is the leading cause of morbidity and mortality in diabetic patients.[1] Besides its role in the accelerated and exaggerated atherosclerosis in the coronary arteries, DM has also direct toxic effects to the myocardium that may cause myocardial fibrosis and diabetic cardiomyopathy.[2,3] Therefore, early detection and accurate management of subclinical abnormalities in the cardiac structure and functions is essential for adequate prevention of established CVDs in diabetic patients.[4] Electrocardiography (ECG) has a crucial role in the diagnosis and monitoring of diabetic cardiomyopathy, and several ECG alterations can be seen in diabetic patients even when cardiac involvement is clinically not yet evident.[5,6] Moreover, ECG alterations may independently predict future cardiovascular events in patients with DM.[7,8] However, no ECG changes have been reported to be specific to diabetic cardiomyopathy yet, and little is still known regarding the association of clinical and glycemic parameters with ECG alterations in diabetic patients without known CVDs.

Fragmented QRS (fQRS) and increased frontal plane QRS-T (fQRS-T) angle are ECG signs of myocardial fibrosis and damage and are independent predictors of adverse cardiovascular events in a wide variety of patients with and without CVDs.[9-16] More importantly, the presence of fQRS on ECG and increased fQRS-T angle, particularly an angle >90°, seem to be associated with subclinical myocardial damage and predict adverse cardiovascular events independently in diabetic patients.[17-19] However, the

Corresponding author: Mehmet Eyüboğlu, MD. İzmir Demokrasi Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 35290 Konak, İzmir, Türkiye.
E-mail: mhmtybgl@gmail.com

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association of glycemic parameters with these ECG abnormalities in patients with DM has not been well established yet.

In the present study, we aimed to investigate the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle in diabetic patients without known CVDs and to identify the predictors of fQRS and increased fQRS-T angle in patients with type 2 DM in the absence of CVD.

PATIENTS AND METHODS

Study population

This prospective study was conducted at Gaziosmanpaşa University School of Medicine, Department of Cardiology between September 2020 and September 2021. A total of 453 consecutive patients with known diagnosis of type 2 DM and without established CVD were screened. Among these, 39 patients were excluded due to presence of complete or incomplete bundle branch block on ECG. Finally, the remaining 414 patients (209 males, 205 females; mean age: 44.7±6.1 years; range, 33 to 61 years) were included in the study. The patients were divided into two groups according to presence or absence of fQRS on ECG. Also, patient characteristics were compared based on fQRS-T angle and DM duration, and the association of clinical and glycemic parameters with fQRS and fQRS-T angle was investigated. Clinical and demographic characteristics of patients were recorded at baseline. Diabetes duration was defined based on the patients' medical records. Biochemical analyses were performed using venous blood samples obtained after an overnight fasting. Echocardiography was performed to all participants to assess the cardiac functions. Hypertension was defined as systolic blood pressure levels of ≥140 mmHg and/or diastolic blood pressure levels of ≥90 mmHg and/or known treatment with antihypertensive medications. Diabetes mellitus was defined as at least two fasting plasma glucose levels of ≥126 mg/dL, or 2-h plasma glucose levels of ≥200 mg/dL, or glycated hemoglobin (HbA1c) levels of ≥6.5% or known treatment with antidiabetic drugs.[20] Smoking was defined as the regular use of cigarettes.

