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Fragmented QRS as a Predictor of Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A 36-Month Follow-Up Data

ORIGINAL INVESTIGATION

ABSTRACT

Background: Major cardiovascular events (MACE) are more common in type 2 diabetes mellitus (T2DM) patients, and early diagnosis can prevent significant morbidity and mortality. The aim of this study was to investigate the predictiveness of fragmented QRS (fQRS) showing MACE in T2DM patients.

Methods: A total of 227 T2DM patients (mean age 52, 51% male) without any cardiovascular disease who came to the cardiology outpatient clinic between March 01 and July 31, 2019, were included in the study. The patients were divided into 2 groups according to fQRS on electrocardiography (ECG), and 36 months of follow-up was done. The development of acute coronary syndrome, coronary revascularization, and cerebrovascular accident were accepted as MACE.

Results: More MACE was seen in the group with fQRS on ECG ($P = .026$). Although there were more fQRS in patients with proteinuria, it was not statistically significant ($P = .069$). More myocardial infarcts (7.9%) and more cerebrovascular events (6.3%) were seen in the group with fQRS. While revascularization was performed on 3 patients in the fQRS group, revascularization was not performed on the patients in the non-fqrs group. In multiple Cox regression analysis, fQRS showed an independent predictor of MACE [$P = .025$, hazard ratio = 2.42 (1.117-5.221)], more MACE was seen in the fQRS (+) group in the kaplan-meier analysis ($P = .022$).

Conclusion: More MACE was seen in the fQRS group in T2DM patients without a previous history of cardiovascular events. Fragmented QRS was found to be an independent predictor in showing MACE. Care should be taken in terms of MACE development in T2DM patients with fQRS.

Keywords: Cardiovascular events, diabetes mellitus, ECG, fQRS

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading health problems in the world. Chronic metabolic imbalance leads to the development of macro- and microvascular complications.[1] Major cardiovascular events (MACE) such as myocardial infarction (MI), stroke, and premature death are significantly increased in T2DM. In addition, complications secondary to T2DM are still the number 1 cause of morbidity and mortality in the world.[2] Predicting cardiovascular events in T2DM patients may allow premature disability to be prevented.

Fragmented QRS (fQRS) is an easily detectable depolarization defect on 12-channel superficial electrocardiography (ECG). Myocardial fibrosis and the island-like structure show the scar tissue around the viable myocardium.[3] Myocardial inflammation or fibrosis can cause conduction delay and may be reflected as fQRS in the superficial ECG.[4] fQRS was also reported as a significant independent predictor for cardiac events (MACE) and cardiac mortality in non-ST elevation MI patients.[5] In recent studies, fQRS has been shown to be associated with coronary artery disease and MI with and without ST elevation.[6] In addition, the presence of fQRS in the ECG has been found to be an indicator of poor prognosis in cerebrovascular events.[7] Previous studies have shown a relationship between T2DM and fQRS, but to our knowledge, no long-term results have been studied.

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In this study, we examined the rates of MACE that developed within 3 years of T2DM patients without a history of coronary artery disease. The aim of this study is to investigate the MACE prediction of fQRS in T2DM patients.

METHODS

Study Population

This retrospective study included 227 T2DM patients who attended the cardiology outpatient clinic between the March 1 and July 31, 2019, for screening for cardiovascular diseases. Patients who did not have detailed data (echocardiography, height/weight, systolic and diastolic blood pressure measurement at admission, smoking and alcohol use, additional disease information) in their files, pregnant women, postpartum women, type 1 diabetes patients, end-stage renal disease, heart failure, advanced liver failure, dementia, psychiatric diseases, patients with a history of stroke, cancer patients, thyroid dysfunction, presence of arrhythmia, cardiac conduction abnormalities, QRS >110 ms, and a history of ischemic heart disease were excluded from the study. This study was event driven with a primary endpoint of MACE, which included MI, coronary revascularization, and cerebrovascular events. The 36-month data of the patients were obtained from the hospital automation system and confirmed by calling the patient or their relatives by phone. Patients with inconsistent data were excluded from the study. The patients were divided into 2 groups depending on the presence of fQRS on the ECG.

