



# 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

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## OBJECTIVE

We investigated the association of cardiovascular risk factors and myocardial fibrosis with early cardiac dysfunction in type 1 diabetes.

## RESEARCH DESIGN AND METHODS

Participants with type 1 diabetes aged 13–39 years without a known history of cardiovascular disease (CVD) ( $n = 1,441$ ) were recruited into the Diabetes Control and Complications Trial (1983–1993) and subsequently followed in the Epidemiology of Diabetes Interventions and Complications study (1994 to present). Seven hundred fourteen participants underwent cardiac magnetic resonance (CMR) imaging (2007–2009) with late gadolinium enhancement sequences to assess ischemic and non-ischemic scars and tagging sequences to evaluate circumferential strain. CMR-derived T1 mapping also was used to assess interstitial fibrosis. The influence of cardiovascular risk factors and myocardial scar on circumferential strain was assessed using linear regression.

## RESULTS

Circumferential dysfunction was consistently associated with older age, male sex, smoking history, obesity, higher blood pressure, lower HDL cholesterol, and higher mean HbA<sub>1c</sub>. Participants with nonischemic scars ( $n = 16$ ) had the worst circumferential function compared with those without scars ( $\beta \pm SE 1.32 \pm 0.60$ ;  $P = 0.03$ ). In sex-adjusted models, the correlation between T1 times and circumferential strain was not significant. In the fully adjusted models, a trend toward circumferential dysfunction in participants with nonischemic scars was found. Left ventricular ejection fraction was not associated with risk factors but was significantly lower if a myocardial scar was present.

## CONCLUSIONS

Traditional CVD risk factors and elevated HbA<sub>1c</sub> levels are major factors related to early cardiac dysfunction in type 1 diabetes. Nonischemic myocardial scar, possibly as a marker of chronic exposure to known risk factors, may predict early cardiac dysfunction mediated by diffuse myocardial fibrosis as seen in diabetic cardiomyopathy.

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\*A complete list of participants in the DCCT/EDIC Research Group can be found at [www.nejm.org/doi/full/10.1056/nejmoa1409463#t=article](http://www.nejm.org/doi/full/10.1056/nejmoa1409463#t=article).

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Diabetes is strongly associated with the incidence and progression of heart failure (HF), although this relationship is not as well studied for type 1 compared with type 2 diabetes (1). The high risk of HF in patients with diabetes is partly explained by the elevated risk of coronary artery disease but may also be related to the presence of diabetic cardiomyopathy (DCM) (2). Controversy exists about the role of diabetes as a cardiomyopathic entity (3–5), but myocardial fibrosis appears to contribute importantly to both ischemic and diabetic heart disease (6). However, whether established risk factors of HF affect early subclinical cardiac dysfunction in individuals with type 1 diabetes is unclear.

Cardiac magnetic resonance (CMR) techniques allow for the assessment of replacement (scar) and diffuse myocardial fibrosis, identifying distribution patterns and estimating the amount of extension in the heart. In the presence of a myocardial scar, CMR may also identify patterns of nonischemic and ischemic myocardial disease, which have been associated with an unfavorable prognosis in patients with diabetes (7,8).

The assessment of left ventricular (LV) myocardial deformation (strain) by CMR tagging has been validated in diverse populations and shown to be robust and reproducible (9). In addition, strain measurements may be more sensitive to changes in contractile function during the early phases of DCM than traditional parameters of cardiac function (10).

We investigated the influence of cardiovascular risk factors on early cardiac dysfunction, as measured by cardiac strain, in patients with type 1 diabetes participating in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. We also assessed how measures of myocardial fibrosis affect these relationships by investigating the association of myocardial scar and diffuse fibrosis with circumferential strain.

