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ORIGINAL ARTICLE

High prevalence of fragmented QRS on electrocardiography in Japanese patients with diabetes irrespective of metabolic syndrome

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ABSTRACT

Aims/Introduction: Fragmented QRS (fQRS) on electrocardiography is a marker of myocardial fibrosis and myocardial scar formation. This study aimed to clarify the relationship of fQRS with diabetes mellitus and metabolic syndrome (MetS) in Japanese patients.

Materials and Methods: Approximately 702 individuals who had a routine health checkup at the Hokuriku Health Service Association (Toyama, Japan) in October 2014 were enrolled and categorized into one of the following four groups based on MetS and diabetes mellitus status: with diabetes mellitus (+) MetS+ (164 participants); diabetes mellitus+ without MetS (Mets–; 103 participants); diabetes mellitus– MetS+ (133 participants); and diabetes mellitus– MetS– (302 participants). fQRS was assessed using the results of electrocardiography.

Results: The prevalence of fQRS was statistically higher in patients with diabetes mellitus+ MetS+ (37%) and diabetes mellitus+ MetS– (35%), than those with diabetes mellitus– MetS+ (14%) or diabetes mellitus– MetS– (10%; $P < 0.0001$). Significant differences were observed between the fQRS(+) and fQRS(–) groups for age, sex, waist circumference, heart rate, hypertension, hemoglobin A1c, total cholesterol, MetS and diabetes mellitus. The area under the receiver operating characteristic curve for traditional risk factors and diabetes mellitus was 0.72 ($P = 0.0007$, 95% confidence interval 0.67–0.76), and for traditional risk factors and MetS it was 0.67 ($P = 0.28$, 95% confidence interval 0.62–0.72). Patients with diabetes mellitus had more than threefold higher likelihood of showing fQRS (odds ratio 3.41; 95% confidence interval 2.25–5.22; $P < 0.0001$) compared with the reference group without diabetes mellitus, after adjusting for age, sex, dyslipidemia, hypertension and waist circumference.

Conclusions: fQRS was observed more frequently in diabetes mellitus patients than in MetS and control individuals. Diabetes mellitus was the most significant determinant for fQRS among MetS and other traditional metabolic risk factors.

INTRODUCTION

A fragmented QRS (fQRS) on a resting 12-lead electrocardiogram (ECG) includes various QRS complex morphologies[1]. QRS complex morphologies include Q wave, various RSR' patterns, additional R wave (R') or notching in the nadir of the S wave and the presence of more than one R' (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory. Several reports have shown that fQRS correlates with the presence of a myocardial scar and fibrous tissues[2,3]. Furthermore, a fQRS reflects myocardial conduction abnormalities, likely due to myocardial fibrosis, which is considered a prognostic marker for lethal cardiac arrhythmias[4].

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Cardiac fibrosis is often observed in the early stage of diabetes mellitus, and myocardial hypertrophy, interstitial fibrosis, capillary endothelial changes and capillary basal laminar thickening are the common histopathological abnormalities in diabetes mellitus[5–7]. Myocardial fibrosis in diabetes mellitus patients manifests as diastolic dysfunction, which results in heart failure with a preserved ejection fraction[8]. The amount of myocardial fibrosis is a predictor of long-term survival for patients with heart failure with a preserved ejection fraction[9]. Furthermore, myocardial fibrosis has a negative impact on regional and global myocardial function and does not regress, even with an intensive glycemic management[10,11]. Due to the negative consequences of a diagnosis of myocardial fibrosis in patients with diabetes mellitus, the detection of these high-risk patients will have a clinically significant impact.

The present study sought to improve the outcome of patients with diabetes mellitus and myocardial fibrosis by investigating the presence and frequency of fQRS in patients with diabetes mellitus and metabolic syndrome (MetS). Using a retrospective analysis of the general Japanese patient population, we report a significant correlation between fQRS and diabetes mellitus; however, no significant correlation was observed in patients with MetS. The link between fQRS and diabetes mellitus provides an important diagnostic tool to assess cardiac dysfunction in patients with this devastating endocrinological condition.

MATERIALS AND METHODS

Study population

This was a retrospective, cross-sectional, observational study. All procedures were carried out 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 a substitute for it, was obtained from all patients included in the study. The study protocol was approved by the ethics committee of the University of Toyama (IRB# R2019028) and the Hokuriku Health Service Association. Written informed consent was obtained from all the participants when they enrolled in the health checkup. The Hokuriku Health Service Association carries out approximately 150,000 annual health examinations on workers and their families, and has recently reported a large-scale study on new-onset atrial fibrillation[12].

We examined the clinical records of patients who had a routine health checkup at Hokuriku Health Service Association (Toyama, Japan) the first week of October 2014. One investigator in the Hokuriku Health Service Association was blinded to the clinical information, except for the existence of diabetes mellitus and MetS in the population. This blinded investigator randomly selected 702 patients from the cohort to have similar numbers of diabetes mellitus patients (+) with Mets (MetS+), diabetes mellitus+ without MetS (–) and diabetes mellitus– MetS+ patients to increase the efficiency of group comparisons.