ECG, fQRS, and fQRS-T angle

A standard 12-lead surface ECG (Nihon Kohden, Tokyo, Japan) using a 0.16 to 100 Hz filter range, 25 mm/s speed, and 10 mm/mV amplitude was obtained from all patients. The fQRS was defined as presence of various morphologies in the original QRS complex (<120 ms) which included an additional R wave (R') or notching in the nadir of the S wave, or >1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory.[21] The fQRS was reported according to its localization on ECG as: fQRS in anterior leads (V1 to V5), inferior leads (DII, DIII, and aVF) and lateral leads (V6, DI and aVL). The fQRS-T angle, which describes the angular difference between depolarization and repolarization vectors, was calculated as absolute difference between QRS axis and T wave axis obtained from automated ECG reports. If the angle exceeded 180°, it was calculated by subtracting from 360°.[12,22] All ECGs were analyzed by two experienced independent cardiologists who were totally blinded to the study protocol. In case of disagreement regarding the presence of fQRS, the final decision was achieved by mutual agreement. Figure 1 demonstrates an example of fQRS and measurement of fQRS-T angle from a 12-lead surface ECG.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The normality distribution of continuous variables was tested using the Kolmogorov-Smirnov or Shapiro Wilk tests. Continuous variables were compared using the independent samples Student t-test and categorical data were compared using chi-square test or Fisher exact test. The Spearman or Pearson correlation coefficients were used to investigate the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle. Multivariate logistic regression analysis was performed to identify the independent predictors of fQRS and increased fQRS-T angle. All variables with a p value of <0.1 in the univariate analysis were included in the model. A p value of <0.05 was considered statistically significant.

RESULTS

The mean DM duration was 4.7±3.3 years and the frequency of fQRS on ECG was 22.9%. The patients with fQRS were older, had significantly higher fasting glucose and HbA1c values, and duration of DM was significantly longer compared to those without fQRS.

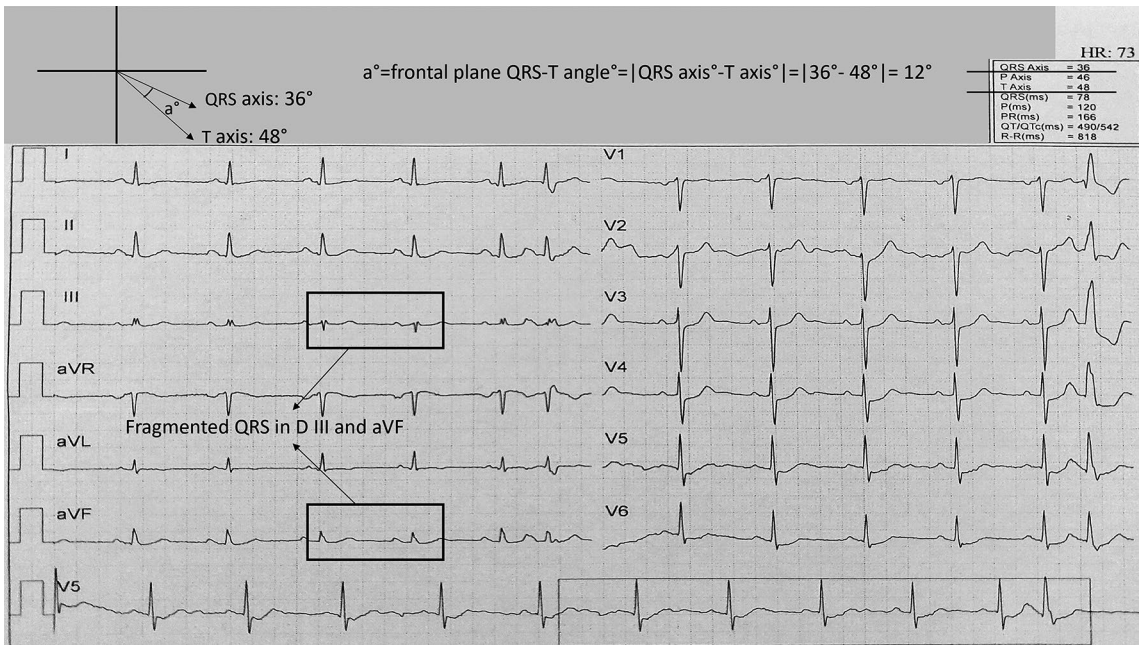

Figure 1. An example of fQRS and measurement of frontal plane QRS-T angle from a 12-lead surface electrocardiography.