## RESEARCH DESIGN AND METHODS

### Study Sample

The DCCT/EDIC study has been previously described in detail (11,12). Briefly, between 1983 and 1989, the DCCT recruited 1,441 patients (aged 13–39 years) with type 1 diabetes who were free of cardiovascular disease (CVD), hypertension, and hypercholesterolemia. DCCT participants

were randomly assigned to either intensive or conventional diabetes treatment (1983–1993). The EDIC study (1994 to present) is the observational follow-up of the DCCT cohort. We included EDIC participants who had contrast-enhanced CMR examinations during the 14th year of the EDIC study, with an average total (DCCT and EDIC) follow-up of 21 years. A total of 1,301 participants (94% of the surviving DCCT cohort) were active in EDIC at the time of the CMR assessment. Of those, 714 had complete data on cardiovascular risk factors and the main parameters of CMR (12). Participant selection procedures are summarized in Fig. 1. Institutional review committees of all participating centers ([www.nejm.org/doi/full/10.1056/nejmoa1409463#t=article](http://www.nejm.org/doi/full/10.1056/nejmoa1409463#t=article)) approved the study, and all participants gave informed consent.

### Assessment of Cardiac Risk Factors

The methods used to characterize complications and risk factors have been described in detail (13). In brief, during the DCCT and EDIC, all participants underwent a complete evaluation annually that included measurements of blood pressure (BP), weight, height, and serum creatinine level and an electrocardiogram. HbA<sub>1c</sub> was measured by high-performance liquid chromatography every 3 months during DCCT and annually during the EDIC study.

Albumin excretion rates and fasting lipid levels were measured annually during DCCT and in alternate years during EDIC. Hypertension was defined as BP  $\geq$  140/90 mmHg or use of an antihypertensive medication. Hypercholesterolemia was defined as LDL cholesterol  $\geq$  130 mg/dL or use of a lipid-lowering medication.

### CMR Protocol

The CMR protocol in EDIC has been described (7). In summary, a uniform CMR protocol was performed at 27 centers between July 2007 and April 2009 that used 1.5-T magnets in 26 centers and a 3-T magnet in 1 center (Espree or Avanto [Siemens Medical Systems, Erlangen, Germany], Intera [Philips Medical Systems, Best, the Netherlands], or SIGNA [GE Medical Systems, Waukesha, WI]). The general CMR protocol included CMR tagging sequences. Late gadolinium enhancement (LGE) was performed by using a 0.15–0.20 mmol/kg dose of gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals, Whippany, NJ) as the contrast agent. Participants with an estimated glomerular filtration rate  $< 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , a history of dialysis or renal transplantation, or a known allergy to gadolinium were not recruited to the LGE protocol. Experienced readers masked to treatment assignment and participant clinical information

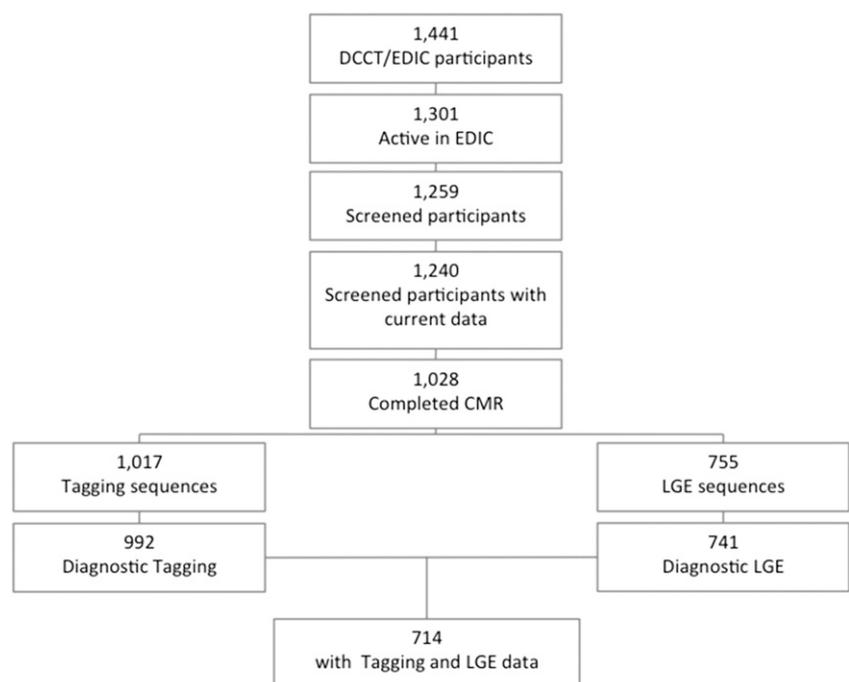


Figure 1—DCCT/EDIC study participant selection.