Annual health examination

The annual health examination includes a 12-lead ECG, chest X-ray, blood pressure (BP) measurement, heart rate, body mass index, blood glucose, hemoglobin A1c, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, uric acid, liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase), renal function (blood urea nitrogen, creatinine), urinalysis, and testing for blood cell count and blood chemistry. The examination also contains a self-reported health questionnaire, which includes information on previous history of stroke, diabetes mellitus, hypertension, dyslipidemia, myocardial infarction, angina pectoris and arrhythmia. Prior cardiovascular disease reported in the questionnaire is listed in Tables 1 and 2.

Assessment of cardiovascular risk factors

Hypertension (HT) with the generally accepted definition was diagnosed if peripheral BP was ≥140/90 mmHg, or if the health questionnaire indicated current antihypertensive medications[13]. Dyslipidemia (DL) with the generally accepted definition was diagnosed if total cholesterol levels were ≥220 mg/dL, or LDL cholesterol levels were ≥140 mg/dL, or HDL cholesterol levels were <40mg/dL levels, or fasting triglyceride levels were >150 mg/dL, or if the health questionnaire indicated current medications for dyslipidemia following the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017[14]. Diabetes mellitus was diagnosed using hemoglobin A1c ≥6.5% (National Glycohemoglobin Standardization Program), a fasting blood glucose concentration of ≥126 mg/dL (7.0 mol/L), or a random blood glucose concentration of ≥200 mg/dL (11.1 mol/L)[15], or if the health questionnaire indicated current medications for diabetes mellitus. MetS was defined using the criteria of the Japanese Society of Internal Medicine[16], which includes a waist circumference >85 cm in men or 90 cm in women and two or more of the following: (i) triglyceride >150 mg/dL (1.7 mmol/L) and/or HDL cholesterol <40 mg/dL (<1.03 mmol/L) for both of men and women, or the health questionnaire indicated current lipid-lowering medications; (ii) a systolic BP of ≥130 mmHg, diastolic BP of ≥85 mmHg or the health questionnaire indicated current antihypertensive medications; or (iii) a fasting blood glucose of 110 mg/dL (6.1 mol/L) or the health questionnaire indicated current medications for diabetes mellitus. Visceral adiposity was diagnosed if waist circumference met the Japanese Society of Internal Medicine MetS criteria. Obesity was defined as body mass index ≥25 kg/m^2 following the Japan Society for the Study of Obesity criteria[17].

ECG acquisition and analysis

A 12-lead surface ECG was obtained from all patients in the supine position with electrocardiogram FCP-7431 (Fukuda Denshi Co., Ltd., Tokyo, Japan; filter range 0.16–100 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV). fQRS was defined following the criteria by Das *et al.*[1]. QRS complex morphologies

Table 1 | A comparison of clinical characteristics between patients with and without fragmented QRS

Parameter	Total	fQRS(+)	fQRS(–)	*P*-value
No. participants	702	144 (21%)	558 (79%)	
Demographic				
Age (years)	51 ± 8	54 ± 8	50 ± 8	<0.0001
Sex, male (%)	532 (76%)	121 (84%)	411 (74%)	0.0096
BMI (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	0.3265
WC (cm)	88 ± 11	90 ± 11	88 ± 11	0.026
Systolic blood pressure (mmHg)	127 ± 16	129 ± 16	127 ± 16	0.1278
Diastolic blood pressure (mmHg)	79 ± 12	79 ± 12	79 ± 12	0.6478
Heart rate (b.p.m.)	71 ± 12	69 ± 10	72 ± 12	0.0025
Smoking, *n* (%)	263 (37%)	56 (39%)	207 (37%)	0.5538
Diseases				
DM (%)	267 (38%)	96 (67%)	171 (31%)	<0.0001
MetS (%)	297 (42%)	78 (54%)	219 (39%)	<0.0001
DM and MetS (%)	164 (23%)	60 (42%)	104 (19%)	<0.0001
HT (%)	276 (39%)	75 (52%)	201 (36%)	0.0004
DL (%)	409 (58%)	79 (55%)	330 (59%)	0.3533
Prior cardiovascular disease (%)	10 (1.7%)	3 (2.3%)	7 (1.5%)	0.4883
Test values				
HbA1c (%)	6.4 ± 1.4	6.8 ± 1.5	6.3 ± 1.3	<0.0001
Total cholesterol (mg/dL)	207 ± 35	198 ± 34	209 ± 35	0.0008
Triglyceride (mg/dL)	125 (78–186)	116 (78–182)	127 (78–187)	0.3587
HDL cholesterol (mg/dL)	58 ± 15	56 ± 14	59 ± 16	0.0542
LDL cholesterol (mg/dL)	126 ± 33	121 ± 32	127 ± 33	0.0604
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.4089
Alanine aminotransferase (U/L)	24 (16–33)	25 (17–33)	24 (16–34)	0.5632

Continuous data given as the mean ± standard deviation, *n* (%) or median (interquartile range) unless otherwise specified. BMI, body mass index; DL, dyslipidemia with generally accepted definition; DM, diabetes; fQRS, fragmented QRS; HDL, high-density lipoprotein; HT, hypertension with generally accepted definition; LDL, low-density lipoprotein; MetS, metabolic syndrome using JIM criteria; WC, waist circumference.

