Incidence and Prognostic Implication of Unrecognized Myocardial Scar Characterized by Cardiac Magnetic Resonance in Diabetic Patients Without Clinical Evidence of Myocardial Infarction

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Background—Silent myocardial infarctions (MIs) are prevalent among diabetic patients and inflict significant morbidity and mortality. Although late gadolinium enhancement (LGE) imaging by cardiac magnetic resonance (CMR) can provide sensitive characterization of myocardial scar, its prognostic significance in diabetic patients without any clinical evidence of MI is unknown.

Methods and Results—We performed clinically indicated CMR imaging in 187 diabetic patients who were grouped by the absence (study group, n=109) or presence (control group, n=78) of clinical evidence of MI (clinical history of MI or Q waves on ECG). CMR imaging and follow-up were successful in 107 study patients (98%) and 74 control patients (95%). Cox regression analyses were performed to associate LGE with major adverse cardiovascular events (MACE), including death, acute MI, new congestive heart failure or unstable angina, stroke, and significant ventricular arrhythmias. LGE by CMR was present in 30 of 107 study patients (28%). At a median follow-up of 17 months, 38 of 107 patients (36%) experienced MACE, which included 18 deaths. Presence of LGE was associated with a >3-fold hazards increase for MACE and for death (hazard ratio, 3.71 and 3.61; $P<0.001$ and $P=0.007$, respectively). Adjusted to a model that combines patient age, sex, ST or T changes on ECG, and left ventricular end-systolic volume index, LGE maintained a >4-fold hazards increase for MACE (adjusted hazard ratio, 4.13; 95% confidence interval, 1.74 to 9.79; $P=0.001$). In addition, LGE provided significant prognostic value with MACE and with death adjusted to a diabetic-specific risk model for 5-year events. The presence of LGE was the strongest multivariable predictor of MACE and death by stepwise selection in the study patients.

Conclusions—CMR imaging can characterize occult myocardial scar consistent with MI in diabetic patients without clinical evidence of MI. This imaging finding demonstrates strong association with MACE and mortality hazards that is incremental to clinical, ECG, and left ventricular function combined. **(*Circulation*. 2008;118:1011-1020.)**

Key Words: diabetes mellitus ■ magnetic resonance imaging ■ morbidity ■ mortality ■ myocardial infarction

The prevalence of diabetes mellitus has been projected to increase steeply in the coming decades,[1] expected to affect >300 million patients worldwide.[2] The burden of cardiovascular disease and premature mortality is expected to rise correspondingly, accounting for an estimated 50% to 80% of all deaths in those with diabetes mellitus.[3] Despite atypical or no cardiovascular symptoms, diabetic patients are at substantially higher risk of serious cardiac events than nondiabetic patients.[4] Late gadolinium enhancement (LGE) imaging with contrast-enhanced cardiac magnetic resonance (CMR) imaging can detect and characterize myocardial scar that is missed by ECG,[5] conventional wall motion,[6] or nuclear scintigraphic techniques[7] but is associated with important cardiac events, including death and recurrent myocardial infarction (MI).[5] In this observational study, we tested the hypothesis that characterization of myocardial scar by LGE imaging can provide strong prognostic value for major adverse cardiac events (MACE), including death, in a clinical cohort of diabetic patients without known prior MI. We also aimed to compare the event-free survival of diabetic patients without any clinical evidence of MI but who were found to have LGE by CMR imaging with a control group of diabetic patients with a known history of MI.

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Methods

Patient Population

We studied a consecutive series of patients with diabetes mellitus who were referred for a clinical CMR. The diagnosis of diabetes mellitus was based on a history of persistent fasting hyperglycemia[1] and antidiabetic drug therapy at the time of the CMR referral. Patients were referred to CMR for recent symptoms suspected to be related to coronary artery disease (Table 1). All patients were referred for assessment of left ventricular (LV) regional and global function. Stress CMR imaging also was requested and performed in 88 patients (47%). LGE imaging was a part of the CMR protocol and performed in all patients. Patients were excluded with suspected or confirmed (by biopsy) myocarditis or infiltrative cardiomyopathy (including cardiac hemochromatosis, amyloidosis, or sarcoidosis), concurrent unstable angina, New York Heart Association class IV heart failure, hemodynamic instability, claustrophobia precluding CMR, and metallic hazards. As illustrated in Figure 1, patients were categorized into 2 groups by clinical evidence of MI: a study group consisting of 109 diabetic patients without clinical evidence of MI (no MI by clinical history or medical record and no evidence of significant Q waves on ECG in ≥2 contiguous leads) and a control group consisting of 78 diabetic patients with clinical evidence of MI (historical evidence or significant Q waves in ≥2 contiguous leads). Patients with prior coronary intervention and ECG T-wave abnormality were excluded from the study group. All patients provided informed consent before CMR imaging, and the institutional ethics committee of Partners Healthcare system approved the study.

Clinical History and ECG Evaluation

All patients underwent a detailed history at the time of CMR. Clinical evidence of MI was based on either documentation of MI by history or medical record or significant Q waves (≥2 contiguous leads) on ECG. History of hypercholesterolemia was defined as any indication for cholesterol-lowering drug treatment according to the Adult Treatment Panel III of the National Cholesterol Education Program guidelines.[8–11] Hypertension history was defined as systolic blood pressure (BP) >140 mm Hg or diastolic BP >90 mm Hg, consistent from ≥2 readings obtained from ≥2 visits, or a need for antihypertensive treatment according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria.[12] Significant smoking was defined as >10 pack-years of tobacco use. Resting 12-lead ECGs were obtained on average 3.7±9.0 days from CMR. We excluded any ECG in which a cardiac event or revascularization occurred between the ECG and the CMR. We applied the Minnesota Code criteria for significant Q waves (codes 1-1 through 1-2 except 1-2-8) as ECG evidence of MI.[13] This was interpreted by computer analysis, followed by visual overreading by a single reader blinded to CMR results and clinical outcome. We used the Sokolow-Lyon index to indicate LV hypertrophy on ECG.[14]