analyzed all CMR examinations for cardiac structure and function (e.g., LV mass, volumes, ejection fraction) in a central reading center. In addition, the readers performed 100 reanalyses to calculate intraclass correlation (0.917–0.978) for the cardiac function variables, as previously described (7).

#### CMR LGE

LGE CMR sequences were used to assess LV replacement fibrosis (scar). Myocardial scar was defined as focal enhancement either in two adjacent short-axis images or in one short-axis image and a long-axis image at a corresponding location and then classified into two categories (types): 1) ischemic when involving the subendocardium in a coronary artery territory or 2) nonischemic when involving predominantly the midwall or subepicardial location without subendocardial involvement in a noncoronary distribution (Fig. 2) (7). The percentage of LV scar was calculated by dividing scar mass by total LV mass (7).

#### CMR T1 Mapping

CMR sequence–acquired T1 mapping images were used to assess diffuse fibrosis in participants without evidence of myocardial scar in LGE images (Fig. 2). We included participants who underwent T1 scout scans with 1.5-T scanners after the infusion of gadolinium-based contrast agent. A detailed description of the protocol has been previously reported (14). Briefly, T1 scout images were obtained by true fast imaging with steady-state free precession Look-Locker acquisition sequences in four-chamber images or LV midventricle short-axis views. Images were analyzed using MASS research software (MASS V2010-EXP; Leiden University Medical Center, Leiden, the Netherlands). The postcontrast T1 times were then normalized according to the gadolinium dose,

glomerular filtration rate, and infusion-acquisition delay times (14). Lower T1 times are associated with higher diffuse fibrosis.

#### CMR Tagging Protocol

Tagging CMR assessed LV strain through a standard protocol (9) (Fig. 2). Tagged images were acquired from short-axis slices at the LV base, mid, and apex. Circumferential strain was acquired from 12 segments and three slices in each study by using the harmonic phase technique. Peak systolic circumferential strain (Ecc) at the midventricular level was acquired by averaging four segments. By convention, Ecc values are negative during systole with circumferential shortening. Thus, a less-negative Ecc value indicates diminished regional LV function.

#### Statistical Analysis

Sex-specific clinical and CMR-derived measures were assessed. The distribution of Ecc was individually assessed according to sex, age, treatment group (intensive/conventional), study cohort (primary/secondary), smoking status, alcohol use, obesity status (BMI  $\geq$  or  $<$ 30 kg/m<sup>2</sup>), renal dysfunction parameters, hypertension, lipids profile, metabolic syndrome criteria, and presence/type of myocardial scar (Supplementary Data). Spearman correlation was used to evaluate the association between diffuse fibrosis assessed by T1 values and Ecc, adjusting for sex. For myocardial scar, the presence (binary: yes/no) and the type of scar (two patterns: ischemic and nonischemic) were assessed as independent variables. The associations between covariates and circumferential deformation (Ecc as the dependent variable) were assessed using minimally adjusted linear regression models, which included a basic model and minimally adjusted risk factor models. Finally, a

multivariate linear regression model that tested the influence of cardiovascular risk factors and myocardial scar on Ecc and LV ejection fraction values was assessed, adjusting for anthropometrics, cardiovascular risk factors, and presence/type of myocardial scar.