Table 2 | Characteristics of bundle branch blocks and fragmented QRS on electrocardiography

Parameter	Total	DM+ MetS+	DM+ MetS–	DM– MetS+	DM– MetS–
No. participants	702	164 (23%)	103 (15%)	133 (19%)	302 (43%)
Blocks					
RBBB	25 (4%)	10 (40%)	7 (28%)	1 (4%)	7 (28%)
LBBB	2 (0.3%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)
fQRS	144 (21%)	60 (37%)	36 (35%)	18 (14%)	30 (10%)
fQRS region					
Inferior leads	108 (75%)	48 (44%)	25 (23%)	15 (14%)	20 (19%)
Anterior leads	66 (46%)	26 (39%)	19 (29%)	6 (9%)	15 (24%)
Lateral leads	10 (7%)	5 (50%)	1 (10%)	0 (0%)	4 (40%)
Multiple regions	36 (25%)	18 (50%)	8 (22%)	3 (8%)	7 (19%)
fQRS form					
Fragmented QRS	8 (6%)	2 (25%)	2 (25%)	1 (13%)	3 (37%)
rSr	5 (3%)	2 (40%)	0 (0%)	0 (0%)	3 (60%)
Notched S	107 (74%)	46 (43%)	28 (26%)	13 (12%)	20 (19%)
RSR′	4 (3%)	1 (25%)	0 (0%)	2 (50%)	1 (25%)
Notched R	102 (71%)	45 (44%)	24 (23%)	12 (12%)	21 (21%)
RSR′ with ST elevation	4 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)

Fragmented QRS (fQRS) finding was categorized following *Circulation* 113(21): 2495–501, 2006 and *Circ Arrhythm Electrophysiol* 1(4):258–68, 2008. DM, diabetes; LBBB, left bundle branch block; MetS, metabolic syndrome using JIM criteria; RBBB, right bundle branch block.

included various RSR' patterns, including an additional R wave (R'), notching of the R wave or the S wave, or the presence of more than one R' (fragmentation) in two continuous leads corresponding to a major lead set for major coronary artery territory. An fQRS was present if found in two or more contiguous anterior leads, lateral leads or inferior leads. In cases with bundle branch block (BBB), we followed the fragmented BBB evaluation[18]. Right BBB and left BBB were defined by the standard ECG criteria (QRS duration ≥120 ms), and f-BBB was defined as various RSR' patterns with or without a Q wave, with more than two R waves (R') or more than two notches in the R wave, or more than two notches in the downstroke or upstroke of the S wave in two contiguous leads corresponding to a major coronary artery territory. Other ECG findings were evaluated with Minnesota-code statements by the ECG records and manual checks. All ECGs were assessed with a single cardiologist blinded to the patients' clinical and laboratory characteristics. The concordance rate in detecting the fQRS was 97% to the other cardiologists who already published studies on fQRS[19,20].

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as percentages. A comparison of the categorical variables between the groups was carried out using a χ^2-test. Continuous variables were compared using an unpaired *t*-test and a Mann–Whitney *U*-test. Multivariable regression analysis was used to assess independent contributors. For stepwise analysis, parameters having an association to fQRS with $P < 0.10$ were entered into the analysis. Odds ratios (ORs) for the existence of fQRS were calculated using logistic regression. The results of multivariate regression analyses were presented as OR with a 95% confidence interval (CI). The predictive ability of diabetes mellitus and other risk factors for the presence of fQRS was evaluated using receiver operating curve (ROC) analysis calculating the area under the curve (AUC) and standard error. $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using JMP Pro 15.3 on Mac (SAS Institute Inc., Cary, NC, USA).

RESULTS

The clinical and laboratory characteristics of patients enrolled in the present study are summarized in Tables 1 and 2. Overall, the prevalence of fQRS was 21% in our study population. The characteristics of fQRS observed in this study are summarized in Table 3. Participants with fQRS, as compared with those without the condition, were different in age, sex, waist circumference, heart rate, hemoglobin A1c, total cholesterol, and the prevalence of HT, MetS and diabetes mellitus.

The prevalence of fQRS was statistically higher in participants with diabetes mellitus (36%) than diabetes mellitus–MetS+ participants (14%) and control participants (10%; $P < 0.001$; Figure 1a). The prevalence of fQRS was statistically higher in participants with diabetes mellitus irrespective of accompanying other risk factors, including visceral adiposity, HT and DL, than the participants with just the risk factors and control participants ($P < 0.001$; Figure 1b–d).

Using ROC analyses for fQRS, the AUC was 0.72 for patients with diabetes mellitus and traditional risk factors (age, gender, HT, DL and smoking; red), 0.68 for patients with MetS and traditional risk factors (green), and 0.66 for patients with traditional risk factors only (blue; Figure 2a). The AUC for the ROC was 0.72 (95% CI 0.67–0.76) for diabetes mellitus and traditional risk factors, which is significantly different than those with traditional risk factors alone ($P = 0.0007$). Conversely, the AUC for the ROC was 0.68 (95% CI 0.63–0.72) for MetS and the traditional risk factors, which was significantly different from that of traditional risk factors alone ($P = 0.0168$).

We next used multivariable analysis to compare the contributions of diabetes mellitus on fQRS. Compared with the reference group without diabetes mellitus, participants with diabetes mellitus had more than a threefold higher likelihood of showing fQRS (OR 3.41, 95% CI 2.25–5.22; $P < 0.0001$), after adjusting for traditional risk factors (Table 3, model 1).