CMR Imaging

All patients were studied supine in a 1.5-T CMR system (Signa CV/i, GE Healthcare, Waukesha, Wis) with a 4- or 8-element phased-array surface coil. CMR study consisted of cine steady-state free precession imaging (repetition time, 3.4 ms; echo time, 1.2 ms; in-plane spatial resolution, 1.6×2 mm) of LV function and LGE imaging (repetition time, 4.8 ms; echo time, 1.3 ms; inversion time, 200 to 300 ms) for myocardial scar. All images were acquired with ECG gating and breath holding. Cine imaging and LGE imaging were obtained in 8 to 14 matching short-axis (8 mm thick with 0-mm spacing) and 3 radial long-axis planes. A previously described segmented inversion-recovery pulse sequence for LGE was used[15] starting 15 minutes after cumulative 0.15-mmol/kg dose of gadolinium DTPA. Parallel imaging techniques (array spatial sensitivity encoding technique [ASSET] with an accelerating factor of 1.5 to 2) were used to shorten the patients' breath-hold duration throughout some studies. A single reader categorized LGE as either typical MI (involving the subendocardium) or atypical (subepicardial, patchy midwall, or diffuse circumferential subendocardial pattern).

Quantitative Analysis of LGE and LV Function Parameters

All images were analyzed with specialized software (CineTool 5.4.1, GE Healthcare) by researchers blinded to clinical outcome, study group assignment, and patient history. We interpreted LGE as present or absent by the consensus of 2 cardiologists. LGE was considered present only if myocardial enhancement was confirmed on both short-axis and matching long-axis locations. The myocardial mass of LGE (grams) was then quantified by a semiautomatic detection method using a signal intensity threshold of >2 SD above a remote reference region as previously reported.[16,17] Following the American Heart Association/American College of Cardiology 17-segment nomenclature,[18] we graded the maximal segmental transmural extent of LGE as 0%, 1% to 25%, 26% to 50%, 51% to 75%, 76% to 99%, and 100%. We also followed the coronary distribution of the 17-segment model and analyzed the maximal transmural extent in the left anterior descending, right coronary, and left circumflex coronary artery distribution. We manually traced epicardial and endocardial borders of matching short-axis cine locations at end systole and end diastole to determine the LV ejection fraction (LVEF), LV end-diastolic volume index, LV end-systolic volume index, and LV myocardial mass (end diastole only).[19,20] LVEF was measured by standard Simpson's rule using summation of short-axis locations without interslice spacing. Segmental wall motion abnormality was graded as present or absent concordant on both the short-axis and the radial long-axis views.

Follow-Up

At least 6 months after the CMR, clinical information was obtained from patient telephone interviews using a standard questionnaire and medical records or by contacting patients' physicians. The median follow-up duration was 17 months (range, 6 to 57 months). Patient survival was obtained from the National Social Security Death Index if patients could not be contacted.[21] MACE included any of the following: all-cause mortality, new acute MI, unstable angina requiring hospitalization, development or progression of heart failure requiring hospitalization, ventricular arrhythmias requiring appropriate discharge from implantable cardioverter-defibrillator (ICD), and acute cerebral vascular accidents confirmed by neurological magnetic resonance or computed tomography imaging. We reviewed all available data, including death certificates from regional registries, to determine whether the immediate cause of death was cardiac related. New acute MI was defined as elevation of serum troponin. Unstable angina was defined as new chest pain hospitalization without noncardiac origin of chest pain and either angiographic coronary stenosis of ≥70% or ischemia on noninvasive imaging. Heart failure was defined by a need for hospitalization for new or worsening symptoms of heart failure. We reviewed any available ICD records in patients who underwent ICD implantation after CMR for ventricular arrhythmias that required ICD discharge. When a patient experienced >1 MACE, the first event was chosen. When ≥2 MACE occurred simultaneously, the worse event was chosen (death>MI>unstable angina>congestive heart failure>ventricular arrhythmias requiring ICD discharge). CMR results, including LGE and LV function parameters, were made available to the attending physicians on the day of the CMR.

Coronary Angiography

Any referral to coronary angiography after CMR was performed at the discretion of the attending physician. Coronary angiography performed after CMR was interpreted by the consensus of 2 cardiologists who reported any significant (≥70%) epicardial coronary stenosis from 2 orthogonal views.