Table 1
Clinical characteristics of patients with and without fragmented QRS

Variables	fQRS (n=95)			No fQRS (n=319)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			46.5±6.4			44.2±5.9	0.001
Sex Male	49	51.6		160	50.2		0.808
Body mass index (kg/m^2)			28.1±2.24			27.8±2.04	0.239
Hypertension	39	41.1		128	40.1		0.872
Smoking	27	28.4		96	30.1		0.754
Fasting glucose (mg/dL)			148±20.7			144±11.5	0.019
HbA1c (%)			7.29±0.80			6.90±0.38	<0.001
Diabetes duration (year)			6.86±3.94			4.11±2.85	<0.001
fQRS-T angle (°)			62.39±39.49			53.47±28.90	0.016
Creatinine (mg/dL)			1.04±0.27			0.98±0.30	0.086
Aspartate aminotransferase (U/L)			21.37±6.82			20.80±5.93	0.431
Thyroid-stimulating hormone (μIU/mL)			2.60±0.65			2.48±0.49	0.058
Hemoglobin (g/dL)			12.75±1.10			12.65±1.15	0.482
White blood cell count (×10^3/μL)			7.79±1.24			7.53±1.06	0.053
Platelet count (×10^3/μL)			262.63±59.16			272.97±56.21	0.121
Triglyceride (mg/dL)			144.56±52.61			140.91±43.84	0.499
LDL-cholesterol (mg/dL)			117.37±30.32			115.82±22.85	0.593
HDL-cholesterol (mg/dL)			41.68±6.14			42.20±4.59	0.370

fQRS: Fragmented QRS; SD: Standard deviation; HbA1c: Hemoglobin A1c; fQRS-T angle: Frontal plane QRS-T angle; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 1 demonstrates the clinical characteristics of patients with and without fQRS.

The mean fQRS-T angle was 55.5°±31.8°, and while 62 (15%) patients had fQRS-T angle >90°, 352 (85%) patients had fQRS-T angle ≤90°. The patients with fQRS-T angle >90° were older, had worse renal functions, and had higher frequency of male gender, hypertension and fQRS compared to those with fQRS-T angle ≤90°. The HbA1c levels were significantly higher and DM duration was also significantly longer in patients with fQRS-T angle >90° compared to patients with fQRS-T angle ≤90°. Table 2 shows the clinical characteristics of patients according to fQRS-T angle.

Additionally, DM duration was ≥10 years in 57 (13.8%) patients. The patients with DM duration ≥10 years were older and had significantly higher HbA1c values. The frequency of fQRS and mean fQRS-T angle were also significantly higher in patients with DM duration ≥10 years compared to those with DM duration <10 years. Table 3 shows the clinical characteristics of patients according to DM duration. The correlation analyses revealed that there was a strong positive correlation between fQRS-T angle and DM duration (r=0.783, p<0.001), a moderate positive correlation between fQRS-T angle and HbA1c (r=0.646, p<0.001), a low positive correlation between fQRS and HbA1c (r=0.472, p<0.001), and a moderate positive correlation between fQRS and DM duration (r=0.558, p<0.001).

The multivariate analysis demonstrated that HbA1c (odds ratio [OR]: 1.136, 95% confidence

Table 2
Comparison of clinical characteristics of patients according to frontal plane QRS-T angle

	fQRS-T angle (>90°) (n=62)			fQRS-T angle (≤90°) (n=352)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.6±5.7			43.3±5.0	<0.001
Sex							0.036
Male	36	58.1		173	49.1		
Body mass index (kg/m^2)			29.3±1.51			27.6±2.08	<0.001
Hypertension	30	48.4		137	38.9		0.022
Smoking	22	35.5		101	28.7		0.118
fQRS	30	48.4		65	18.5		<0.001
Localization of fQRS							0.227
Anterior	11	36.7		18	27.7		
Inferior	11	36.7		36	55.4		
Lateral	8	26.6		11	16.9		
Fasting glucose (mg/dL)			145±16.0			145±13.9	0.968
HbA1c (%)			7.90±0.55			6.78±0.33	<0.001
Diabetes duration (year)			10.68±3.01			3.69±2.04	<0.001
Creatinine (mg/dL)			1.41±0.28			0.92±0.23	<0.001
Aspartate aminotransferase (U/L)			21.06±4.84			20.90±6.34	0.854
Thyroid-stimulating hormone (μIU/mL)			2.25±0.43			2.55±0.54	0.042
Hemoglobin (g/dL)			12.21±0.91			12.76±1.16	0.016
White blood cell count (×10^3/μL)			7.53±0.99			7.60±1.31	0.622
Platelet count (×10^3/μL)			205.32±66.80			282.10±46.50	0.006
Triglyceride (mg/dL)			138.18±59.31			142.51±41.94	0.371
LDL-cholesterol (mg/dL)			120.81±24.01			115.36±24.80	0.110
HDL-cholesterol (mg/dL)			41.94±6.52			42.11±4.28	0.486

fQRS: Fragmented QRS; SD: Standard deviation; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 3
Clinical characteristics of patients according to diabetes duration

