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Relationship Between Left Ventricular Structural and Metabolic Remodeling in Type 2 Diabetes

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METABOLISM

Concentric left ventricular (LV) remodeling is associated with adverse cardiovascular events and is frequently observed in patients with type 2 diabetes mellitus (T2DM). Despite this, the cause of concentric remodeling in diabetes per se is unclear, but it may be related to cardiac steatosis and impaired myocardial energetics. Thus, we investigated the relationship between myocardial metabolic changes and LV remodeling in T2DM. Forty-six nonhypertensive patients with T2DM and 20 matched control subjects underwent cardiovascular magnetic resonance to assess LV remodeling (LV mass–to–LV end diastolic volume ratio), function, tissue characterization before and after contrast using T1 mapping, and ^{1}H and ^{31}P magnetic resonance spectroscopy for myocardial triglyceride content (MTG) and phosphocreatine-to-ATP ratio, respectively. When compared with BMI- and blood pressure–matched control subjects, subjects with diabetes were associated with concentric LV remodeling, higher MTG, impaired myocardial energetics, and impaired systolic strain indicating a subtle contractile dysfunction. Importantly, cardiac steatosis independently predicted concentric remodeling and systolic strain. Extracellular volume fraction was unchanged, indicating the absence of fibrosis. In conclusion, cardiac steatosis may contribute to concentric remodeling and contractile dysfunction of the LV in diabetes. Because cardiac steatosis is modifiable, strategies aimed at reducing MTG may be beneficial in reversing concentric remodeling and improving contractile function in the hearts of patients with diabetes.

Diabetes (DM) is associated with an increased risk of both heart failure (1) and cardiovascular mortality (2), even in the absence of coronary artery disease (CAD). The reasons for this are not clear, but one candidate mechanism that has emerged is concentric left ventricular (LV) hypertrophy, which is frequently observed in patients with type 2 DM (T2DM) (3,4) preceding the development of clinical heart failure (5) and is shown to be a strong predictor of adverse cardiovascular events (6).

Concentric remodeling of the left ventricle is characterized by an increased LV mass–to–LV end diastolic volume ratio (LVMVR) but a normal LV mass index (7). The precise mechanism underlying concentric LV remodeling in patients with DM, in the absence of significant arterial hypertension, remains unclear. One potential driver of LV concentric remodeling in patients with T2DM is cardiac steatosis, whereby excess myocyte accumulation of triglyceride leads to hypertrophic signaling (8,9). The link between lipotoxicity and concentric LV remodeling has been demonstrated in animal models of excess lipid accumulation (7,10) and in humans (11), particularly patients with generalized lipodystrophy (12) who exhibit severe concentric LV hypertrophy and significant cardiac steatosis. Proton (^{1}H) magnetic resonance spectroscopy (MRS) allows for the noninvasive measurement of cardiac triglyceride content. Using this technique, cardiac steatosis has been shown to be a prominent and early feature of diabetic cardiomyopathy (13).

In addition, impaired myocardial high-energy phosphate metabolism is another important feature of diabetic cardiomyopathy (14). ^{31}P-MRS allows for cardiac energetics to be measured noninvasively. Whether a relationship between concentric LV remodeling and impaired myocardial energetics exists in T2DM is unknown, but given the

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link between the phosphocreatine (PCr)-to-ATP ratio and mortality (15), this is worthy of investigation.

Interstitial fibrosis has also been implicated in the pathogenesis of LV hypertrophy (16) and has been identified in the more advanced stages of diabetic cardiomyopathy (17). The role of interstitial fibrosis in the pathogenesis of LV hypertrophy in stable/early diabetic cardiomyopathy is much less clear, since abnormal myocyte hypertrophy, rather than fibrosis, seems to predominate in the early stages (18). Cardiac magnetic resonance (CMR) T1 mapping for extracellular volume (ECV) quantification allows for noninvasive quantification of fibrosis (19), correlating closely with the proportionate area of collagen on histology (20).

Thus, we used CMR imaging, combined with ^{1}H-MRS and ^{31}P-MRS, to assess the relationship among LV concentric remodeling, cardiac fibrosis, steatosis, and myocardial energetics in T2DM, and compared the results with those of age-, BMI-, and blood pressure (BP)-matched control subjects without diabetes.

RESEARCH DESIGN AND METHODS

The study complies with the Declaration of Helsinki; it was approved by the National Research Ethics Committee (REC Ref 13/SW/0257), and informed written consent was obtained from each participant. All patients were recruited from the general practice surgeries in Oxfordshire, U.K. Forty-six patients with stable T2DM (diagnosed according to the World Health Organization criteria [21]) and 20 control subjects were recruited to the study.

Inclusion and Exclusion Criteria

The diabetes population assessed in this study comprises only patients with stable T2DM and no known diabetes complications. Subjects were excluded if they had a history of cardiovascular disease, chest pain, smoking, hypertension (resting systolic BP >140 mmHg and diastolic BP >90 mmHg), contraindications to MRI, ischemic changes on 12-lead electrocardiography, or renal impairment (estimated glomerular filtration rate <30 mL/min). Participants with T2DM were excluded if they had HBA_{1c} >9% or were taking insulin.

