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Evaluation of myocardial fibrosis in diabetes with cardiac magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c

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ABSTRACT

Aim: The aim of the study was to assess the extracellular volume fraction (ECV) in type 2 diabetes mellitus (T2DM) patients with different level of hemoglobin A1c (HbA1c) by cardiac magnetic resonance (CMR), and the ability of HbA1c to predict myocardial fibrosis.

Methods: In total, 80 T2DM patients and 20 age- and sex-matched controls were prospective enrolled and underwent CMR to obtain ECV value and LV function parameters. We divided all patients into a group of HbA1c < 7.0% and a group of HbA1c ≥ 7.0%.

Results: In the higher HbA1c group the ECV value (all $p < 0.001$) was higher than both lower HbA1c group (36.23% vs. 32.19%, $p < 0.001$) and controls (36.23% vs. 29.73%, $p < 0.001$). HbA1c was positively associated ($\beta = 0.36$, $p = 0.004$) with ECV, and it was also an independent predictor of myocardial fibrosis (OR = 2.00, P = 0.014). The ROC analysis showed that 7.1% was the optimal cutoff value of HbA1c that predicted the risk of myocardial fibrosis with high diagnostic accuracy (area under the curve = 0.78).

Conclusion: T1 mapping provided myocardial fibrosis information in T2DM patients. HbA1c is positively correlated with myocardial fibrosis and can be an independently predictor of myocardial fibrosis, which may be helpful for the clinical decision-making of blood glucose control.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide, which leads to myocardial dysfunction and even heart failure in long-term follow-up [1–3]. The potential pathomechanism of diabetic myocardial damage is multifactorial and result in diffuse myocardial fibrosis [4,5]. Myocardial fibrosis is related to the pathogenesis of left ventricle hypertrophy and has been confirmed in the middle or later stage of diabetic cardialmyopathy, which paly an important role in cardiac structure change and the abnormality of cardiac function [6,7]. AHA/ACC/ADA have conservatively endorsed the cardiovascular benefits of glycemic control in 2009 [8]. Hemoglobin A1C (HbA1c) as an important biomarker for blood glucose control in T2DM patients, can effectively reflect to the recent blood glucose levels. Previous studies have reported that the process of endothelial dysfunction, and even myocardial fibrosis might be associated with hyperglycemia by accumulation of glycosylation end-products [9,10]. Therefore, for T2DM patients, effective HbA1c control is of great significance to the early monitoring of myocardial fibrosis, but there is still controversy in this aspect at present.

Myocardium biopsy as an interventional examination is the gold standard for evaluating myocardial fibrosis. Cardiovascular magnetic resonance (CMR) as a non-invasive method can provide functional and tissue characterization parameters is wildly using recent years [11,12]. Diffuse myocardial fibrosis can cause excessive accumulation of type I collagen and leads to the expansion of expansion of extracellular matrix (ECM), which is related to total myocardial volume. The Extracellular volume fraction (ECV) of T1-mapping technique in CMR can noninvasively quantify detect the expansion of ECM, which might represent the exists and degree of myocardial fibrosis [13,14].

Previous studies reported the ECV has highly sensitive and reproducible with the histology [15–17], and now it has been as an effect biomarker for evaluate diffuse myocardial fibrosis [15,18,19]. Furthermore, ECV and adverse cardiovascular events are associated, the ECV is regarded as a significant predictor in terms of cardiovascular events such as cardiac mortality, heat failure and survival [20,14].

The purpose of our study is to assess the ECV in patients with T2DM with different levels of HbA1c using CMR and the ability of HbA1c in predicting myocardial fibrosis.

2. Methods and materials

2.1. Study population

The institutional ethics committee of our hospital confirmed in this study; we obtained the informed consent of each participant before the investigation. From March 2016 to October 2017 we prospectively enrolled 84 T2DM patients who was diagnosed with T2DM by the standards of the World Health Organization [21]. All the patients performed CMR. The exclusion criteria included: (1) contraindication of CMR; (2) history of myocardial infarction and other organic heart disease; (3) hypertension which is uncontrolled by drugs; (4) coronary heart disease (CHD); (4) chest pain, palpitation or dyspnea; (5) poor image quality. Finally, a total of 80 T2DM patients (47 males, age 58.26 ± 11.65 years) remained. In addition, age-, sex- and body mass index-marched healthy volunteers were recruited as the controls group. The exclusion criteria of the controls group included: DM; history of cardiovascular disease, electrocardiogram abnormalities and cardiovascular abnormal detected by CMR (myocardial late-gadolinium enhancement, abnormal ventricular motion and valvular stenosis). Finally, 20 healthy controls (8 males, age 54.06 ± 13.19 years) were included.