Laboratory data within the last month was obtained from the hospital automation system. Those patients whose albumin to creatinine ratio was measured twice at 6-month intervals and was found to be above 30 were considered to have proteinuria. Glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease method.[8] The presence of GFR <60 or proteinuria was evaluated as chronic kidney disease (CKD). The diagnosis of acute coronary syndrome was made according to the guidelines.[9] Those with coronary balloon, stent or cardiac bypass for any reason were considered as coronary revascularization. Those with acute ischemic focus in cerebrovascular system were considered as cerebrovascular event.

HIGHLIGHTS

- Major cardiovascular events (MACE) are more common in type 2 diabetes mellitus (T2DM) patients, and early diagnosis can prevent significant morbidity and mortality.
- The aim of this study is to investigate the MACE prediction of fQRS in T2DM patients.
- More MACE were seen in the fQRS group in T2DM patients without a previous history of cardiovascular events.
- Fragmented QRS was determined to be an independent predictor of MACE.
- In the presence of fQRS in T2DM patients without a history of cardiovascular events, attention should be paid to MACE and it should be followed closely.

The study was initiated after the approval of the Local Ethics Committee. All participants were informed about the study, and their written informed consent was obtained. Electrocardiography was taken and resting blood pressure was measured for all patients who applied to the cardiology outpatient clinic in our hospital.

Electrocardiographic Assessment

The ECGs of the patients were taken from the patient files and evaluated by 2 cardiologists who were unaware of each other. An ECG paper speed of 25 mm/s and an amplitude of 10 mm/mV were used for the analyses. Fragmented QRS was defined as the presence of an additional R wave (R′), notching of the R or S wave, or the presence of >1 R′ in 2 consecutive leads that corresponded to the major coronary artery regions in a normal QRS interval.[3]

Echocardiographic Measurements

Echocardiographic data were obtained and analyzed by 2 cardiologists who were unaware of the participants' subgroups. All echocardiographic measurements were performed on a Philips Affiniti 70 ultrasound machine (Philips Healthcare Inc., Andover, Mass, USA) equipped with an S5-1 (1.7-3.5 MHz) transducer. Single-lead ECG recordings were obtained simultaneously. Two-dimensional, M-mode, and color flow Doppler echocardiograms were obtained according to the guidelines.[10] Left ventricular ejection fraction was calculated by the biplane Simpson method in apical 4-chamber view. Left ventricular end-diastolic dimension, interventricular septum thickness (IVS), and left ventricular posterior wall thickness (LVPW) were measured at the level of the mitral valve in parasternal long-axis view. Left ventricular mass (LVM) was calculated according to the Devereux formula.[11] Left ventricular mass index (LVMI) was obtained by dividing body surface area by LVM.

Statistical Analysis

SPSS 16.0 software (SPSS Inc., Chicago, Ill, USA) was used for the statistical analysis. In this study, the suitability of continuous variables to normal distribution was tested with the Kolmogorov–Smirnov normality test. Continuous variables were compared using independent samples *t*-tests or the Mann–Whitney *U*-test between the 2 groups. Normal distribution is shown as mean ± standard deviation, and non-normal distribution is shown as the median value. Categorical data were compared using the chi-square test or Fischer's exact test and reported as percentages. A *P*-value of less than .05 was considered statistically significant. Univariate and then multiple Cox regression analysis of gender, age, body mass index (BMI), smoking, presence of hypertension, CKD, LDL-C, fQRS, and HbA1c was performed. Kaplan–Meier analysis was performed between fQRS and cardiovascular event.