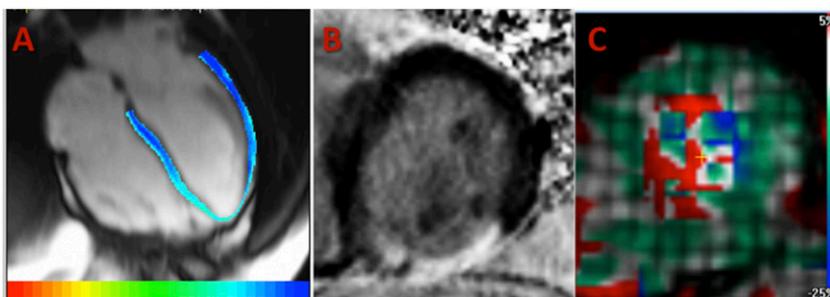
## RESULTS

Of the 1,017 DCCT/EDIC study participants who underwent diagnostic CMR imaging, 714 were included in the analysis. The mean age of the included participants was 49 years; 42% were female; and the mean duration of type 1 diabetes was 28 years (Supplementary Table 1).

Circumferential deformation was worse (less-negative Ecc values) in participants who were male, older, smokers, and obese and with hypertension, hypercholesterolemia, the metabolic syndrome, proliferative diabetic retinopathy, and impaired renal function (Table 1). These relationships were consistent in all age strata, although the differences between men and women tended to converge in the oldest age-groups (Supplementary Fig. 1). Compared with women, men had greater LV mass, a higher prevalence of myocardial scar, and more interstitial fibrosis as measured by postcontrast T1 times (Supplementary Table 1).

Worse circumferential deformation was also found in participants with poor glycemic control and in the presence of myocardial scar (Table 1). Participants with nonischemic myocardial scars had less circumferential deformation (less-negative Ecc values) compared with those with ischemic scars. In sex-adjusted models, the correlation between T1 times and Ecc was not significant ( $\beta \pm SE -0.002 \pm 0.003$  ms/%;  $P = 0.55$ ).

The minimally adjusted linear regression models are shown in Table 2. Consistently, female sex was associated with more circumferential deformation (more-negative Ecc values) than male sex. Older participants had less circumferential deformation, although this relationship was attenuated in the fully adjusted model. When risk factors were individually added to the basic model, smoking, obesity, elevated BP, worse metabolic profile, higher HbA<sub>1c</sub>, proliferative diabetic retinopathy, and renal dysfunction were consistently associated with less circumferential deformation (less-negative Ecc values). However, LV mass was not a significant predictor of circumferential deformation



**Figure 2**—Images from the CMR protocol in the DCCT/EDIC study. A: T1 mapping assessment of the LV from a four-chamber view using a T1 scout Look-Locker sequence. B: LGE image in a short-axis view of the LV (presence of transmurular scar in the inferior wall). C: Assessment of LV deformation (strain map) from tagging sequences in a midventricular short-axis view.

**Table 1—Distribution of LV circumferential strain**

	<i>n</i>	Ecc (%)	<i>P</i> value
Sex			
Female	303	−19.2 ± 2.4	
Male	411	−18.3 ± 2.4	<0.0001
Age			
<50 years	390	−18.9 ± 2.4	
≥50 years	324	−18.4 ± 2.4	0.0064
Treatment group			
Intensive	371	−18.8 ± 2.4	
Conventional	343	−18.6 ± 2.4	0.3183
Study cohort			
Primary	353	−18.8 ± 2.4	
Secondary	361	−18.6 ± 2.4	0.2351
Current smoker			
No	631	−18.8 ± 2.4	
Yes	83	−18.1 ± 2.6	0.0097
Alcohol			
No	385	−18.7 ± 2.5	
Yes	329	−18.7 ± 2.3	0.4766
BMI ≥30 kg/m <sup>2</sup>			
No	488	−18.9 ± 2.4	
Yes	226	−18.3 ± 2.4	0.0025
AER ≥300 μg/min or ESRD			
No	679	−18.7 ± 2.4	
Yes	35	−17.8 ± 2.2	0.0150
Sustained AER ≥30 μg/min or ESRD			
No	565	−18.8 ± 2.4	
Yes	149	−18.2 ± 2.5	0.0030
Any proliferative diabetic retinopathy*			
No	596	−18.8 ± 2.4	
Yes	118	−18.2 ± 2.5	0.0256
Hypertension†			
No	373	−19.0 ± 2.3	
Yes	341	−18.4 ± 2.4	0.0004
Hypercholesterolemia‡			
No	248	−19.0 ± 2.4	
Yes	466	−18.5 ± 2.4	0.0030
Metabolic syndrome§			
No	460	−18.9 ± 2.4	
Yes	226	−18.1 ± 2.4	<0.0001
Myocardial scar			
None	682	−18.7 ± 2.4	
Any	32	−17.7 ± 2.7	0.0294
Ischemic	16	−18.4 ± 2.7	0.0205
Nonischemic	16	−17.0 ± 2.4	(df = 2)