We collected clinical data regarding subject age, sex, basic anthropometry (height, weight), blood pressure, heart rate, the duration of diabetes and metabolic indexes (hematocrit (HCT), serum glucose, HbA1c, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL))for all patients and healthy controls. Blood pressure were detected about 20 min before CMR examinations. Blood sampling for metabolic indexes were obtained within 1 week of the CMR scan. According to Standards of Medical Care in Diabetes—2016 Abridged for Primary Care Providers, a reasonable HbA1c control target is < 7% [22], so we divided all the T2DM patients into a low HbAlc level group (HbA1c < 7.0%) and a high HbAlc level group (HbA1c ≥ 7.0%).

2.2. CMR scanning protocol

All patients and normal controls were examined in the supine position by using a 3.0-T whole-body scanner (Skrya; Siemens Medical Solutions, Erlangen, Germany). A dedicated two-element cardiac-phased array coil was used for signal detection. A manufacture's standard ECG-triggering device and end-inspiratory breath holding were used when examination, no one received tranquilizer. Following a survey scan, cine images such as long-axis four-chamber views and short-axis two-chamber views were acquired with a steady-state free-precession (SSFP) sequence (TR/TE 39.34/1.22 ms, flip angle 38 degrees, slice thickness 8 mm, field of view 360 × 300 mm^2 matrix size 256 × 166). Gadobenate dimeglumine (MultiHance; 0.5 mmol/ml; Bracco, Milan, Italy) was intravenously injected at a dose of 0.2 ml/kg body weight with an injection rate of 2.5–3.0 ml/s.

The prototype sequence used for T1 mapping was a modified look-locker inversion recovery (MOLLI) (TR/TE 346.56/1.12 ms, 8 mm thickness, field of view 360 × 300 mm^2, matrix size 256 × 166, flip angle 35 degrees, 7/8 partial-Fourier k-space sampling, PAT factor 2). Native and post-contrast T1 mapping were performed at basal, middle, and apical short axis of left ventricular slices. T1 maps were generated immediately after the scan and the motion correction (MOCO) technique was used. All the acquisition was performed during the end-inspiratory breath holding and all the subjects' condition was feasible and stable during the whole examination period

2.3. CMR data analysis

All images data of the T2DM patients and healthy controls were uploaded to an offline workstation using semiautomated software (cvi42; Circle Cardiovascular Imaging, Inc., Calgary, Canada). The endocardial and epicardial traces were manually delineated by two experienced radiologists in the serial short-axis slices at the end-diastolic and end-systolic phases. The moderator bands and papillary muscles should be excluded fiom the left ventricle. The left ventricular functional parameters including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF) and left ventricular mass were automatically acquired. The left ventricular end-diastolic dimension (LVEDD) and right ventricular end-diastolic dimension (RVEDD) were measured using 4-chamber view in all the patients and controls (Fig. 1). The left ventricle remodeling was characterized by the ratio of LV mass to LVEDV (LVMVR).

According to CVI software, the values of native T1, post-contrast T1 and ECV were automatically measured by the manually delineated mid-layer myocardium of left ventricular basal, middle and apical segments. The ECV measurements was calculated with the following formula [23]:

$$ECV = (1 - \text{haematocrit}) \times \frac{\left(\frac{1}{T1myopost}\right) - \left(\frac{1}{T1myopre}\right)}{\left(\frac{1}{T1bloodpost}\right) - \left(\frac{1}{T1bloodpre}\right)}$$

During the process of calculation, we excluded any myocardial segments disturbed with artifact, and finally obtained the global T1 value and ECV value (Fig. 2).

2.4. Statistical analysis

Statistical analyses were performed with commercially available SPSS (version 21.0 for windows; SPSS, Inc., Chicago, IL, USA). The results were expressed as the mean ± standard deviation (SD). One-way analysis of variance (ANOVA) test was used to evaluated the differences among normal controls and the T2DM patients with different HbA1c level. Bonferroni's correction for multi-group comparisons, the p-value of <0.017 was considered statistically significant. Univariable and multivariable stepwise linear regression analyses were performed to identify the relationship between hyperglycemia and adverse myocardial fibrosis. Multivariable logistic regression analyses were performed to identify the predictor of myocardial fibrosis. The receiver operating characteristic (ROC) analysis was also performed to assess whether the cut-off value for HbA1C can use to differentiating the diffuse myocardial fibrosis. We use the median of the ECV value of all our patients as the grouping basis for different degrees of myocardial fibrosis.