Table 1. Demographic Characteristics

	Study Group (n=107)	LGE Absent (n=77)	LGE Present (n=30)	P*	Control Group (n=74)	P†
Clinical characteristics						
Age, y	59±13	57±12	63±13	0.06	64±10	0.002
Female sex, n (%)	40 (37)	32 (42)	8 (27)	0.19	25 (34)	0.64
White race, n (%)	56 (52)	36 (47)	20 (67)	0.09	28 (38)	0.07
High body mass index (≥30 kg/m^2), n (%)	57 (55)	43 (58)	14 (47)	0.38	28 (41)	0.09
Presenting symptoms at time of CMR, n (%)						
Chest pain	42 (39)	30 (39)	12 (40)	0.99	31 (42)	0.99
Dyspnea	35 (33)	21 (27)	14 (47)	0.07	27 (36)	0.07
Syncope/arrhythmia/ECG abnormality	30 (28)	26 (34)	4 (13)	0.05	16 (22)	0.05
Duration of diabetes diagnosis, y	10.7±8.5	10.6±9.0	11.0±7.1	0.86	11.0±8.3	0.85
HbA_{1c}, %	7.3±1.6	7.4±1.6	7.2±1.7	0.73	7.6±2.0	0.22
Resting SBP, mm Hg	142±27	142±24	142±34	0.99	131±25	0.003
Resting heart rate >100 bpm, n (%)	7 (7)	7 (9)	0 (0)	0.19	4 (5)	0.99
History of hypertension, n (%)	76 (71)	55 (71)	21 (70)	0.99	57 (77)	0.40
History of hypercholesterolemia, n (%)	75 (70)	53 (69)	22 (73)	0.81	61 (82)	0.08
Total cholesterol level, mg/dL	158±37	161±32	151±47	0.24	148±33	0.08
HDL cholesterol level, mg/dL	41±10	42±10	40±10	0.44	38±7	0.03
Total/HDL cholesterol ratio	3.9±1.0	4.0±0.9	3.9±1.3	0.66	4.0±1.0	0.81
Heavy tobacco use, n (%)	25 (23)	17 (22)	8 (27)	0.62	22 (30)	0.39
Family history of CAD, n (%)	15 (14)	12 (16)	3 (10)	0.55	17 (23)	0.16
History of peripheral vascular disease, n (%)	11 (10)	9 (12)	2 (7)	0.72	11 (15)	0.36
History of percutaneous coronary intervention, n (%)	9 (8)	4 (5)	5 (17)	0.11	20 (27)	0.002
History of cardiac bypass surgery, n (%)	13 (12)	6 (8)	7 (23)	0.04	20 (27)	0.02
UKPDS 5-y probability of MACE	0.08±0.08	0.07±0.07	0.11±0.10	0.02	0.11±0.07	0.04
Medication, n (%)						
β-Blocker	62 (58)	42 (55)	20 (67)	0.28	64 (86)	<0.001
Calcium blocker	24 (22)	15 (19)	9 (30)	0.30	12 (16)	0.35
Angiotensin-converting enzyme inhibitor	60 (56)	43 (56)	17 (57)	0.99	52 (70)	0.06
Aspirin	60 (57)	39 (51)	21 (70)	0.09	66 (89)	<0.001
Rest ECG						
Nonsinus rhythm, n (%)	6 (6)	4 (6)	2 (7)	0.67	4 (5)	0.99
LV hypertrophy on ECG, n (%)	4 (4)	1 (1)	3 (11)	0.07	4 (5)	0.73
QRS duration, ms	97±20	94±18	105±22	0.01	102±20	0.09
Left bundle-branch block, n (%)	7 (7)	3 (4)	4 (14)	0.10	5 (7)	0.99
Right bundle-branch block, n (%)	5 (5)	3 (4)	2 (7)	0.62	4 (5)	0.99
ST depression ≥1 mm, n (%)	11 (11)	5 (7)	6 (21)	0.07	21 (29)	0.005
T inversion in >2 contiguous leads, n (%)	21 (21)	12 (17)	9 (32)	0.11	36 (49)	<0.001
Corrected QT interval, ms	439±32	436±29	448±37	0.10	436±42	0.60
CMR						
Total LV mass, g	142±49	136±44	154±55	0.08	148±43	0.37
Average LVEF, %	56±15	60±12	47±18	<0.001	42±18	<0.001
LVEDV index, mL/m^2	82±26	74±17	102±34	<0.001	114±43	<0.001
LVESV index, mL/m^2	39±26	30±14	61±37	<0.001	73±46	<0.001
Presence of wall motion abnormality, n (%)	30 (28)	8 (10)	22 (73)	<0.001	58 (79)	<0.001

HDL indicates high-density lipoprotein; CAD, coronary artery disease; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume.
*Comparison within the study group, LGE absent vs LGE present.
†Comparison between the study and control groups.

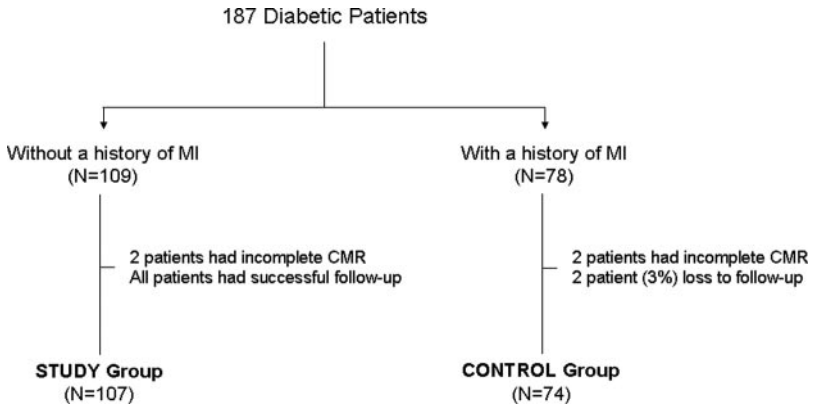

Figure 1. Composition of the study and control groups.

Statistical Analysis

Demographic characteristics by LGE presence were compared by Student *t* test or Fisher exact test. The survival functions of the cohort patients with and without LGE were compared by use of Kaplan–Meier statistics and tested for difference by the log-rank tests. To determine the rate of hazard change over time in this patient cohort, we plotted the cumulative hazard function for MACE and all-cause mortality using the log–event-free-survival plot and log-survival plot, respectively. We fitted Cox proportional-hazards models to estimate the unadjusted hazard ratios (HRs) of all the variables. A value of $P<0.05$ was used to determine significance in all testing. The interobserver agreement in qualitative interpretation of LGE has previously been demonstrated by Bland-Altman analysis.[5]

We performed 2 separate multivariable Cox regression analyses. In the first analysis, we determined the set of predictors that formed the best overall models for the prediction of MACE and for all-cause mortality. All clinical, ECG, and CMR variables were considered using a stepwise forward selection strategy with $P<0.05$ as the inclusion and exclusion levels. We also determined the strongest multivariable predictor for MACE and mortality, respectively, when all variables were considered. In the second analysis, we determined whether any incremental prognostic information was present by LGE imaging beyond patient age, sex, and LV systolic function. In each of the final models, the validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable for each of the predictors in the models. This assumption was validated for all the variables in the final models. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC) for Windows.