RESULTS

Table 1 shows the demographic, clinical, and laboratory parameters of T2DM patients. The basic characteristic parameters were observed to be similar. Hypertension, CKD, and smoking were found to be statistically similar between both groups. No difference was observed between the 2

Table 1. Demographic and Clinical Parameters of Type 2 Diabetic Patients

Variables	Total (n = 227)	fQRS (+) (n = 63)	fQRS (−) (n = 164)	*P*
Age (years)	52.16 ± 7.38	53.14 ± 7.65	51.79 ± 7.27	.216
Male n (%)	96 (42.3)	32 (50.8)	64 (39.0)	.073
BMI (kg/m^2)	29.51 ± 3.64	30.02 ± 3.03	29.32 ± 3.84	.194
Hypertension n (%)	97 (42.7)	25 (39.7)	72 (43.9)	.336
Kidney disease n (%)	130 (57.3)	39 (61.9)	91 (55.5)	.235
Duration of diabetes (years)	6.0 (3.0-10.0)	6.0 (3.0-10.0)	6.0 (3.0-10.0)	.564
Smoking, n (%)	59 (26.0)	20 (31.7)	39 (23.8)	.146
Primary prevention (%)	90 (39.6)	22 (34.9)	68 (41.5)	.367
MACE n (%)	26 (11.5)	12 (19.0)	14 (8.5)	.026
Medicine use				
Insulin n (%)	15 (6.6)	4 (6.3)	11 (6.7)	.923
OAD n (%)	141 (62.1)	38 (60.3)	103 (62.8)	.729
Mix n (%)	71 (31.3)	21 (%33.3)	50 (30.5)	.679
Ace inh/ARB n (%)	97 (42.7)	24 (38.1)	73 (44.5)	.381
Statin use n (%)	73 (32.2)	20 (31.7)	53 (32.3)	.934

ACE inh, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; fQRS, fragmented QRS; MACE, major cardiovascular events; OAD, oral antidiabetic drug.

groups in the use of diabetic medications (oral antidiabetic, insulin, or mixed therapy). Statistically more events were seen in patients with fQRS (*P* = .026).

Laboratory and echocardiographic parameters according to the presence of fQRS in T2DM patients are shown in Table 2. Basal characteristic parameters were found to be similar. Interventricular septum thickness, LVPW, and LVMI were not significant between both groups. Proteinuria was observed more in the group with fQRS, but it was not statistically significant (*P* = .069).

Table 3. Major Cardiovascular Events Ratio According to the Presence of Fragmented QRS

Variables	fQRS (+) (n = 63)	fQRS (−) (n = 164)
Myocardial infarction n (%)	5 (7.9)	9 (5.5)
Coronary revascularization n (%)	3 (4.8)	---
Cerebro vascular event n (%)	4 (6.3)	5 (3.0)
Death n (%)	0 (0)	0 (0)

Table 3 shows the frequency of the events occurring in the fQRS group. While the majority of events are composed of MI, a small number of them are caused by revascularization (elective stent implantation, CABG). Major cardiovascular events were more common in the fQRS group.

Major cardiovascular events-related univariate and multiple Cox regression analysis is shown in Table 4. In the univariate cox regression analysis, it was seen that it had no effect on sex, age, BMI, smoking, hypertension, CKD, LDL-cholesterol, or MACE. In multiple Cox regression analysis, fQRS was determined to be an independent predictor of MACE [*P* = .025, hazards ratio = 2.42 (1.117-5.221)].

Figure 1 shows the Kaplan–Meier survival analysis. As a result of 3-year follow-up, more MACE were detected in those with fQRS (*P* = .022).

DISCUSSION

Our main findings in this study: more MACE is observed in patients with fQRS than in patients without fQRS, and fQRS is an independent predictor of MACE in T2DM patients. Major