3. Results

3.1. Patient characteristics and metabolic parameters

Of the 80 T2DM patients, 41 s (16 males, mean age 59.65 ± 11.16 years, duration of diabetes 9.99 years) had a HbA1c < 7.0% and 39 (16 males, mean age 56.78 ± 13.38 years, duration of diabetes 9.3 years) had a HbA1c ≥ 7.0%. Table. 1 show all the baseline characteristics and metabolic parameters. The systolic pressure was higher in DM patients than normal controls, and the remaining baseline characteristics had no statistically significant difference among these three groups.

Fasting blood glucose and HbA1c were significantly higher in T2DM patients than that in normal controls, and these two parameters had statistically significant differences between the higher and lower T2DM patients' group (Glu: 10.20 ± 5.14 vs. 6.79 ± 1.85, mmol/l $p < 0.001$; HbA1c: 9.04 ± 2.63 vs. 6.37 ± 0.40, mmol/l $p < 0.001$). T2DM patients were also had a higher value of TG, TC and lower value of LDL, however, the values were not statistically significant (Table 1).

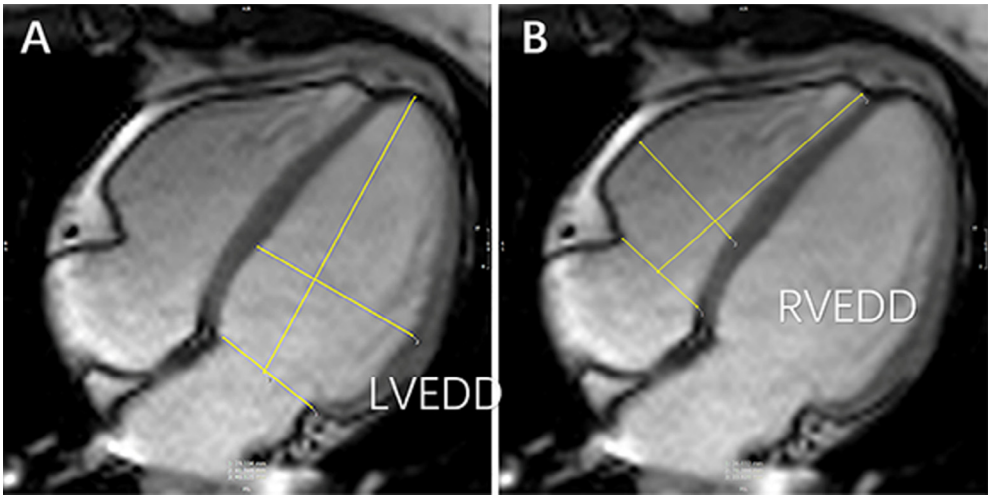

Fig. 1 – Measurement of LV, and RV (in DM patients) dimensions from four-chamber views in end-diastole (A and B). (LVEDD: left ventricular end-diastolic dimension; RVEDD: right ventricle end-diastolic dimension).