Prognostic Implication of LGE by CMR Compared With Standard Validated Risk Model for Diabetic Patients

We used the validated diabetes-specific United Kingdom Prospective Diabetes Study (UKPDS) risk engine by Stevens et al[21a] to assess the 5-year probability of a cardiac event in the study group patients. The UKPDS risk model for $R_T(t=5)$, the 5-year probability of MACE in a patient who had diabetes mellitus diagnosed for T years, with the assumption of an absence of noncardiac death, was calculated by the following equation: $R_T(t=5)=1-\exp[-q\times d^{T\times}(1-d^t)/(1-d)]$, where d is the risk ratio of 1.087 per year of diabetes diagnosis; $q=q_0\beta_1^{\text{Age}-55}\beta_2^{\text{Sex}}\beta_3^{\text{Race}}\beta_4^{\text{Smoking}}\beta_5^{\text{HbA1c}-6.72}\beta_6^{(\text{SBP}-135.7)/10}\beta_7^{\ln(\text{LR})-1.59}$; age is the patient age at diagnosis of diabetes mellitus; sex=1 for female or 0 otherwise; race=1 for black race or 0 otherwise; smoking=1 for current cigarette smoking or 0 otherwise; HbA_{1c}=hemoglobin A_{1c} in percent obtained within 2 years; SBP = systolic BP in mm Hg obtained at the time of CMR; and ln(LR) = natural log of the ratio of total cholesterol to high-density lipoprotein obtained within 2 years. As defined by Stevens et al, the parameter estimates by maximum likelihood were as follows: $q_0=0.0112$, $\beta_1=1.059$, $\beta_2=0.525$, $\beta_3=0.39$, $\beta_4=1.35$, $\beta_5=1.183$, $\beta_6=1.088$, and $\beta_7=3.845$. We determined the univariable prognostic association of $R_T(t=5)$ with MACE and death. We then sought to determine the prognostic value of LGE by CMR after adjustment to $R_T(t=5)$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics of the Study Group

Demographic characteristics of the study group, stratified by the presence of LGE, are shown in Table 1. In a consecutive series of 109 patients, 2 (2%) had incomplete CMR study and were excluded from further analysis. Both of these patients were uneventful at the end of the study period. The remaining 107 (67 male; mean age, 59±13 years) formed the study cohort. A high prevalence of concurrent coronary risk factors such as hypertension and hypercholesterolemia was found, and a minority of patients had prior coronary intervention. On average, study patients had diabetes mellitus diagnosed for 10.7±8.5 years. LGE by CMR was present in 30 of 107 patients (28%) in the study group. Presence of LGE on CMR was associated with a history of cardiac bypass surgery, significant T-wave abnormality, elevated 5-year UKPDS event probability, prolonged QRS duration, presence of wall motion abnormality, and reduced global LV function (LVEF, LV end-diastolic volume index, and LV end-systolic volume index).

Cardiovascular Outcome of the Study Group

At the end of study follow-up (median, 17 months; range, 6 to 57 months), 38 patients (36%) in the study group experienced MACE, including 18 deaths, 2 acute MIs, 10 unstable angina, 5 exacerbations of heart failure, 1 cerebral vascular accident, and 2 ventricular tachycardia necessitating ICD discharge. We could confirm that 14 of the 18 deaths (78%) were cardiac, 2 (11%) were unknown, and 2 (11%) were noncardiac (both with metastatic cancers). Among the cardiac deaths, all had LV dysfunction; 12 of the 14 died as a result of worsening heart failure, and 2 had sudden arrhythmic events that failed resuscitation. The 2 patients who developed an acute MI had ST elevation with elevated troponins and severe angiographic coronary stenoses. During follow-up, 28 of the 107 study patients (26%) were referred to coronary angiography at an average of 160±278 days (range, 3 to 1282 days) after CMR. Of these 28, 19 patients (68%) had angiographically significant coronary stenosis, with 10 (53%)

Table 2. Univariable Association With MACE and Mortality of Patients in the Study Group

	MACE			All-Cause Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Patient age	1.00	0.98–1.03	0.81	1.05	1.00–1.09	0.04
Female sex	0.84	0.42–1.67	0.61	1.08	0.40–2.95	0.88
Body mass index >30 kg/m^2	0.66	0.34–1.27	0.22	0.44	0.16–1.19	0.11
Years of diabetes diagnosis	0.98	0.94–1.02	0.39	0.99	0.93–1.05	0.70
HbA_{1c}, %	0.87	0.67–1.12	0.27	0.91	0.62–1.33	0.61
Resting heart rate >100 bpm	0.95	0.29–3.12	0.93	0.75	0.10–5.71	0.78
History of PCI	2.41	1.00–5.81	0.05	2.00	0.58–6.94	0.28
History of CABG	1.43	0.56–3.71	0.46	0.46	0.06–3.49	0.45
History of hypertension	0.65	0.32–1.29	0.22	0.61	0.23–1.66	0.34
History of hypercholesterolemia	0.63	0.33–1.23	0.18	0.48	0.19–1.23	0.13
Total cholesterol value	1.00	0.99–1.00	0.32	0.99	0.97–1.00	0.06
HDL cholesterol	1.00	0.97–1.03	0.81	1.01	0.97–1.05	0.62
Total/HDL cholesterol ratio	0.83	0.55–1.23	0.34	0.42	0.22–0.81	0.009
Heavy tobacco use	1.16	0.58–2.33	0.67	1.94	0.75–5.03	0.17
Family history of CAD	0.57	0.18–1.87	0.35	0.82	0.19–3.59	0.79
Systolic BP at rest, mm Hg	1.00	0.98–1.01	0.55	1.00	0.98–1.02	0.80
UKPDS 5-y probability of MACE	0.22	0.01–15.53	0.49	7.38	0.06–986.72	0.42
β-Blocker	0.89	0.47–1.71	0.74	0.87	0.34–2.20	0.76
Calcium blocker	1.18	0.58–2.39	0.64	0.84	0.27–2.54	0.75
Angiotensin-converting enzyme inhibitor	0.75	0.40–1.42	0.37	0.71	0.28–1.81	0.50
Cholesterol-lowering medication	0.80	0.41–1.54	0.50	0.37	0.15–0.95	0.04
Aspirin	1.20	0.63–2.31	0.57	1.22	0.47–3.16	0.68
Nonsinus rhythm	1.71	0.60–4.91	0.32	1.62	0.37–7.11	0.99
LVH on ECG	1.13	0.27–4.70	0.87	. . .	. . .	. . .
Left bundle-branch block	1.77	0.62–5.05	0.28	2.31	0.66–8.04	0.19
Right bundle-branch block	. . .	. . .	. . .	. . .	. . .	. . .
QRS duration	1.00	0.98–1.02	0.90	1.01	0.98–1.03	0.65
Corrected QT interval	0.99	0.98–1.00	0.24	0.99	0.97–1.01	0.22
ST depression ≥1 mm	1.99	0.82–4.84	0.13	1.72	0.49–5.98	0.40
T inversion in >2 contiguous leads	1.80	0.89–3.64	0.10	2.10	0.81–5.44	0.12
LV mass	1.01	1.00–1.01	0.09	0.99	0.98–1.00	0.23
LVEDD, per mm	1.00	0.95–1.05	0.91	0.97	0.91–1.04	0.38
LVEDV index, per 10 mL/m^2	1.19	1.05–1.34	0.006	1.02	0.86–1.21	0.79
LVESV index, per 10 mL/m^2	1.18	1.07–1.31	<0.001	1.04	0.89–1.21	0.63
LVEF, per 10%	0.79	0.65–0.96	0.02	0.96	0.72–1.30	0.81
Resting wall motion abnormality	1.91	0.99–3.67	0.05	1.90	0.75–4.83	0.18
Presence of LGE	3.71	1.93–7.12	<0.001	3.61	1.42–9.19	0.007
LGE, % of LV mass, per 10%	1.63	1.12–2.38	0.01	1.60	0.87–2.92	0.13
TE_{Mean}	2.04	0.72–5.75	0.18	3.97	1.09–14.48	0.04
TE_{Max}	1.26	0.99–1.61	0.06	1.32	0.96–1.82	0.09
TE_{Max} (LAD territory)	0.98	0.61–1.56	0.92	1.22	0.76–1.96	0.42
TE_{Max} (RCA territory)	1.51	1.15–1.98	0.003	1.51	1.08–2.12	0.02
TE_{Max} (LCx territory)	1.08	0.47–2.47	0.85	1.47	0.44–4.84	0.53
No. of segments with LGE	1.14	0.96–1.36	0.14	1.26	1.02–1.56	0.03
No. of segments with LGE (LAD)	1.11	0.62–2.00	0.73	1.61	0.86–2.99	0.14
No. of segments with LGE (RCA)	1.59	1.11–2.29	0.01	1.50	1.03–2.17	0.03
No. of segments with LGE (LCx)	1.25	0.65–2.41	0.50	1.67	0.77–3.64	0.20