Data are mean ± SD unless otherwise indicated. More-negative Ecc values indicate more myocardial circumferential deformation. AER, albumin excretion rate; ESRD, end-stage renal disease. \*During the DCCT/EDIC study. †Defined as BP ≥140/90 mmHg or treatment with an antihypertensive medication. ‡Defined as LDL ≥130 mg/dL or treatment with a lipid-lowering medication. §Defined as at least two of the four components: systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or any antihypertensive agent, including ACE/angiotensin receptor blocker for all reasons, female waist circumference ≥88 cm or male waist circumference ≥102 cm, female HDL cholesterol <50 mg/dL or male HDL cholesterol <40 mg/dL, and triglycerides ≥150 mg/dL.

when included in the basic model. The presence of myocardial scar was associated with marginal significance ( $P = 0.09$ ) with circumferential dysfunction when added to the basic model, and the association became significant ( $P = 0.027$ ) when participants with nonischemic

scars were compared with those without scars. The amount of diffuse fibrosis assessed by T1 times was not a significant predictor of circumferential dysfunction when added to the basic model.

The multivariate regression model for circumferential strain and ejection

fraction is shown in Table 3. Less circumferential shortening (less-negative Ecc values) was associated with older age, male sex, smoking, higher BMI, higher BP, lower HDL cholesterol, and higher HbA<sub>1c</sub> mean values during the cohort follow-up period. A trend in significance showed less circumferential deformation in participants with nonischemic myocardial scars compared with those without scars. LV ejection fraction was not associated with cardiovascular risk factors. However, compared with those without myocardial scar, ejection fraction was significantly lower in participants with either ischemic or nonischemic myocardial scars.

## CONCLUSIONS

This study investigated a large unique cohort of subjects with type 1 diabetes from the DCCT/EDIC study with more than two decades of follow-up who underwent a comprehensive CMR assessment. The CMR analyses included functional measures, deformation evaluation, myocardial scar identification and classification, and diffuse fibrosis quantification. In addition to the expected influence of age and sex, we show that smoking, obesity, high BP, the presence of the metabolic syndrome, and chronic high glucose levels are the main factors related to early subclinical cardiac dysfunction as assessed by circumferential deformation. The presence of myocardial scar, although infrequent, may also play a role in the cardiac dysfunction of this population, particularly in the presence of a nonischemic pattern.

This study includes data on cardiac deformation as measured by LV strain by using a validated technique that is available in clinical settings (15). The results show small differences for strain values between groups. Small differences in LV deformation are expected in groups of generally healthy participants without known clinical CVD. LV strain allows for early identification of subclinical cardiac dysfunction and relates to future clinical events (16,17). The ability to detect early dysfunction may lead to preventive strategies through clinical decision making.