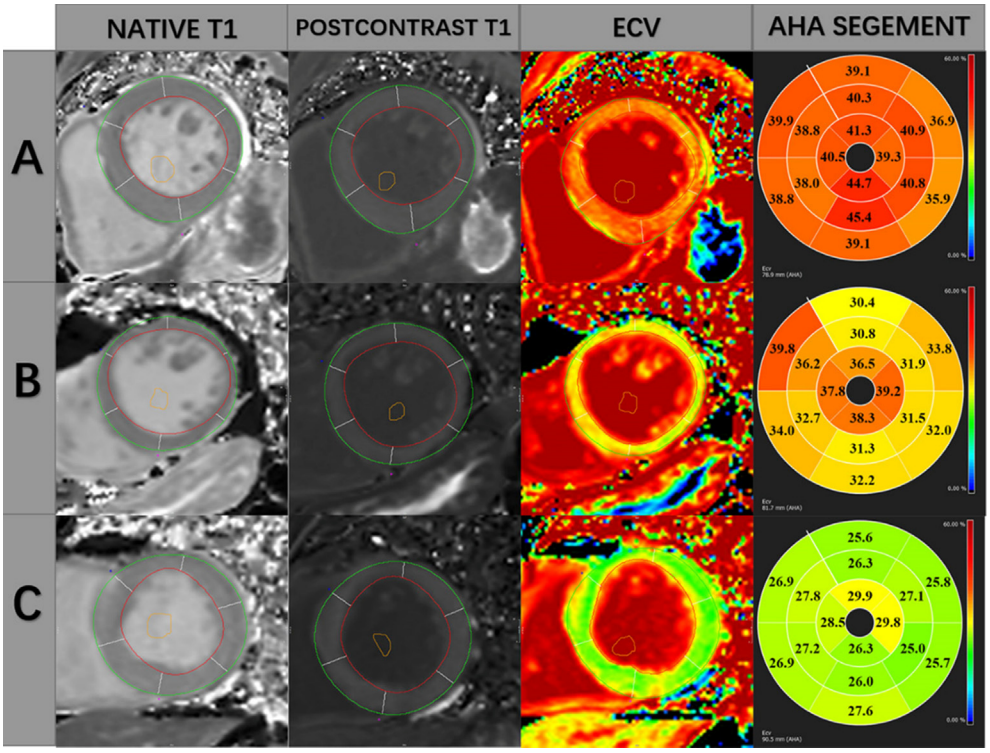

Fig. 2 – Representative T1 maps for a DM patient with HbA1c > 7.0% (A, HbA1c = 9.5%), a DM patient with HbA1c < 7.0%(B, HbA1c = 6.2%) and a normal controls (C). The endocardial and epicardial traces were delineated manually, native T1 value, postcontrast T1 value and ECV values based on the CVI software automatically. The AHA Bull's eye diagram shows the ECV value of each myocardial segment.

3.2. *CMR functional and dimensional parameters*

The results for the functional and dimensional parameters are summarized in Table 2. The T2DM patents with different HbA1c level had a significance lower value of LVEF and higher value of LV mass than normal control (all $p < 0.017$). There were no statistically differences of LVEDV and LVESV among these two DM patients' groups and normal group. Meanwhile, the results showed patients was associated with an increased LVMVR at 25%, (0.69 ± 0.16 vs 0.55 ± 0.10 g/ml, $P < 0.001$) in lower HbA1c group and 31%, (0.72 ± 0.17 vs 0.55 ± 0.10 g/ml, $P < 0.001$) in higher HbA1c group (Table 2). Regarding the dimensional parameters of DM patients, the RVEDD (higher HbA1c vs. normal: 42.15 ± 5.49 vs. 38.77 ± 4.32 mm; lower HbA1c vs. normal: 41.08 ± 4.78 vs. 38.77 ± 4.32 mm; all $p < 0.017$) and LVEDD (higher HbA1c vs. normal: 47.64 ± 6.48 vs. 45.44 ± 3.34 mm; lower HbA1c vs. normal: 47.88 ± 6.17 vs. 45.55 ± 3.34 cm; all $p < 0.017$) was significantly larger in T2DM patients than the controls, however, there were no statistically significant differences between these two DM patients' groups.

The myocardial systolic strain assessment revealed no significant differences in the left ventricular global radial, circumferential and longitudinal strain (all $p > 0.005$) among the two T2DM patients' group and the normal controls.

3.3. *T1 Mapping parameters*

Regarding for T1 mapping parameters (Table 2), the higher HbA1c group had a statistically significant higher ECV value than that of both the normal controls (36.23 ± 4.62 vs. $29.73 \pm 2.28\%$, $p < 0.001$) and the lower HbA1c group (36.23 ± 4.62 vs. $32.19 \pm 3.63\%$, $p < 0.001$). The lower HbA1c group also had a statistically significant higher ECV value (32.71 ± 2.41 vs. $29.73 \pm 2.28\%$, $p < 0.001$) than the normal controls. There was no statistically difference for native T1 value and post-contrast T1value among these three groups.