Our stepwise analysis showed that age and diabetes mellitus were significant contributors to the presence of fQRS. Participants with diabetes mellitus had more than a threefold higher incidence of fQRS than those without diabetes mellitus (OR 3.81, 95% CI 2.55–5.76; $P < 0.0001$) after adjusting for age (Table 3, model 2). The AUC for the ROC analyses of fQRS was 0.71 for diabetes mellitus and age (red), 0.66 for MetS and age (green) and 0.64 for only age (blue; Figure 2b). The AUC for the ROC with diabetes mellitus and age was only significantly different from age ($P < 0.0001$). Together taken, the present data show a significant correlation between fQRS and diabetes mellitus, which might hold clinical significance potential in the future.

DISCUSSION

The objective of the present study was to determine whether diabetes mellitus or MetS were significant risk factors for fQRS using electrocardiography. A higher frequency of patients with fQRS was observed among participants with diabetes mellitus, compared with those without diabetes mellitus. Diabetes mellitus was characterized by cryptic progressive accumulation of interstitial myocardial fibrosis and impairment of diastolic function in patients with long-standing diabetes mellitus. The degree of myocardial fibrosis appeared to have a significant effect on clinical progression, resulting in heart failure with a preserved ejection fraction. Myocardial fibrosis could not be detected by standard echocardiographic examination until it had progressed. It has been shown that the amount of myocardial fibrosis detected on contrast-enhanced magnetic resonance imaging is closely correlated to quantitative histopathology[21]. Even though it has high sensitivity and specificity, the applicability of magnetic resonance imaging to all diabetes mellitus patients is limited due to technical and financial issues.

Table 3 | Binary logistic regression analysis of independent predictors for the presence of fragmented QRS

Independent variables	Model 1 OR (95% CI)	*P*-value	Model 2 OR (95% CI)	*P*-value
DM	3.41 (2.25–5.22)	<0.0001	3.81 (2.55–5.76)	<0.0001
Age (every 10 years-of-age)	1.39 (1.07–1.81)	0.0127	1.46 (1.13–1.89)	0.0035
VA	1.38 (0.88–2.17)	0.1597	–	–
DL	1.28 (0.85–1.94)	0.2402	–	–
Sex (male/female)	1.34 (0.80–2.29)	0.2777	–	–
HT	1.21 (0.80–1.82)	0.3732	–	–

Model 1: Odds ratios (ORs) for fragmented QRS were calculated using logistic regression with adjustment for age, sex, hypertension, dyslipidemia, diabetes (DM) and waist circumference meeting the Japanese Society of Internal Medicine metabolic syndrome criteria. Model 2: ORs for fQRS were calculated using logistic regression with adjustment for age and DM after pre-elimination of the variables with the backward logistic regression method. Hypertension (HT) was diagnosed if peripheral blood pressure was ≥140/90 mmHg or if the health questionnaire indicated current antihypertensive medications. Dyslipidemia (DL) was diagnosed if total cholesterol levels were ≥220 mg/dL, low-density lipoprotein cholesterol levels were ≥140 mg/dL or high-density lipoprotein cholesterol levels were <40 mg/dL or fasting triglyceride levels were >150 mg/dL or if the health questionnaire indicated current medications for dyslipidemia. CI, confidence interval; VA, visceral adiposity following Japanese Society of Internal Medicine MetS criteria; WC, waist circumference.

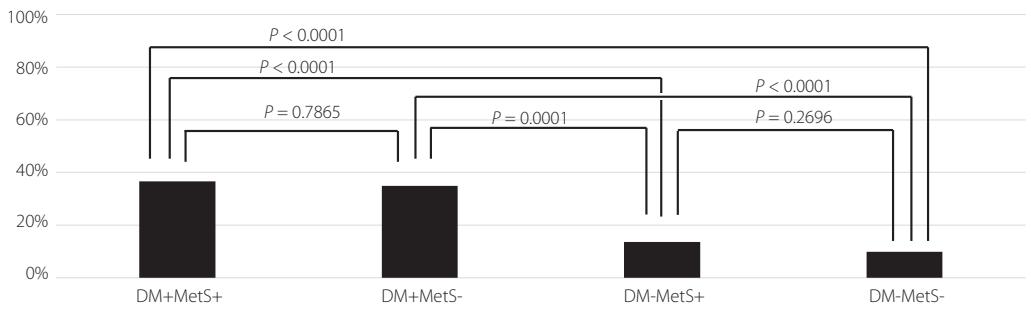
fQRS on a standard 12-lead ECG is a sensitive and highly specific diagnostic marker of myocardial fibrosis in patients with known or suspected coronary artery disease and congenital heart disease[18,22,23]. In previous studies, significant elevation in the frequency of fQRS has been observed in diabetes mellitus, MetS and other diseases without obvious cardiovascular symptoms. Bayramoglu *et al.*[24] reported a prevalence of fQRS of 28%, Eren *et al.*[25] reported 37.5% among diabetes mellitus patients in a Turkish population and using coronary angiography, Mahfouz *et al.*[26] reported 62% in Egyptian diabetes mellitus patients. In previous studies on MetS, 20% of patients showed fQRS in one study[27], and 26.1% of MetS patients compared with 14.6% of control participants in another study[28]. Among patients with systemic lupus erythematosus at diagnosis, 59.1% had fQRS[29]. fQRS was detected in 32.4% of ankylosing spondylitis patients compared with 7.14% in the control group[30]. A total of 37.5% of patients with rheumatoid arthritis compared with 5% of control participants had fQRS[31]. In thalassemia major, 86% of patients with cardiac involvement had fQRS, and 22% of patients with non-involvement[32]. The present results are consistent with these previous studies, highlighting the clinical usefulness of determining fQRS for diabetes mellitus and MetS patients with subclinical myocardial fibrosis.