	Duration ≥10 years (n=57)			Duration <10 years (n=357)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.7±5.8			43.5±5.1	<0.001
Sex							
Male	31	54.4		178	49.8		0.271
Body mass index (kg/m^2)			29.2±1.35			27.6±2.11	<0.001
Hypertension	29	50.9		138	38.7		0.008
Smoking	19	33.3		104	29.1		0.356
fQRS-T angle (°)			112±20.4			47±22.9	<0.001
fQRS	25	43.9		70	19.6		<0.001
Localization of fQRS							0.124
Anterior	10	40.0		19	27.1		
Inferior	8	32.0		39	55.7		
Lateral	7	28.0		12	17.1		
Fasting glucose (mg/dL)			145±16.2			145±13.8	0.855
HbA1c (%)			7.86±0.57			6.80±0.37	<0.001
Creatinine (mg/dL)			1.43±0.26			0.93±0.24	<0.001
Aspartate aminotransferase (U/L)			20.86±4.44			20.94±6.37	0.923
Thyroid-stimulating hormone (μIU/mL)			2.24±0.46			2.57±0.56	0.028
Hemoglobin (g/dL)			12.32±0.88			12.73±1.03	0.044
White blood cell count (×10^3/μL)			7.49±0.92			7.62±1.16	0.562
Platelet count (×10^3/μL)			245.43±56.72			274.46±61.36	0.088
Triglyceride (mg/dL)			140.26±47.61			142.21±51.67	0.613
LDL-cholesterol (mg/dL)			121.22±22.46			116.16±28.44	0.362
HDL-cholesterol (mg/dL)			40.86±5.37			42.31±4.81	0.058

SD: Standard deviation; fQRS: Fragmented QRS; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 4
Independent predictors fragmented QRS and frontal plane QRS-T angle >90° in multivariate analysis

	OR	95% CI	*p*
Fragmented QRS			
HbA1c	1.136	1.054-1.918	<0.001
Diabetes duration	1.201	1.176-2.132	<0.001
Frontal plane QRS-T angle >90°			
Creatinine	1.447	1.157-1.985	<0.001
Age	1.572	1.168-2.241	<0.001
HbA1c	1.772	1.314-2.612	<0.001
Diabetes duration	2.463	1.854-3.217	<0.001

OR: Odds ratio; CI: Confidence interval; HbA1c: Hemoglobin A1c.

interval [CI]: 1.054-1.918, p<0.001) and DM duration (OR: 1.201, 95% CI: 1.176-2.132, p<0.001) were the independent predictors of fQRS on ECG, and creatinine level (OR: 1.447, 95% CI: 1.157-1.985, p<0.001), age (OR: 1.572, 95% CI: 1.168-2.241, p<0.001), HbA1c (OR: 1.772, 95% CI: 1.314-2.612, p<0.001) and DM duration (OR: 2.463, 95% CI: 1.854-3.217, p<0.001) were the independent predictors of fQRS-T angle >90°. Table 4 shows the independent predictors fQRS and fQRS-T angle >90° in the multivariate analysis.

DISCUSSION

The main finding of the present study was that HbA1c and DM duration were significantly associated with the presence of fQRS on ECG and increased fQRS-T angle in DM patients, even in the absence of clinically evident CVDs. These results suggest that both ECG parameters may be useful to demonstrate and monitor the subclinical myocardial damage in DM patients without established CVDs.