3.4. *HbA1c prediction of myocardial fibrosis*

ECV as a continuous variable was used as a surrogate for adverse myocardial fibrosis for multivariable linear and logistic regression analysis. The Pearson analysis showed that the HbA1c was positive relationship with ECV ($R = 0.33$, $P = 0.003$, Fig. 3). In multivariable stepwise linear regression analysis, HbA1c ($\beta = 0.36$, $p = 0.004$), systolic blood pressure ($\beta = 0.28$, $p = 0.021$) and LVEDV ($\beta = 0.26$, $p = 0.033$) were independently associated with ECV value (Model.4: $R^2 = 0.31$) (Table 3). The multivariable backward logistic regression analysis indicted the HbA1c was a favorable predictor (OR = 2.00, $P = 0.014$, Table. 4) for myocardial fibrosis, with the adjust of the duration of diabetes, hypertension, hyperlipidemia, BMI, and LVEF.

Table 1 – Baseline and metabolic parameters T2DM patients and the normal controls.

	Control (n = 20)	T2DM	
		HbA1c (%) < 7.0 (n = 41)	HbA1c (%) ≥ 7.0 (n = 39)
Baseline characteristics			
Age, y	54.06 ± 13.19	59.65 ± 11.16	56.78 ± 13.38
Male gender, n	8 (40.0%)	17(41.5%)	16(51.6%)§
Duration of diabetes, y	–	9.30 ± 7.36	9.99 ± 6.28
Height, cm	162.45 ± 4.36	163.65 ± 7.74	165.59 ± 8.29
Weight, kg	62.07 ± 2.64	63.79 ± 7.89	65.93 ± 10.18
BMI, kg/m^2	21.40 ± 1.98	23.83 ± 2.60	24.15 ± 2.96
Systolic pressure, mmHg	117.8 ± 5.13	132.82 ± 16.04*	135.23 ± 18.26*
Diastolic pressure, mmHg	79.4 ± 5.13	85.08 ± 10.27	77.16 ± 10.04
Heart rate, bpm	72.5 ± 12.42	74.15 ± 12.04	73.03 ± 10.75
Metabolic characteristics			
HbA1c, %	5.37 ± 0.38	6.37 ± 0.40*	9.04 ± 2.63*§
Glu, mmol/l	5.18 ± 0.31	6.79 ± 1.85*	10.20 ± 5.14*§
TG, mmol/L	1.22 ± 0.30	1.49 ± 1.116	1.43 ± 0.67
TC, mmol/L	4.17 ± 0.85	4.26 ± 0.86	4.46 ± 1.16
HDL, mmol/L	1.26 ± 0.18	1.27 ± 0.31	1.21 ± 0.33
LDL, mmol/L	2.86 ± 0.62	2.39 ± 0.71	2.61 ± 0.99
Medication, n (%)			
Insulin	–	17(21)	20(25)
Metformin	–	25(31)	19(24)
Sulfonylurea	–	13(16)	14(18)
α-glucosidase inhibitor	–	16(20)	18(22)
ACEI	–	8(10)	7(9)
β-blockers	–	3(4)	4(5)
Statin		18(43)	13(33)

Notes: The values are the mean ± SD, Numbers in the brackets are percentages. BMI: body Mass Index; TG: triglycerides; TC: triglyceride; HDL: high-density lipoprotein cholesterol; Glu: glucose; HbA1c: glycated hemoglobin.

* P < 0.017 versus normal group.

§ P < 0.017 versus T2DM with low level HbA1c.

Table 2 – CMR findings and T1 mapping parameters for T2DM patients with different HbA1c level and the normal controls.

	Control (n = 20)	T2DM	
		HbA1c (%) < 7.0 (n = 41)	HbA1c (%) ≥ 7.0 (n = 39)
Cardiac function			
LVEF, %	61.24 ± 2.54	58.15 ± 9.12*	57.63 ± 9.57*
LVEDV, ml/m^2	76.13 ± 9.34	71.91 ± 22.36	75.57 ± 19.36
LVESV, ml/m^2	29.52 ± 4.61	30.01 ± 17.01	31.16 ± 14.57
LVSV, ml/m^2	46.57 ± 5.83	41.89 ± 10.33*	44.46 ± 12.10
LV mass, g/m^2	45.70 ± 9.34	58.57 ± 16.47*	60.72 ± 15.57*
LVEDD, mm	45.55 ± 3.34	47.88 ± 6.17*	47.64 ± 6.48*
RVEDD, mm	38.77 ± 4.32	41.08 ± 4.78*	42.15 ± 5.49*
RVEDD/LVEDD	0.85 ± 0.12	0.86 ± 0.13	0.90 ± 0.15
LVMVR	0.55 ± 0.10	0.69 ± 0.16*	0.72 ± 0.17*
LVGRS	40.22 ± 7.81	42.08 ± 10.76	40.55 ± 13.90
LVGCS	−18.10 ± 2.07	−17.74 ± 2.99	−17.71 ± 3.56
LVGLS	−15.77 ± 1.97	−14.86 ± 2.62	−14.41 ± 3.00
T1 MAPPING			
Native TI, ms	1279.83 ± 121.85	1285.00 ± 54.09	1285.46 ± 68.82
Postcontrast T1, ms	503.50 ± 24.2	498.25 ± 50.92	523.06 ± 54.23
ECV, %	29.73 ± 2.28	32.19 ± 3.63*	36.23 ± 4.62*§