From the present study, we were able to draw several important conclusions. First, fQRS has a stronger correlation with hyperglycemia than with insulin resistance. The Japanese Society of Internal Medicine criteria refer to MetS as an insulin-resistant state, as abdominal adiposity is an indispensable component of this criterion[33]. No previous reports have compared the contribution of diabetes mellitus and MetS on fQRS. In the present study, using a routine health checkup in a Japanese patient cohort separated according to the presence of diabetes mellitus and MetS, we found a higher frequency of fQRS in participants with diabetes mellitus, compared with those with MetS. Hypertension is the most prevalent MetS component in the general Japanese population. A previous report showed a high prevalence of fQRS in participants with hypertension[34]. In the current study, the contribution of hypertension on fQRS was not significant. As cardiac fibrosis in hypertension parallels left ventricular hypertrophy[35], we consider that participants with hypertension in the present study could be well managed with blood pressure medication.

In relation to diabetic cardiomyopathy (DCM)[36,37], it is conceivable to postulate that myocardial scar formation relates to the initial appearance of myocardial damage in DCM

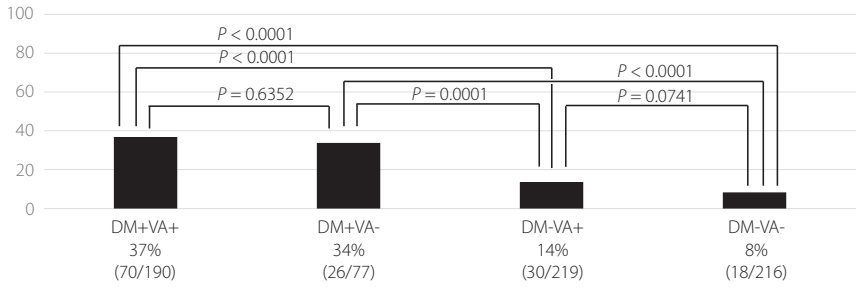
Figure 1 | Prevalence of fragmented QRS (fQRS) among the following groups: (a) with diabetes (DM+) with metabolic syndrome (MetS+), DM+ without Mets (MetS–), without diabetes- (DM–) MetS+ and DM– without MetS (MetS–). The table below the graph indicates the corresponding MetS component factors for each group. MetS was defined using Japanese Society of Internal Medicine (JIM) criteria. High blood pressure meeting JIM MetS criteria was diagnosed if systolic blood pressure was ≥130 mmHg, diastolic blood pressure ≥85 mmHg or the health questionnaire indicated current antihypertensive medications. Dyslipidemia meeting the JIM MetS criteria was diagnosed if TG was >150 mg/dL (>1.7 mmol/L) and/or high-density lipoprotein cholesterol was <40 mg/dL (<1.03 mmol/L) or the health questionnaire indicated current lipid-lowering medications; (b) DM+ with visceral adiposity (VA+), DM+ without visceral adiposity (VA–), without diabetes (DM–) with visceral adiposity (VA+) and DM– VA–; (c) DM+ with hypertension (HT+), DM+ without hypertension (HT–), DM– HT+ and DM– HT–; and (d) DM+ with dyslipidemia (DL+), DM+ without dyslipidemia (DL–), DM– DL+ and DM– DL–. HT was diagnosed if peripheral blood pressure was ≥140/90 mmHg or if the health questionnaire indicated current antihypertensive medications. DL was diagnosed if total cholesterol levels. were≥220 mg/dL or low-density lipoprotein cholesterol levels ≥140 mg/dL or high-density lipoprotein cholesterol levels <40mg/dL levels or fasting triglyceride levels were >150 mg/dL or if the health questionnaire indicated current medications for dyslipidemia. VA was diagnosed as a waist circumference >85 cm in men or >90 cm in women. A comparison of the categorical variables between the groups was carried out using a χ^2-test. FPG, fasting plasma glucose.

(a)

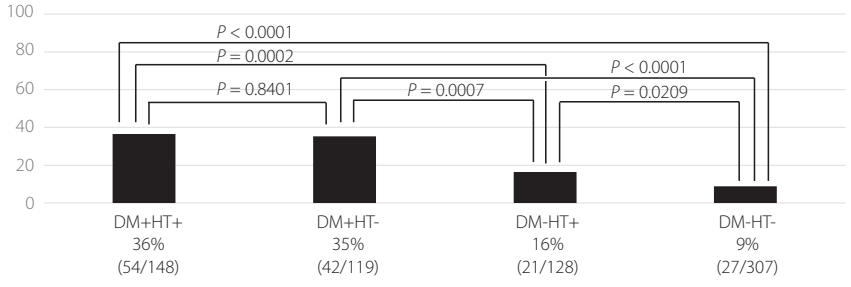


DM	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
MetS	+	+	+	-	-	-	-	-	+	+	+	-	-	-	-	-	-	-
	37% (60/164)			35% (36/103)					14% (18/133)			10% (30/302)						
VA	+	+	+	-	-	-	+	-	+	+	+	+	+	+	-	-	-	-
nonDM and FPG≥110	-	-	-	-	-	-	-	-	+/-	+	+	-	-	+/-	+/-	+/-	+/-	+/-
high blood pressure meeting JIM MetS criteria	+	+	-	+	+	-	-	-	+	+	-	+	-	-	+	+	-	-
dyslipidemia meeting JIM MetS criteria	+	-	+	+	-	+	-	-	+	-	+	-	+	-	+	-	+	-
	38% (29/77)	38% (24/64)	30% (7/23)	38% (6/16)	23% (7/31)	22% (2/9)	38% (10/26)	52% (11/21)	14% (18/129)	0% (0/3)	0% (0/1)	28% (7/25)	7% (2/30)	10% (3/31)	0% (0/12)	12% (6/49)	0% (0/16)	9% (12/139)