Table 2. Laboratory and Echocardiographic Parameters of Type 2 Diabetic Patients

Variables	Total (n = 227)	fQRS (+) (n = 63)	fQRS (−) (n = 164)	*P*
LVEDd (mm)	47.61 ± 4.15	48.37 ± 3.89	47.32 ± 4.21	.085
LVEF (%)	60.60 ± 2.22	60.31 ± 2.63	60.71 ± 2.04	.234
IVS (mm)	9.49 ± 1.15	9.47 ± 1.09	9.49 ± 1.18	.896
LVPW (mm)	9.34 ± 1.18	9.52 ± 0.98	9.27 ± 1.24	.106
LVMI (mm)	81.47 ± 15.17	82.99 ± 14.04	80.89 ± 15.58	.350
Systolic blood pressure (mm Hg)	111.61 ± 8.95	111.90 ± 9.00	111.49 ± 8.95	.757
Diastolic blood pressure (mm Hg)	69.10 ± 8.91	69.05 ± 8.97	69.12 ± 8.91	.959
Fasting glucose (mg/dL)	151 (117-216)	145 (121-219)	152 (117-214)	.733
Creatinine (mg/dL)	0.81 ± 0.23	0.84 ± 0.23	0.80 ± 0.22	.200
LDL - cholesterol (mg/dL)	124.69 ± 37.95	124.80 ± 41.72	124.65 ± 36.53	.978
Non-HDL - cholesterol (mg/dL)	162.67 ± 46.04	166.59 ± 53.44	161.17 ± 42.94	.428
Triglycerides (mg/dL)	161 (120-232)	159 (120-215)	161 (120-238)	.886
GFR (mL/min/1.73 m^2)	93.20 ± 23.47	91.41 ± 23.67	93.89 ± 23.42	.477
TSH (mIU/L)	1.68 (1.18-2.50)	1.68 (1.14-2.51)	1.68 (1.18-2.48)	.785
HbA1c (%)	8.0 (6.60-9.33)	8.10 (6.60-9.33)	7.95 (6.63-9.08)	.593
Proteinuri n (%)	58 (25.6)	21 (33.3)	37 (22.6)	.069

fQRS, fragmented QRS; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; IVS, interventricular septum; LDL, low density lipoprotein; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall;TSH, thyroid stimulating hormone.

Table 4. Univariate and Multiple Cox Regression Analysis for Major Cardiovascular Events

	Univariate Analysis			Multiple Analysis		
Prognostic factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex	1.422	0.627-3.223	0.399			
Age	1.039	0.981-1.101	0.188			
BMI	0.978	0.875-1.094	0.700			
Smoking	1.307	0.536-3.188	0.556			
Hypertension	0.981	0.429-2.241	0.963			
CKD	1.206	0.547-2.658	0.642			
LDL-cholesterol	0.989	0.977-1.001	0.075			
fQRS	2.52	1.095-5.804	0.03	2.42	1.117-5.221	.025
HbA1c	1.136	0.927-1.391	0.220			

BMI, body mass index; CKD, chronic kidney disease; fQRS, fragmented QRS; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin.

cardiovascular events, such as coronary artery disease, coronary revascularization, and cerebrovascular events, are more common in T2DM patients than in the general population.[12] Type 2 DM lays the groundwork for MACE.[13] The increase in oxidative stress and inflammation starts from the first years of diabetes in T2DM patients and may cause vascular endothelial dysfunction.[14] Chronic inflammation and endothelial dysfunction can cause atherosclerosis in the vascular bed and cause fibrosis in the myocardium.[15] Early diagnosis of cardiovascular events is important in order to prevent premature death and disability in T2DM patients.

It has been shown that fQRS is associated with coronary ischemia and MACE in ECG, which is an inexpensive and easily accessible test.[16,17] Fragmented QRS is defined as the presence of additional r or r waves on the ECG without bundle branch block, or an RSR' pattern in the QRS wave, in 2 consecutive leads affecting the major coronary artery area.[18] As a mechanism, myocardial fibrosis and scarring interrupt the continuity of myocardial depolarization, and as a result fQRS formation may occur. In addition, a slowdown in myocardial depolarization may occur secondary to myocardial scarring, resulting in notch formation in the QRS wave.[19] Fragmented QRS was found to be associated with in-hospital mortality and long-term MACE in patients with acute MI.[20] Interstitial fibrosis, capillary endothelial changes, and capillary basal laminar thickening begin in the early phase of diabetes.[21] Chronic hyperglycemia may cause fibrosis in the cardiac and other organs.[22] Fragmented QRS is an ECG finding that develops as a result of cardiac fibrosis and scar.[18] In our study, more MACE was seen in patients with fQRS in the 36-month follow-up of T2DM patients.