Notes: The values are the mean ± SD, Numbers in the brackets are percentages. LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVSV: left ventricular stroke volume, LVEDD: left ventricular end-diastolic dimension; RVEDD: right ventricle end-diastolic dimension; LVMVR: LV mass to LV end diastolic volume ratio. GRS: global radial strain, GCS: global circumferential strain, GLS: global longitudinal strain, ECV: extracellular volume.

* P < 0.017 versus normal group.

§ P < 0.017 versus T2DM with low level HbA1c.

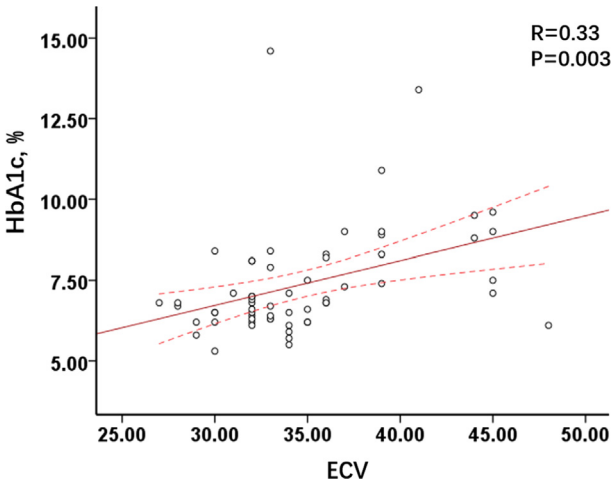

Fig. 3 – Relationship between HbA1c and ECV.

3.5. *ROC curve analysis*

In our study, according to the median value of ECV (value = 34) we divided patients into moderate-severe myocardial fibrosis and mild fibrosis. ROC analysis showed that 7.1 was the optimal cutoff values of HbA1c that predicted the risk of myocardial fibrosis (sensitivity 66.7%, specificity 83.3%, and area under the curve (AUC):0.79, Fig. 4). The Youden index of the HbA1c was 0.50.

4. Discussion

Myocardial fibrosis, as an important pathophysiological mechanism of cardiac structure and function changes in diabetic patients, has been reported to be associated with hyperglycemic metabolism [9,10]. Nowadays, studies have proved that the ECV of CMR T1 mapping technique is an important parameter that effectively reflects diffuse myocardial fibrosis [13,14]. The following principal findings were obtained through CMR: the ECV value was significantly higher in DM patients, especially in patients with HbA1 level $\geq$ 7.0%; HbA1c had a positive correlation with ECV and can be an independently predictor of myocardial fibrosis.

Diabetes is a chronic metabolic disease and heart failure is one of the serious complications. Diffuse myocardial fibrosis as one of the important stage of diabetic cardiomyopathy, may lead to cardiac dysfunction and even heart failure in long-term duration [1–3]. Previous studies have reported that the determination of ECV using CMR T1 mapping can be effective and noninvasive to detect the presence and degree of myocardial fibrosis [16,17].

Myocardium fibrosis as the most common middle or later phase pathophysiological change of diabetic myocardium, have been implicated in the pathogenesis of left ventricular hypertrophy and will cause cardiac structure change and cardiac dysfunction [9]. As an important stage of cardiac struc-

Table 3 – Model of multivariable linear regression analysis between ECV and Hemoglobin A1C.