Although risk factors related to the late clinical manifestation of HF are well known, we now show determinants of early subclinical cardiac dysfunction in a large cohort of participants with type 1 diabetes. These findings demonstrated that LV ejection fraction was not related

**Table 2—Minimally adjusted linear regression of circumferential strain (Ecc, %) in relation to cardiovascular risk factors**

Covariate	Estimate of $\beta \pm SE$	P value
Basic model <sup>1</sup>		
Age (per 10 years of age)	0.26 $\pm$ 0.13	0.0498
Sex (female vs. male)	-0.86 $\pm$ 0.18	<0.0001
Cohort (primary vs. secondary intervention)	-0.12 $\pm$ 0.18	0.4906
Minimally adjusted risk factor models <sup>2</sup> (basic model + 1 covariate)		
Group (intensive vs. conventional)	-0.18 $\pm$ 0.18	0.2997
Smoking (yes vs. no)	0.68 $\pm$ 0.27	0.0125
BMI (kg/m <sup>2</sup> )	0.08 $\pm$ 0.02	<0.0001
BMI $\geq$ 30 kg/m <sup>2</sup> (yes vs. no)	0.64 $\pm$ 0.19	0.0008
Natural waist circumference (cm)	0.03 $\pm$ 0.01	<0.0001
Mean systolic BP (mmHg)	0.04 $\pm$ 0.01	0.0007
Mean diastolic BP (mmHg)	0.09 $\pm$ 0.02	<0.0001
Hypertension (yes vs. no)	0.50 $\pm$ 0.18	0.0055
Mean HDL cholesterol (mg/dL)	-0.02 $\pm$ 0.01	0.0014
Mean LDL cholesterol (mg/dL)	0.01 $\pm$ 0.004	0.0070
Mean total cholesterol (mg/dL)	0.01 $\pm$ 0.004	0.0326
Mean triglycerides (mg/dL)	0.01 $\pm$ 0.002	<0.0001
Hypercholesterolemia (yes vs. no)	0.21 $\pm$ 0.19	0.2808
HbA <sub>1c</sub> (%)		
Before CMR	0.28 $\pm$ 0.07	0.0002
Mean during DCCT	0.14 $\pm$ 0.07	0.0397
Mean during the EDIC study	0.37 $\pm$ 0.09	<0.0001
Mean during the DCCT/EDIC study	0.38 $\pm$ 0.10	<0.0001
Metabolic syndrome (yes vs. no)	0.81 $\pm$ 0.19	<0.0001
Sustained AER $\geq$ 30 $\mu$ g/min or ESRD (yes vs. no)	0.61 $\pm$ 0.22	0.0055
Any PDR (yes vs. no)	0.58 $\pm$ 0.24	0.0169
AER $\geq$ 300 $\mu$ g/min or ESRD (yes vs. no)	0.69 $\pm$ 0.41	0.0915
LV end-diastolic mass (g)	0.004 $\pm$ 0.004	0.2993
LV end-diastolic mass/BSA	0.001 $\pm$ 0.008	0.8725
Myocardial scar		
Any scar (ischemic or nonischemic) vs. none	0.73 $\pm$ 0.43	0.0904
Nonischemic vs. none	1.32 $\pm$ 0.60	0.0274
Ischemic vs. none	0.14 $\pm$ 0.59	0.8156
Nonischemic vs. ischemic	1.18 $\pm$ 0.83	0.1544
Normalized myocardial T1 (ms) (n = 200)	-0.002 $\pm$ 0.003	0.5515

Positive regression coefficients indicate a decrease in function because Ecc has a negative value. Normalized myocardial T1: postcontrast CMR-derived T1 times were normalized by gadolinium dose, glomerular filtration rate, and infusion-acquisition delay times. Lower values are related to higher diffuse fibrosis. AER, albumin excretion rate; BSA, body surface area; ESRD, end-stage renal disease; PDR, proliferative diabetic retinopathy. <sup>1</sup>Basic model was also adjusted for CMR machine type. <sup>2</sup>Minimally adjusted model, separate model for each covariate, was also adjusted for age, sex, primary vs. secondary cohort, and CMR machine type.

to clinical risk factors but was lower when more advanced disease (as assessed by the presence of myocardial scar) was present. The findings indicate that known risk factors of cardiovascular outcomes in the general population similarly affect early cardiac dysfunction in type 1 diabetes and support approaches for primary prevention of CVD in this population.