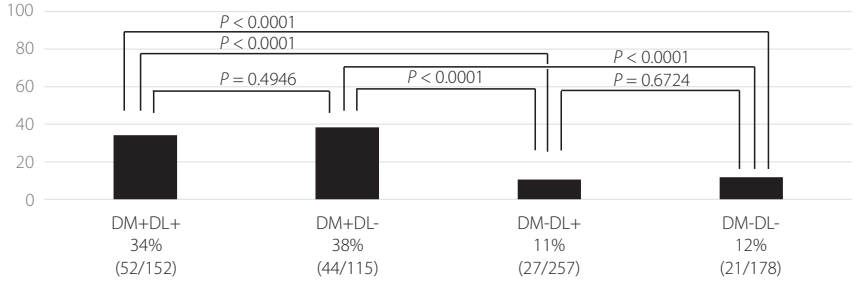
(b)

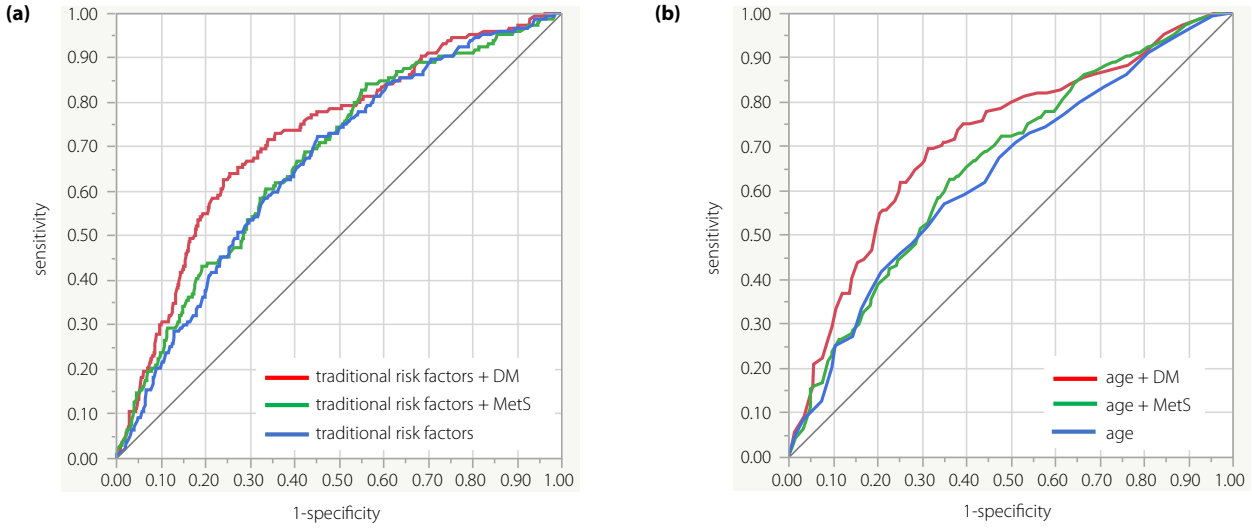


(c)



(d)





	AUC	SE	95%CI	*P*-value to *
traditional risk factors + DM	0.72	0.024	0.67-0.76	0.0007
traditional risk factors + MetS	0.68	0.024	0.63-0.72	0.0168
* traditional risk factors only	0.66	0.025	0.61-0.71	-

	AUC	SE	95%CI	*P*-value to *
age + DM	0.71	0.025	0.66-0.76	<0.0001
age + MetS	0.66	0.025	0.61-0.70	0.1287
* age only	0.64	0.026	0.58-0.68	-

Figure 2 | The predictive ability of diabetes (DM) and other traditional risk factors for the presence of fragmented QRS (fQRS) was evaluated using receiver operating characteristic curve analysis calculating the area under the curve (AUC) and standard error (SE). Receiver operating characteristic curve analyses showed the predictive values for established fQRS and risk factors. Traditional risk factors included age, gender, smoking, hypertension, dyslipidemia and smoking. Hypertension was diagnosed if peripheral blood pressure was ≥140/90 mmHg, or if the health questionnaire indicated current antihypertensive medications. Dyslipidemia was diagnosed if total cholesterol levels were ≥220 mg/dL or low-density lipoprotein cholesterol levels ≥140 mg/dL or high-density lipoprotein cholesterol levels <40 mg/dL levels or fasting triglyceride levels >150 mg/dL or if the health questionnaire indicated current medications for dyslipidemia. Smoking was applied to current smokers. (a) Red line represents diabetes and traditional risk factors (AUC 0.72); the green line metabolic syndrome (MetS) and traditional risk factors (AUC 0.68); and the blue line is traditional risk factors only (AUC 0.66). (b) The red line represents diabetes and age (AUC 0.71); the green line MetS and age (AUC 0.66); the blue line representing age only (AUC 0.64). The red lines in (a) and (d) were consistent with model 1 and model 2 presented in Table 3, respectively. CI, confidence interval.