	β (95% CI)	R	R^2	P value
Model 1				
HbA1c	0.33 (0.23–1.08)	0.33	0.11	0.003
Model 2				
HbA1c	0.37 (0.27–1.11)			
Duration of diabetes		0.37	0.14	0.002
Model 3				
HbA1c	0.40 (0.27–1.09)			0.002
Systolic blood pressure	0.32 (0.02–0.14)			0.011
Duration of diabetes, Age, Sex, BMI, Diastolic blood pressure, TG, TC		0.49	0.24	
Model 4				
HbA1c	0.36 (0.22–1.01)			0.004
Systolic blood pressure	0.28 (0.11–0.13)			0.021
LVEDV	0.26 (0.02–0.06)			0.033
Duration of diabetes, Age, Sex, BMI, Diastolic blood pressure, TG, TC, LVESV, LVEF		0.56	0.31	

Note: β: multivariable standardized regression coefficient; CI: confidence interval, other abbreviations are the same as in Tables 1 and 2.

Table 4 – Multivariable logistic regression analysis of independent predictors of myocardial fibrosis in diabetes patients.

	Univariable Analysis		Multivariable Analysis	
	R	P value	OR (95% CI)	P value
HbA1c	0.33	0.003	2.00 (1.15–3.47)	0.014
Duration of diabetes	0.07	0.568	–	–
Hypertension	−0.167	0.177	–	–
Hyperlipidemia	−0.167	0.144	–	–
BMI	−0.009	0.934	–	–
LVEF	0.105	0.308		

Note: β: multivariable standardized regression coefficient; OR: odd ratio, other abbreviations are the same as in Tables 1 and 2.

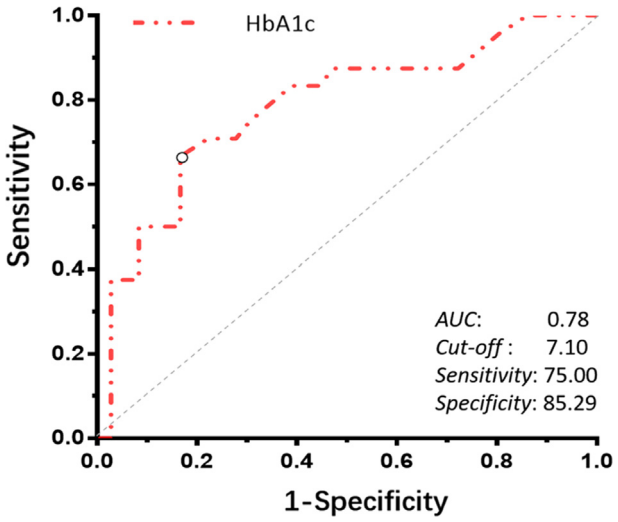

Fig. 4 – ROC analysis to predict the relationship between the high-level HbA1c and myocardial fibrosis. In ROC analysis, the sensitivity and specificity of HbA1c (HbA1c > 7.1) for predicting myocardial fibrosis in DM patients were 75.0% and 85.3%

ture changes, concentric LV remodeling often precedes the development of clinical heart failure, is a strong predictor of poor prognosis, and has greater significance than eccentricity reconstruction [6]. When concentric left ventricular remodeling occurs and progresses, it may lead to further myocardial structure changes, even heart failure and severs cardiovascular event. Therefore, it seems particularly important to monitor of myocardial fibrosis.

ECV of T1 mapping is a non-invasive indicator of myocardial fibrosis that is highly coincident with myocardium biopsy results [13,14]. In our study, T2DM patients had a significantly higher ECV value than normal controls, which was similar to previous studies [24]. The accumulation of excess type I collagen was the main change in myocardial fibrosis and it results in expansion of the ECM and the total myocardial volume [25]. ECV obtained from native T1 and post-contrast T1 can measure expanded ECM, so the ECV is assumed to reflect myocardial fibrosis when the myocardium is without edema or protein deposition. In contrast to the native T1, the ECV combinate the variation both native and post-contrast T1 and measure the fraction of water volume of occupied by the extracellular space in myocardium, which may be more sensitive [26].