We found that obesity and high BP were among the main factors related to early subclinical cardiac dysfunction in type 1 diabetes as assessed by circumferential deformation, which is consistent with previous studies in generally healthy populations that found obesity and hypertension to be related to cardiac

measures, early ventricular dysfunction, and hard clinical events that start in early adulthood (18–20). Furthermore, increases in BMI and BP are main determinants of cardiac remodeling over decades of adulthood (21,22). In fact, more severe obesity appears to be implicated with hospitalization for HF in patients with type 1 diabetes (23). Smoking, particularly current smoking status, is known to be related to incident clinical HF (24). In the current study, smoking status also is a determinant of early subclinical LV dysfunction in type 1 diabetes.

Over the past three decades, the DCCT/EDIC study has documented the impact of chronic hyperglycemia on

adverse outcomes in participants with type 1 diabetes (13,25). In fact, glycemic exposure appears to be a major determinant of cardiac remodeling in type 1 diabetes (26). In the current study, we found that early subclinical cardiac dysfunction in type 1 diabetes is associated with a worse lipid profile and hyperglycemia. The Swedish National Diabetes Registry assessed 20,985 patients with type 1 diabetes and found that having an HbA<sub>1c</sub>  $\geq$ 10.5% increased the risk of developing clinically manifested HF by approximately fourfold compared with a well-controlled group (HbA<sub>1c</sub> <6.5%) (27). Similarly, Konduracka et al. (28) reported that longer diabetes duration and increased HbA<sub>1c</sub> levels are predictors of clinical HF in longstanding ( $\geq$ 10 years) type 1 diabetes. The current findings support the role of exposure to chronic hyperglycemia as a major determinant of preclinical cardiac dysfunction in type 1 diabetes. Of note, we show that the mean glucose levels over a long-term follow-up affect early cardiac dysfunction in patients with type 1 diabetes. These findings highlight the importance in clinical practice of pursuing optimal glucose control in patients with type 1 diabetes.

The difference between the DCCT treatment groups in the current study essentially reflects the long-term effects of the 2% difference in HbA<sub>1c</sub> that was maintained over an average of 6.5 years. Thus, the lack of a difference between groups reflects the weak association of the mean HbA<sub>1c</sub> over those 6.5 years of the DCCT with the CMR Ecc parameter measured 14–16 years later in the EDIC study ( $P = 0.04$ ) (Table 2). In this case, the analysis of HbA<sub>1c</sub> as a quantitative variable will have greater power (smaller  $P$  value) than the qualitative treatment group comparison. Furthermore, the DCCT HbA<sub>1c</sub> is different from the weighted mean HbA<sub>1c</sub> that reflects the glycemic exposure over the total 20.5–22.5 years of follow-up that shows a strong association with Ecc ( $P < 0.0001$ ). Thus, the difference between DCCT treatment groups and the DCCT HbA<sub>1c</sub> did not have a long-term effect on CMR parameters, but the overall glycemic exposure over the 20.5–22.5 years had a strong association.

Patients with type 1 diabetes are at a high risk for coronary artery disease and are therefore susceptible to ischemic cardiomyopathy (ICM) (29). In fact, both ICM and DCM share some of the same risk

**Table 3—Multivariate linear regression of LV circumferential strain and ejection fraction in relation to cardiovascular risk factors**