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; HDL, high-density lipoprotein; CAD, coronary artery disease; LVH, LV hypertrophy; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; TE, transmural extent of late gadolinium enhancement; LAD, left anterior descending artery; RCA, right coronary artery; and LCx, left circumflex artery. Entries without values indicate that events were too low for HR estimation.

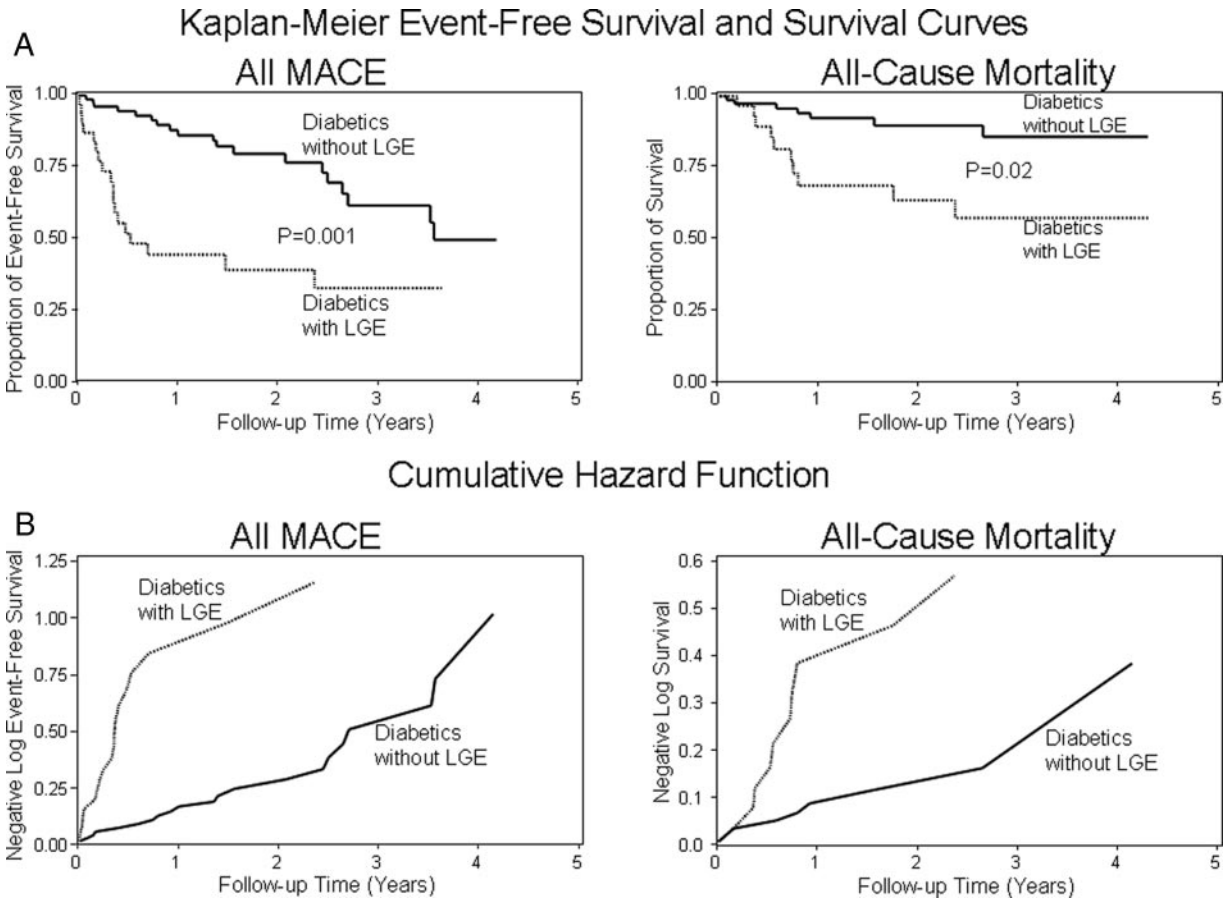

Figure 2. Kaplan–Meier event-free survival and survival curves (A) and cumulative event-free survival and survival functions (B) of the study group.