Diabetes mellitus causes significant changes in the physiological properties of the myocardium that leads myocardial fibrosis and diabetic cardiomyopathy,[2,3] and CVD is the major cause of mortality in patients with type 2 DM.[1,23] Of note, ECG has a crucial role in the monitoring of diabetic cardiomyopathy and ECG alterations detected in the clinical follow-up of DM patients are associated with both clinical and subclinical myocardial involvement, and significantly predict adverse cardiovascular events.[5-8] However, little is known regarding the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle in asymptomatic patients with type 2 DM. The fQRS is a depolarization abnormality that is an ECG sign of myocardial fibrosis and damage and is an independent predictor of future cardiovascular events in a wide variety of patients with and without CVD.[9-11,24-26] More importantly, fQRS is significantly associated with subclinical myocardial fibrosis, deteriorated cardiac functions, and adverse events in DM patients even in the absence of apparent CVD.[17,18,27,28] Additionally, as a sign of ventricular repolarization heterogeneity, increased fQRS-T angle is a predictor of abnormal cardiac functions and is associated with adverse cardiovascular events independent of underlying cardiovascular status.[12,13] Moreover, increased fQRS-T angle is significantly associated with diabetic cardiomyopathy and adverse cardiovascular events in DM patients.[19] In this context, both ECG parameters seem to be useful in the monitoring of diabetic cardiomyopathy and to demonstrate the early-stage myocardial fibrosis and damage before the emergence of manifest CVD in patients with DM.

The HbA1c level is a sign of mean blood glucose concentrations over the preceding three months, considered as a cardiovascular risk factor and is significantly associated with cardiovascular complications and adverse cardiovascular events in patients with DM.[1,8] More importantly, hyperglycemia and HbA1c is the leading cause of ECG abnormalities in patients with DM.[5,8] However, little is known regarding the relationship of HbA1c with fQRS and fQRS-T angle in DM patients without known CVD. The results of our study demonstrated that HbA1c was an independent predictor of fQRS on ECG and increased fQRS-T angle and we found a significant positive correlation between HbA1c levels and both ECG parameters. Therefore, our results suggest that fQRS and fQRS-T angle may be useful ECG findings to demonstrate the hyperglycemia related subclinical myocardial damage in the early phase of diabetic cardiomyopathy before the occurrence of clinically evident CVD. Additionally, DM duration is usually considered as a cardiovascular risk factor and is significantly associated with diabetic cardiomyopathy and future cardiovascular events in asymptomatic patients with type 2 DM independent of coexisting risk factors.[8,29] Nevertheless, the impact of DM duration on ECG parameters has not been well described yet. In the present study, we demonstrated that prolonged DM duration was the most powerful predictor of presence of fQRS on ECG and increased fQRS-T angle in DM patients without known CVD. In this context, both ECG parameters may be considered as the ECG signs of prolonged DM duration related subclinical diabetic cardiomyopathy. Hence, fQRS and fQRS-T angle may have a significant association with prolonged hyperglycemia and DM duration and may be useful in the monitoring of subclinical diabetic cardiomyopathy.

Nonetheless, there are some limitations in this study. The main limitation was the lack of data regarding the clinical events. However, this study was not a follow-up study and the association of both ECG parameters with cardiovascular events is well described in previous studies. Also, the clinical importance of our findings needs to be investigated in further

studies to demonstrate whether effective treatment of DM leads disappearance of fQRS or narrowing in the fQRS-T angle. Finally, the absence of confirmation of subclinical myocardial fibrosis with cardiac magnetic resonance imaging is another limitation.

In conclusion, type 2 DM confers a significant increase in the risk of CVD and CVD is the leading cause of mortality in DM patients. The ECG has an important role in the monitoring of diabetic cardiomyopathy and demonstrating the cardiovascular involvement in patients with type 2 DM. Our study results demonstrated that glycemic parameters HbA1c and DM duration were significantly associated with fQRS and increased fQRS-T angle in type 2 DM patients without manifest CVDs. Therefore, both ECG parameters may be useful in the monitoring glycemic status and cardiovascular involvement in type 2 DM patients without known CVDs.

Ethics Committee Approval: The study protocol was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (date: 25.06.2020, no: 20-KAEK-151). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, data collection and/or processing, writing the article: M.E.; Design, control/supervision, analysis and/or interpretation, literature review, critical review: M.E., A.Ç.

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