Covariate	Ecc (%)		Ejection fraction (%)	
	$\beta \pm SE$	<i>P</i> value	$\beta \pm SE$	<i>P</i> value
Age (per 10 years of age)	0.30 $\pm$ 0.13	<b>0.0236</b>	0.80 $\pm$ 0.35	<b>0.0226</b>
Sex (female vs. male)	−0.44 $\pm$ 0.20	<b>0.0318</b>	1.77 $\pm$ 0.54	<b>0.0012</b>
Cohort (primary vs. secondary intervention)	−0.15 $\pm$ 0.17	0.3926	0.34 $\pm$ 0.46	0.4592
Smoking (yes vs. no)	0.64 $\pm$ 0.27	<b>0.0188</b>	−0.16 $\pm$ 0.72	0.8184
BMI (kg/m <sup>2</sup> )	0.04 $\pm$ 0.02	<b>0.0367</b>	0.05 $\pm$ 0.05	0.3832
Mean diastolic BP (mmHg)	0.07 $\pm$ 0.02	<b>0.0002</b>	0.02 $\pm$ 0.05	0.7521
Mean HDL cholesterol (mg/dL)	−0.02 $\pm$ 0.008	<b>0.0236</b>	0.02 $\pm$ 0.02	0.2383
Mean HbA <sub>1c</sub> during the DCCT/EDIC study	0.28 $\pm$ 0.10	<b>0.0043</b>	−0.20 $\pm$ 0.26	0.4343
Myocardial scar				
Nonischemic vs. none	1.13 $\pm$ 0.58	<b>0.0518</b>	−8.93 $\pm$ 1.54	<b>&lt;0.0001</b>
Ischemic vs. none	−0.04 $\pm$ 0.58	0.9506	−3.67 $\pm$ 1.53	<b>0.0164</b>

Only the most significant lipid variable (i.e., HDL cholesterol) was included in the final model. The model was also adjusted for CMR machine type. Positive regression coefficients indicate a decrease in function because Ecc has a negative value. Boldface values indicate significance or clear trend at  $P \leq 0.05$ .

factors, such as smoking, hypertension, hyperlipidemia, and hyperglycemia (30,31). The presence of DCM often is a diagnosis of exclusion in patients with diabetes and clinical HF (2).

The pathophysiological mechanisms for DCM are still not clear, but myocardial fibrosis seems to be an underlying contributor in the early stages (6). Myocardial fibrosis relates to both ICM and DCM and may be seen in various histological presentations (32,33). Diffuse fibrosis seems to appear early with chronic cardiac exposure to risk factors (32,34). DCCT/EDIC study participants were shown to have higher LV diffuse fibrosis compared with low-risk volunteers without diabetes in a previous study (14). In the current study, however, T1 times (as a measure of diffuse fibrosis) did not relate to early cardiac dysfunction as assessed by circumferential deformation. The distribution of T1 times possibly is not adequate to identify small differences in the presence of diffuse fibrosis in the DCCT/EDIC study population because all participants have longstanding type 1 diabetes, which is related to increased fibrosis. In addition, the method of acquisition used in this study is not optimal, and superior methods for T1 and extracellular space quantification have been developed (34).

DCM also has been related to microangiopathy in patients with diabetes (35). In fact, this study shows that proliferative diabetic retinopathy, a known marker of diabetes-related microangiopathy, is

associated with subclinical impaired deformation (Tables 1 and 2). The myocardial scar (replacement fibrosis) pattern assessed by CMR may help to differentiate the underlying etiologies for myocardial damage and identify the stage of progression of cardiac diseases (32). In a previous report by Turkbey et al. (7), myocardial scar was identified in 4.3% of the DCCT/EDIC study participants included in the LGE protocol. Scars could be further classified as nonischemic or ischemic, with one-half in each category.

In the current analysis, the presence of myocardial scar was significantly associated with circumferential deformation, particularly in participants with a nonischemic scar pattern. Nonischemic scar is a probable indicator of advanced stages of diffuse disease and a possible indicator of relevant cardiac damage seen in pre-clinical phases of DCM. This relationship was substantially attenuated when multivariate regression models included clinical risk factors. These findings suggest that the relationship between myocardial scar and cardiac dysfunction may be mediated by chronic exposure to known risk factors.

In summary, we assessed a large cohort of participants with type 1 diabetes with a comprehensive CMR assessment and found that older age, male sex, smoking, obesity, high BP, the presence of the metabolic syndrome, and chronic high glucose levels are the main factors related to early subclinical cardiac dysfunction in this population. Myocardial scar also

appears to relate to early cardiac dysfunction, is influenced by chronic exposure to known risk factors, and is an indicator of advanced diffuse cardiac damage as seen in DCM.

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