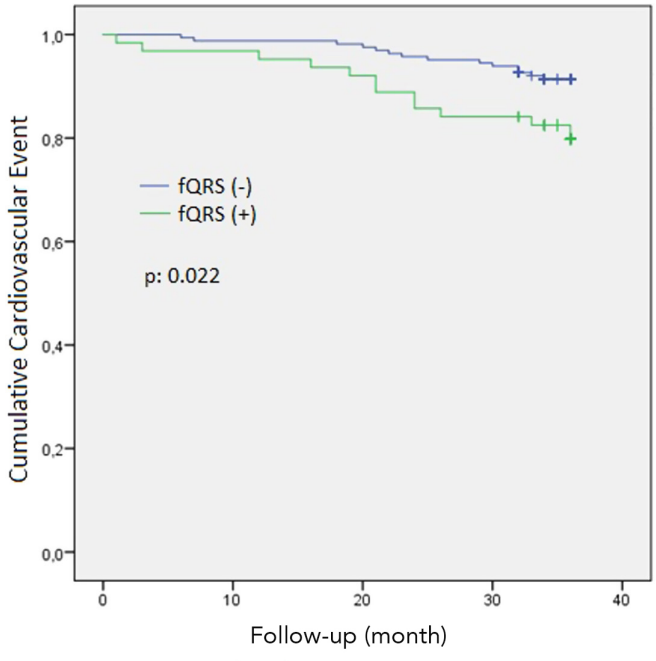

Figure 1. Kaplan–Meier analysis of major adverse cardiac events in patients with and without fragmented QRS.

In the study conducted by Şahin et al,[7] it was observed that patients with fQRS were associated with a poor prognosis in the 2-year follow-up of stroke patients. In our study, more strokes occurred in the fQRS group. Unlike the study performed by Sahin et al,[7] in our study patients who did not have a previous cardiovascular event were included in this study, and the predictor of MACE including stroke was examined. A meta-analysis by Luo et al[20] found that fQRS was associated with in-hospital and long-term MACE in MI patients. The most important feature that distinguishes our study from the study of Luo et al[20] is that the in our study population, patients did not have a previous cardiovascular event.

In summary, in this study, more MACE were seen in T2DM patients with fQRS, and fQRS was found to be an independent predictor of MACE. Interstitial fibrosis and capillary endothelial changes may be the reasons for detecting more fQRS in this study.[21] In the presence of fQRS in T2DM patients without a previous history of cardiovascular disease, it is useful to follow the patients closely in terms of MACE.

Study Limitations

Fragmented QRS reflects myocardial scar and fibrosis. These scar and fibrosis can be detected by Single Photon Emission Computed Tomography (SPECT) or magnetic resonance imaging (MRI). However, SPECT and MRI could not be performed in our study due to their high cost. Second, the sample size of the study is small and the follow-up period is

short, and it is a non-randomized study. This study can be confirmed by large sample size, prospective, randomized, and long-term studies.

CONCLUSION

A higher rate of MACE was seen in fQRS T2DM patients at 3-year follow-up, and fQRS was found to be an independent predictor of MACE. In the presence of fQRS in T2DM patients without a history of cardiovascular events, attention should be paid to MACE and it should be followed closely.

Ethics Committee Approval: Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital (decision date: November 7, 2019; decision number: 066).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – All authors; Design – All authors; Supervision – All authors; Data Collection and/or Processing – Ş.Ç., A.B., Ö.D.; Analysis and/or Interpretation – Ş.Ç., K.Ö.K., E.Y.; Literature Search – Ş.Ç., K.Ö.K., E.Y.; Writing – Ş.Ç., E.Y.; Critical Review – K.Ö.K., E.Y.

Declaration of Interests: The authors have no conflicts of interest to declare.

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