The previous studies have mentioned that presence and degreed of myocardium fibrosis is associated with abnormal metabolism [27], such as hyperglycemia, hyperlipidemia and so on. The Standards of Medical Care in Diabetes—2016 Abridged for Primary Care Providers and Committee of 2018 European society of cardiology (ESR) recommend that as the treatment targets, the HbA1c level in DM patients should be < 7.0% [22]. When HbA1c in high level (≥7.0%), it might cause a trend of complications, and the heart damage was the most serious complication [28]. In our study, The ECV value was significantly increased in higher HbA1c level group than both lower HbA1c level group and normal controls, which means the higher level HbA1c diabetes patients might be more severe myocardial fibrosis. Our result indicated that the HbA1c was independently positively correlated with myocardial fibrosis, and we added individual base line parameters and cardiac function parameters in the multiple logistic model to eliminate the bias from individual factors, the final regression model showed HbA1c was a favorable predictor of ECV, which is also consistent with the ROC results. Previous studies have reported that the acute hyperglycemia increases intercellular adhesion molecule-1 levels or P-selectin, which would cause plug of leukocytes in capillaries and no reflux phenomenon in microcirculations [29]. Meanwhile, higher blood glucose or poor blood glucose control (HbA1c ≥ 7.0%) leads to increased accumulation of glycosylation end-products and production of reactive oxygen species and inflammatory cytokines, which accelerate the process of collagen crosslinking or increased myocardial stiffness and even myocardial fibrosis [9,10].

However, in our study, the correlation between FBG and myocardial fibrosis was not statistically significant. The FBG reflect the present instant blood glucose, which has a shorter timeliness and might be susceptible to fluctuations by diet and exercise in recent days, so it is difficult to accurate predict the change on ECV or myocardial fibrosis. On the contrary, HbA1c reflect the blood glucose control level in recent months, has a better timeliness. The higher HbA1c values show that the recent several months is likely to be in a state of unstable or high blood sugar, which is more potential to cause myocardial cell injury and even lead to different degree of myocardial fibrosis.

In addition, our results showed that diabetes patients had a significantly higher value of LVMVR than normal controls. Furthermore, for the poorly control of HbA1c (≥7.0%) group the LVMVR value was slightly higher than those with well control of HbA1c. We speculate the higher HbA1c level will cause the decrease of the oxygen-binding capacity of hemoglobin and the affinity of erythrocytes to oxygen and cause the possibility of hypoxia in cardiac muscle cells, finally resulting in functional damage and even ventricular remodeling.

Previous studies have pointed out that left ventricle strain of DM patients may be impaired even there still have a normal LVEF, and it could be regarded as an indicator of myocardial injury. However, in this study, whether the higher level of HbA1c group, or lower level of HbA1c group, the LV global strain (GRS, GCS and GLS) have no difference among these three groups, and the mean LV function and LV strain value were within the normal range among all groups. Myocardial fibrosis, as an early change in diabetic cardiomyopathy, may not lead to definite impairment of cardiac function when patients present with varying degrees of diffuse fibrosis, indicating that there may be a certain compensatory period.

Combined with the above discussion of the relationship between HbA1c and myocardial fibrosis, we think that a high HbA1c level may be more likely to cause certain damage to cardiomyocytes and capillaries and result in the blockage of these vessels, however, there may be remained normal in cardiac function. Therefore, it indicates that even the patient's cardiac function is preserved, cardiomyocytes damage or structure remodeling still can't be excepted. To sum up, HbA1c is not only an effective response to blood glucose control, but also a powerful predictor of myocardial fibrosis.

HbA1c may be helpful for the clinical decision-making of blood glucose control, so it is necessary for diabetic patients to take regular monitoring of HbA1c.

5. Limitations

There are some limitations in this study. First, there was a likely assembly bias. Patients selected for CMR were all from our hospital, thus, the derived relationship can't be applied to the entire population of patients with T2DM. Second, myocardial biopsy is the gold standard of the detection of myocardial fibrosis, but due to the invasive character and the ethical aspects prevented us to perform this standard examination in our patients. Third, not all patients underwent coronary angiography to exclude CHD, which is to reduce the patient's radiation burden. But all the patients included in this study underwent echocardiography, electrocardiogram, or angiography and so on to exclude the possibility of CHD. Finally, we have no followed-up or secondary CMR examinations, and It is not clear whether the long-term controls of HbA1c can relieve or aggravate myocardial fibrosis in long-term. We will continue to verify this question in future follow-up studies.

6. Conclusion

In summary, CMR T1 mapping might be a powerful technique for early helpful diagnosis and for cardiomyopathy. Our study demonstrates that there is an association between higher HbA1c and diffuse myocardial fibrosis, and that HbA1c can be a favorable predictor to detect the presence and degree of myocardial fibrosis. HbA1c may be helpful for the clinical decision-making of blood glucose control, therefore, it is necessary forT2DM patients to take regular monitoring of HbA1c.

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Prof. Ying-kun Guo is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

The authors declared that no competing interests exist.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.004.

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