undergoing coronary interventions. Coronary intervention during follow-up was not associated with MACE in the study patients (HR, 0.75; 95% CI, 0.31 to 1.85; $P=0.39$). Univariable associations of clinical, ECG, and CMR variables with MACE and all-cause mortality are illustrated in Table 2. In the study cohort, although percutaneous coronary intervention, resting wall motion abnormality, LV end-systolic volume index, LV end-diastolic volume index, and LVEF were significant predictors of MACE, the presence of LGE demonstrates the strongest association with MACE (χ^2 likelihood ratio, 15.54; HR, 3.71; $P<0.001$) and all-cause mortality (χ^2 likelihood ratio, 7.27; HR, 3.61; $P=0.007$). The myocardial extent of LGE (as a percent of total LV mass) was associated with hazards for MACE during the study follow-up period, with an estimated 63% increase in hazards for every 10% increase in the myocardial extent of LGE. Average segmental transmural extent of LGE and the number of myocardial segments with LGE were significantly associated with all-cause mortality. Maximal transmural extent of LGE demonstrated a trend association with increased hazards for MACE and with increased hazards for death. LGE involvement in the right coronary artery territory (by maximal transmural extent or number of segments with scar) had a stronger association with MACE or with all-cause mortality than the other 2 coronary territories. Among study patients with resting wall motion abnormality, hypokinesis/akinesis was observed in the anterior, inferior, and lateral LV in 16 (15%), 17 (16%), and 9 (8%) patients, respectively. The location of wall motion abnormality did not demonstrate independent association with MACE or death.

Temporal Pattern of Hazards of Patients in the Study Group

Kaplan–Meier curves, stratified by the presence of LGE, for MACE (left) and all-cause mortality (right) of patients in the study group are illustrated in Figure 2 (top). Both MACE and all-cause mortality were significantly increased in diabetic patients with LGE compared with those without LGE. Figure 2 (bottom) also illustrates the corresponding cumulative hazard function for MACE (left) and all-cause mortality (right) over time during the follow-up period. The rate of hazard increase is demonstrated by the slope of the cumulative hazard function curves. The left plot demonstrates that study patients who had LGE experienced MACE at a substantially higher rate than patients who did not have LGE in the first 1 year after study entry. However, patients who were found to have no LGE at study entry developed an increasing rate of experiencing hazards in MACE after the first 2 years of study follow-up. The right plot demonstrates the cumulative hazard function for patient mortality in the study cohort. A pattern of increasing hazards for patient mortality similar to MACE was observed. Hazards of all-cause mortality in-

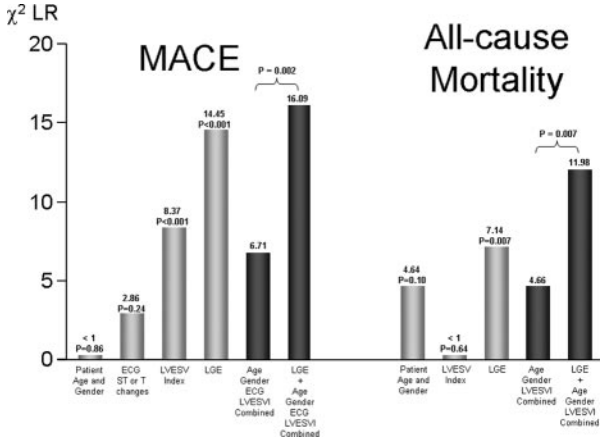

Figure 3. Comparison of univariable (light bar) and incremental multivariable (dark bar) model χ^2 likelihood ratio (χ^2 LR) for MACE and all-cause mortality in the study group. LVESV indicates LV end-systolic volume; LVESI, LV end-systolic volume index.

creased at an increasing rate beyond the first 2 years of study follow-up.

Multivariable Analyses of Patients in the Study Group

When all variables in Table 1 were considered in the multivariable forward selection strategy, presence of LGE was the strongest multivariable predictor selected for association with MACE and all-cause mortality. At the predefined selection level of entry ($P=0.05$), no other variable qualified to enter the selection models after LGE was selected for MACE and for all-cause mortality. Furthermore, after adjustment for patient age, gender, any abnormal ST or T changes on ECG, and LV end-systolic volume index, the presence of LGE showed significant incremental prognostic value for MACE, increasing model χ^2 by 9.38 ($P=0.002$) with a >4-fold adjusted hazards increase for MACE (adjusted HR, 4.13; 95% CI, 1.75 to 9.74; $P=0.001$; Figure 3). In addition, after adjustment for patient age, sex, and LV end-systolic volume index, the presence of LGE had significant incremental predictive value for all-cause mortality, increasing model χ^2 likelihood ratio by 7.32 ($P=0.007$) with a >5-fold adjusted hazards increase for all-cause mortality (adjusted HR, 5.03; 95% CI, 1.62 to 15.58; $P=0.005$; Figure 3). After adjustment for the effects of resting wall motion abnormality, LGE provided incremental association with MACE and death (adjusted HR, 4.59; $P<0.001$; and adjusted HR, 4.73; $P=0.01$, respectively).