patients[8,38,39]. Furthermore, in patients with diabetes mellitus, the amount of myocardial fibrosis significantly affects clinical status, as well as long-term mortality and morbidity. Also, several studies have shown that a quantitative assessment of myocardial fibrosis can provide additional prognostic information in patients with diabetes mellitus[40–42]. The clinical significance of fQRS is related to its association with myocardial fibrosis and heterogeneity in myocardial conduction[43]. It has been shown that patients with fQRS have significant heterogeneity of myocardial conduction and an increased risk of ventricular tachycardia[44]. Accordingly, the evaluation of fQRS in diabetes mellitus patients appears to be particularly important when we speculate on the possibility of DCM[24,45].

Although the present study was comprehensive in nature, retrospective analyses always carry a degree of limitation. Specifically, our study lacked a clinical follow up, therefore, we could not conclude whether or not the presence of fQRS was clinically significant in patients with diabetes mellitus. Furthermore, we did not carry out cardiac magnetic resonance imaging, which is considered to be a gold standard in myocardial fibrosis and a meaningful tool to evaluate DCM, irrespective of myocardial damage[46]. Participants with prior cardiovascular disease in the present study were low (1.7%) and did not correlate with fQRS. Further studies are required to improve the predictive efficacy of fQRS in diabetes mellitus patients and provide the experimental impetus to further inform on the pathophysiology of DCM.

The primary objective of the present study was to find a useful diagnostic tool to detect CHF candidates in the very early stage. A high prevalence of fQRS in diabetes mellitus patients suggests the need for an additional biomarker to clarify them as candidates of heart failure. The present study provides the groundwork to further investigate these important correlations between myocardial fibrosis and diabetes mellitus.

We compared the prevalence of fQRS in patients with diabetes mellitus and MetS to examine the contribution of persistent hyperglycemia and the insulin-resistant state. We found that patients with diabetes showed a higher prevalence of fQRS compared with those with MetS. We postulate that the persistent hyperglycemic state contributed to the existence of fQRS

suggesting myocardial fibrosis. The present findings suggest that fRQS could be a biomarker for diabetic cardiomyopathy with increased myocardial fibrosis.

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REFERENCES

1. Das MK, Khan B, Jacob S, *et al*. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation* 2006; 113: 2495–2501.
2. Ahn MS, Kim JB, Joung B, *et al*. Prognostic implications of fragmented QRS and its relationship with delayed contrast-enhanced cardiovascular magnetic resonance imaging in patients with non-ischemic dilated cardiomyopathy. *Int J Cardiol* 2013; 167: 1417–1422.
3. Das MK, Saha C, El Masry H, *et al*. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm* 2007; 4: 1385–1392.
4. Brenyo A, Pietrasik G, Barsheshet A, *et al*. QRS fragmentation and the risk of sudden cardiac death in MADIT II. *J Cardiovasc Electrophysiol* 2012; 23: 1343–1348.
5. Fischer VW, Barner HB, Larose LS. Pathomorphologic aspects of muscular tissue in diabetes mellitus. *Hum Pathol* 1984; 15: 1127–1136.
6. Nunoda S, Genda A, Sugihara N, *et al*. Quantitative approach to the histopathology of the biopsied right ventricular myocardium in patients with diabetes mellitus. *Heart Vessels* 1985; 1: 43–47.
7. Campbell DJ, Somaratne JB, Jenkins AJ, *et al*. Impact of type 2 diabetes and the metabolic syndrome on myocardial structure and microvasculature of men with coronary artery disease. *Cardiovasc Diabetol* 2011; 10: 80.
8. Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An update of mechanisms contributing to this clinical entity. *Circ Res* 2018; 122: 624–638.
9. Roy C, Slimani A, de Meester C, *et al*. Associations and prognostic significance of diffuse myocardial fibrosis by cardiovascular magnetic resonance in heart failure with preserved ejection fraction. *J Cardiovasc Magn Reson* 2018; 20: 55.
10. Asbun J, Villarreal FJ. The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. *J Am Coll Cardiol* 2006; 47: 693–700.
11. Ares-Carrasco S, Picatoste B, Benito-Martin A, *et al*. Myocardial fibrosis and apoptosis, but not inflammation, are present in long-term experimental diabetes. *Am J Physiol Heart Circ Physiol* 2009; 297: H2109–2119.
12. Nagata Y, Yamagami T, Nutbeam D, *et al*. Incremental yield of ECG screening repeated annually over 4 years in an adult Japanese population without prior atrial fibrillation: a retrospective cohort study. *BMJ Open* 2020; 10: e035650.
13. Shimamoto K, Ando K, Fujita T, *et al*. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2014). *Hypertens Res* 2014; 37: 253–390.
14. Kinoshita M, Yokote K, Arai H, *et al*. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *J Atheroscler Thromb* 2018; 25: 846–984.
15. Araki E, Goto A, Kondo T, *et al*. Japanese clinical practice guideline for diabetes 2019. *Diabetol Int* 2020; 11: 165–223.
16. Matsuzawa Y. Metabolic syndrome-definition and diagnostic criteria in Japan. *J Jpn Soc Int Med* 2005; 94: 188–203 (Japanese).
17. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66: 987–992.
18. Das MK, Suradi H, Maskoun W, *et al*. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. *Circulation Arrhyth Electrophysiol* 2008; 1: 258–268.
19. Konno T, Hayashi K, Fujino N, *et al*. Electrocardiographic QRS fragmentation as a marker for myocardial fibrosis in hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2015; 26: 1081–1087.
20. Nomura A, Konno T, Fujita T, *et al*. Fragmented QRS predicts heart failure progression in patients with hypertrophic cardiomyopathy. *Circ J* 2015; 79: 136–143.
21. Azevedo CF, Nigri M, Higuchi ML, *et al*. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol* 2010; 56: 278–287.
22. Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. *Curr Opin Cardiol* 2010; 25: 59–64.