Prognostic Association of LGE Adjusted to the UKPDS 5-Year Probability Risk Model and Metabolic Parameters in the Study Group

Metabolic panel (HbA_{1c} and fasting lipoprotein ratio) performed within 12 months of CMR was available in 98 of 107 study patients (92%). Mean $R_T(t=5)$ in the study group was 0.082 ± 0.078 (range, 0.003 to 0.395). Although a significantly higher mean $R_T(t=5)$ was found among study patients with LGE (0.111 ± 0.088 versus 0.070 ± 0.062; $P=0.01$), $R_T(t=5)$ did not demonstrate significant prognostic association with MACE or death. After adjustment for $R_T(t=5)$, LGE maintained a strong association with MACE (HR, 3.89; 95% CI, 1.92 to 7.87; $P<0.001$) and death (HR, 3.38; 95% CI, 1.24 to 9.25; $P=0.02$). After adjustment for HbA_{1c}, duration of diabetes mellitus in years, lipoprotein ratio, and systolic BP, LGE maintained a strong association with MACE (HR, 3.37, $P<0.001$; HR, 3.46, $P<0.001$; HR, 3.37, $P<0.001$; and HR, 3.74, $P<0.001$, respectively) and with death (HR, 3.49, $P=0.01$; HR, 3.46, $P=0.01$; HR, 3.05, $P=0.03$; and HR, 3.62, $P=0.007$, respectively). In addition, LGE percent (per 10% of LV mass involved) maintained a significant association with MACE adjusted to $R_T(t=5)$, HbA_{1c}, duration of diabetes mellitus in years, lipoprotein ratio, and systolic BP (HR, 1.61, $P=0.02$; HR, 1.60, $P=0.02$; HR, 1.58, $P=0.03$; HR, 1.61, $P=0.02$; and HR, 1.64, $P=0.01$, respectively).

Comparing the Demographic Features and Outcomes of the Study and Control Groups

Demographic characteristics of the study and the control groups were compared and are illustrated in Table 1. Compared with the study group, patients in the control group were older, had more frequent coronary intervention, had lower LVEF and larger LV end-diastolic volume index, and were more likely to have wall motion abnormality. In the first 12 months after CMR, 25 of the 74 patients (34%) had coronary angiography at an average of 48 ± 78 days (range, 26 to 303 days) after the CMR study. A high burden of coronary artery disease was found, with 22 of these 25 patients (88%) having coronary stenosis (>70%) involving at least 1 vessel.

At the end of the study follow-up period, patients in the control group experienced 33 MACE, including 13 deaths, 4 acute MIs, 8 unstable angina hospitalizations, and 8 heart failure hospitalizations. Among the 13 patient deaths, 10 (77%) were confirmed to have been caused by worsening heart failure, 2 (15%) were unknown, and 1 (8%) had a noncardiac cause (history of mesothelioma on chemotherapy). Figure 4 (left) demonstrates the event-free survival function by Kaplan–Meier curves comparing the study group (stratified by presence or absence of LGE) and the control group. Consistent with existing literature, patients in the control group (diabetics with clinical evidence of MI) had significantly worse event-free survival compared with patients in the study group without LGE ($P=0.001$). However, those patients in the study group with LGE by CMR followed a worsened event-free survival distribution that was similar to that of patients in the control group ($P=0.18$). The range of the median event-free survival times from the study group with LGE (0.43 years; range, 0.005 to 3.62 years; interquartile range, 0.21 to 1.46 years) fell within the range of the control group (0.90 years; range, 0.002 to 4.58 years; interquartile range, 0.23 to 1.95). Figure 4 (right) demonstrates that patients in the study group with LGE by CMR experienced a high rate of hazards increase, similar to patients in the control group, throughout the course of the follow-up period.

Discussion

The present study found a high prevalence (28%) of myocardial scar detected by LGE on CMR in diabetic patients without clinical evidence of MI. Importantly, LGE was associated with substantial hazards to MACE and all-cause

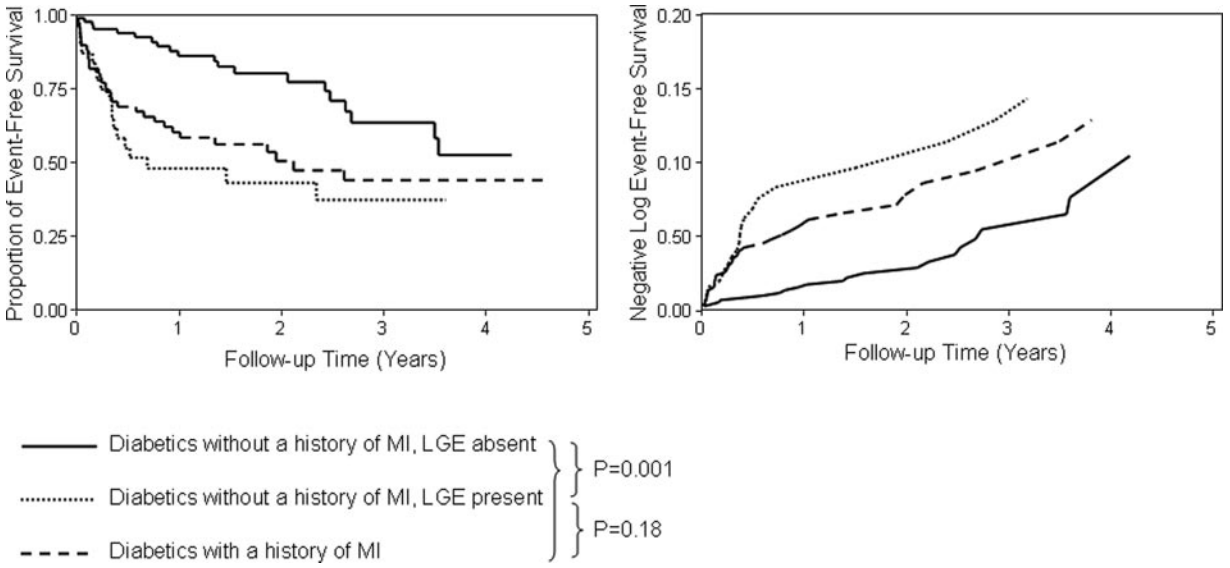

Figure 4. Kaplan–Meier event-free survival curves and log event-free survival of patients from both the study and control groups combined.

mortality (>3-fold hazards increase for MACE and mortality). Furthermore, diabetic patients without clinical evidence of MI but with LGE evidence of myocardial scar had a cardiac event rate that was very similar to that of diabetic patients with clinical evidence of prior MI. Among diabetic patients without clinical evidence of MI, LGE was the strongest (and the only significant) multivariable predictor of MACE and mortality. It added incremental prognostic value to common clinical risk markers such as patient age, gender, ST-T changes on ECG, LV global systolic function, and UKPDS 5-year risk model.