23. Park SJ, On YK, Kim JS, *et al*. Relation of fragmented QRS complex to right ventricular fibrosis detected by late gadolinium enhancement cardiac magnetic resonance in adults with repaired tetralogy of fallot. *Am J Cardiol* 2012; 109: 110–115.
24. Bayramoglu A, Tasolar H, Kaya Y, *et al*. Fragmented QRS complexes are associated with left ventricular dysfunction in patients with type-2 diabetes mellitus: a two-dimensional speckle tracking echocardiography study. *Acta Cardiol* 2018; 73: 449–456.
25. Eren H, Kaya U, Ocal L, *et al*. Presence of fragmented QRS may be associated with complex ventricular arrhythmias in patients with type-2 diabetes mellitus. *Acta Cardiol* 2019. https://doi.org/10.1080/00015385.2019.1693117
26. Mahfouz R, Arab M, El-Dosoky I. Fragmented QRS complex is independently associated with coronary microvascular function in asymptomatic patients with diabetes mellitus. *J Indian College Cardiol* 2019; 9: 136–140.
27. Bayramoglu A, Tasolar H, Bektas O, *et al*. Association between metabolic syndrome and fragmented QRS complexes: Speckle tracking echocardiography study. *J Electrocardiol* 2017; 50: 889–893.
28. Oner E, Erturk M, Birant A, *et al*. Fragmented QRS complexes are associated with left ventricular systolic and diastolic dysfunctions in patients with metabolic syndrome. *Cardiol J* 2015; 22: 691–698.
29. Hosonuma M, Yajima N, Takahashi R, *et al*. Fragmented QRS complex in patients with systemic lupus erythematosus at the time of diagnosis and its relationship with disease activity. *PLoS One* 2020; 15: e0227022.
30. Inanir A, Ceyhan K, Okan S, *et al*. Frequency of fragmented QRS in ankylosing spondylitis: a prospective controlled study. *Z Rheumatol* 2013; 72: 468–473.
31. Kadi H, Inanir A, Habiboglu A, *et al*. Frequency of fragmented QRS on ECG is increased in patients with rheumatoid arthritis without cardiovascular disease: a pilot study. *Mod Rheumatol* 2014; 22: 238–242.
32. Bayar N, Kurtoglu E, Arslan S, *et al*. Assessment of the relationship between fragmented QRS and cardiac iron overload in patients with beta-thalassemia major. *Anatol J Cardiol* 2015; 15: 132–136.
33. Kanauchi M, Kawano T, Kanauchi K, *et al*. New "pre-diabetes" category and the metabolic syndrome in Japanese. *Horm Metab Res* 2005; 37: 622–626.
34. Eyuboglu M. Fragmented QRS as a marker of myocardial fibrosis in hypertension: a systematic review. *Curr Hypertens Rep* 2019; 21: 73.
35. Diez J. Mechanisms of cardiac fibrosis in hypertension. *J Clin Hypertens (Greenwich)* 2007; 9: 546–550.
36. Bauters C, Lamblin N, Mc Fadden EP, *et al*. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol* 2003; 2: 1.
37. Fuentes-Antras J, Picatoste B, Ramirez E, *et al*. Targeting metabolic disturbance in the diabetic heart. *Cardiovasc Diabetol* 2015; 14: 17.
38. Yue Y, Meng K, Pu Y, *et al*. Transforming growth factor beta (TGF-beta) mediates cardiac fibrosis and induces diabetic cardiomyopathy. *Diabetes Res Clin Pract* 2017; 133: 124–130.
39. Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. *Diabetologia* 2018; 61: 21–28.
40. Armstrong AC, Ambale-Venkatesh B, Turkbey E, *et al*. Association of cardiovascular risk factors and myocardial fibrosis with early cardiac dysfunction in type 1 diabetes: The diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 2017; 40: 405–411.
41. Kwong RY, Sattar H, Wu H, *et al*. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008; 118: 1011–1020.
42. Jellis C, Martin J, Narula J, *et al*. Assessment of nonischemic myocardial fibrosis. *J Am Coll Cardiol* 2010; 56: 89–97.
43. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart Rhythm* 2009; 6: S8–14.
44. Morita H, Kusano KF, Miura D, *et al*. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation* 2008; 118: 1697–1704.
45. Lorenzo-Almoros A, Tunon J, Orejas M, *et al*. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol* 2017; 16: 28.
46. Hamai J, Nakamura A, Kato S, *et al*. The association of cardiac function, structure, and glycemic control in patients with old myocardial infarction: a study using cardiac magnetic resonance. *Diabetol Int* 2017; 8: 23–29.