Clinical Implications

A clear need exists to identify diabetic patients at high risk of cardiovascular events. We found that LGE imaging can detect a high prevalence of myocardial scar that represented "footprints" of prior subclinical coronary events. These occult myocardial scars were associated with a high risk of future cardiac events and therefore identify a subpopulation of diabetic patients who may benefit from more intensive medical or revascularization treatment strategies. Although other imaging techniques have reported value for risk stratification of diabetic patients without prior MI,[22,23] LGE imaging by CMR may offer a unique noninvasive method for detecting unrecognized myocardial scar at high spatial resolution and tissue contrast. Furthermore, CMR may detect subclinical MI missed by nuclear methods[7,24] or cine imaging[25] and therefore may be more sensitive for detecting patients at risk for important cardiac events. Although the burden of diabetes mellitus has been predicted to reach an epidemic level in the next decades, affecting 12% to 15% of the US population,[26] our results highlight that LGE imaging may provide a noninvasive risk-stratifying tool for moderate- to high-risk diabetics.

As a corollary finding, diabetic patients in our cohort without evidence of MI by history or LGE imaging enjoyed an initial 2-year period of relatively low rates of hazards increases for cardiac events. These findings are consistent with the temporal pattern of cardiac events experienced by diabetic patients enrolled in large epidemiological studies.[27] However, we found that the rate of developing MACE steeply increased after the first 2 years in patients without a history of MI who had negative LGE imaging. We postulate that some patients in this group who had no LGE at the time of CMR remained at ongoing risk for progressive coronary disease and may have developed subsequent subclinical myocardial scarring sometime after 2 years with an associated increased cardiac event rate. Thus, it appears that in diabetic patients without clinical evidence of MI who have negative CMR studies for scar, a limited 2-year "warranty period" exists. Such a limited warranty also has been described with normal stress nuclear perfusion or dobutamine stress echocardiography, especially in populations of patients with known coronary artery disease or with diabetes mellitus.[28–31] In these patients without evidence of myocardial ischemia, the annual cardiac death or MI rate is very low (0.5% to 0.9% per year) for the first 3 to 5 years and then increases by 80% to 160% over the next 3 years.[30] The present study, however, characterized the presence and extent of LGE indicative of MI undetected by clinical evaluation. With a higher sensitivity for small subendocardial MI than cine[25] or nuclear methods,[7,24] LGE by CMR may provide improved risk stratification of diabetic patients complementary to current methods for evaluating myocardial ischemia.

Study Limitations

Our study has a number of limitations. First, because CMR is a new and costly imaging modality among other available noninvasive modalities, it is possible that selection bias exists from clinicians' referral at our institution. The study group demonstrated high prevalence of coronary risk factors, evident by a history of hypertension in 71% of patients, hypercholesterolemia in 70%, and a long duration of diabetes mellitus (average, 11 years; range, 1 to 49 years). We postulate that selection bias likely has sampled high-risk diabetics with a high prevalence of subclinical coronary disease and thus an elevated mortality rate of 17% at 4.7

years' follow-up. Although we reported strong association of LGE with MACE and death in the present study patients, whether any prognostic association of LGE with MACE exists in diabetics at lower pretest likelihood of coronary artery disease requires future study. Furthermore, our study involved patients presenting with recent symptoms and likely represented a higher-risk population; whether the present results apply to asymptomatic diabetic patients is unclear. A second study limitation relates to the selection of control patients based on evidence of prior MI. As a result, some characteristics such as age and history of prior coronary intervention were not matched between the study and control groups. However, it is intriguing that study group patients, despite being younger with less frequent history of coronary intervention, had a markedly reduced event-free survival when LGE was present, comparable to control patients (Figure 4). The small patient numbers may have limited the power of the log-rank test in detecting a statistical difference between these 2 groups. We believe that these patients represent a high-risk group who had suffered a silent MI undetected by clinical examination and ECG but characterized by CMR. Finally, no conclusion can be drawn about the prognostic value of CMR compared with other imaging or diagnostic techniques for risk stratification of diabetic patients. We believe that as a noninvasive technique capable of concurrent stress perfusion or cine function in the same imaging session, CMR offers a strong potential for risk stratification and treatment guidance of diabetic patients at high risk of adverse outcomes.

Conclusions

Diabetic patients without clinical evidence of MI have a high prevalence of myocardial scar consistent with MI detected by CMR that is associated with a significant risk of important cardiac events, including death. Furthermore, LGE by CMR provides incremental prognostic information to MACE or all-cause mortality, beyond clinical and LV function variables combined, and may serve as a valuable noninvasive risk-stratifying tool in these patients with a known high prevalence of coronary artery disease.

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Disclosures

None.

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CLINICAL PERSPECTIVE

With a high prevalence of atypical cardiac symptoms and ECG findings nonspecific for acute coronary syndrome, a noninvasive technique that improves the detection of occult myocardial infarction (MI) in diabetic patients may serve to advance the management of the cardiovascular complications of this current global epidemic. In this study, we report the clinical utility and prognostic implication of late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging in detecting myocardial scar from MI in a diabetic cohort without any history or ECG evidence of MI. With excellent tissue contrast and spatial resolution, LGE imaging offers a novel method of myocardial characterization not otherwise captured by regional contractile function and nuclear scintigraphy. A high prevalence of LGE at 28% was present among diabetics without a history of MI. This finding was associated with a >3-fold increase in cardiac events and death. Among patients who were detected by LGE imaging to have an unrecognized MI, the reduced median event-free survival was not different from that of a diabetic control cohort who presented with a clinical MI. Furthermore, this study demonstrated that LGE findings provide incremental prognostic value compared with patient age, sex, ST-T changes on ECG, left ventricular systolic function, and the validated United Kingdom Prospective Diabetes Study 5-year risk engine. In summary, LGE by cardiac magnetic resonance imaging can detect subclinical MI and characterize a group of diabetic patients at high risk of cardiac events and death.