Anthropometric Measurements

Height and weight were recorded and BMI was calculated. BP was recorded as an average of 3 supine measurements taken over 10 min (DINAMAP-1846-SX; Critikon Corp). Fasting venous blood was drawn to measure glucose, triglycerides, HBA_{1c}, renal function, and free fatty acids in full blood count tests as previously described (22). Fasting insulin was also recorded for all patients with diabetes. In agreement with the diabetes management guidelines (23), albumin concentrations from spot (random) urine samples and the albumin-to-creatinine ratio were assessed in the majority of patients with T2DM (~69%; n = 32).

Coronary Computed Tomographic Angiography

An optional scan of coronary computed tomographic angiography (CCTA) was offered to patients with diabetes to exclude obstructive CAD (>50% of luminal stenosis). CCTA scans were performed on 64-slice computed tomography scanner (Discovery 690; GE Healthcare, Princeton, NJ) in accordance with performance guidelines from the Society of Cardiovascular Computed Tomography (24). Participants received β-blockade (intravenous metoprolol) and sublingual glyceryl trinitrate (if necessary and safe) before the scan to achieve a heart rate of <65 bpm. During the CTCA acquisition, 80 mL of iodinated contrast (Visipaque; GE Healthcare) was injected, followed by a 50-mL saline flush.

Echocardiography

Transthoracic echocardiography was performed with the subjects at rest using a commercially available ultrasound transducer and equipment (iE33 Medical System; Philips, the Netherlands). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5; GE-Vingmed). LV diastolic function was measured according to the guidelines of the American Society of Echocardiography (25). The following diastolic indices were obtained: transmitral early (E) and late (A) diastolic velocities and E-to-A ratio.

Cardiac Magnetic Resonance Protocol

All LV imaging was performed using a 3.0 Tesla magnetic resonance system (Siemens, Germany). Images of LV volumes and diastolic function were acquired using a steady-state free precession sequence and analyzed using cmr42 (Circle Cardiovascular Imaging Inc., Canada), as previously described (26).

To determine midventricular peak systolic circumferential strain and diastolic strain rate, myocardial tagging was performed as described previously (27,28). Tagged images were analyzed using Cardiac Image Modeler software (CimTag2D version 7; Auckland Medical Research, Auckland, New Zealand). Semiautomated analysis was performed by aligning a grid to the myocardial tagging planes at end diastole.

T1 mapping and ECV quantification were performed using a shortened modified look-locker inversion recovery sequence (29). T1 maps were generated from the mid-short-axis images, as described previously (29). Consistent with earlier reports of ECV estimation (19,30), we measured myocardial and blood T1 values before and after contrast, and the estimation of ECV and λ was based on multipoint regression, incorporating all available points before and after contrast to increase the robustness of the estimates by increasing the number of underlying data points. ECV was calculated as (1 – hematocrit). For calculation of T1 values after contrast, the T1 map acquired at 15 min after contrast was used to calculate ECV. Images at baseline and 15 min after contrast were contoured by two observers (EL and SKP) in a blinded fashion, using dedicated software, as previously described (31).

Late gadolinium enhancement (LGE) imaging was performed to exclude the presence of previous silent myocardial infarction or regional fibrosis, and it was

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acquired according to standard clinical protocols and analyzed qualitatively.

^{31}P Magnetic Resonance Spectroscopy

^{31}P-MRS was performed to obtain the at-rest PCr-to-ATP ratio from a voxel placed in the midventricular septum, with the subjects lying prone with their heart over the center of the ^{31}P heart/liver coil in the isocenter of the magnet, as previously described (32). ^{31}P-MRS postprocessing analysis was performed using in-house software within MATLAB version R2012a (MathWorks, Natick, MA) as previously described (32).

Cardiac ^{1}H-MRS

Myocardial ^{1}H magnetic resonance spectra were obtained from the mid-interventricular septum as previously described (33). Spectroscopic acquisitions were performed using an electrocardiographic trigger at end-expiration to minimize motion artifacts. Water-suppressed spectra were acquired to measure myocardial lipid content, and spectra without water suppression were acquired as an internal standard. Spectra were analyzed using MATLAB and the AMARES algorithm in Java-based magnetic resonance user interface, as previously described (33). Myocardial lipid content was calculated as a percentage relative to water: (signal amplitude of lipid/signal amplitude of water) $\times$ 100.

Statistical Analysis

All statistical analysis was performed with commercially available software packages (IBM SPSS Statistics, version 20). All data were checked for normality using the Kolmogorov–Smirnov test and are presented as means $\pm$ standard deviations or median (interquartile range), as appropriate. Normally distributed data sets were analyzed with the independent Student t test. The χ^2 test was used to compare discrete data, as appropriate. Bivariate correlations were performed using Pearson's or Spearman's method, as appropriate. To assess the associations between concentric remodeling and metabolic parameters, linear regression across all subjects was performed. Linearity was assessed visually. Variables with $P < 0.05$ and the strongest relationship with concentric remodeling were then included in multiple linear regression models using a stepwise selection method to assess the "best" subset in predicting cardiovascular remodeling. Significance was assumed at $P < 0.05$.

RESULTS

Participant Characteristics

Demographic, clinical, and biochemical data are shown in Table 1. Forty-six patients with T2DM (24 male, mean age 55 $\pm$ 9 years, BMI 29.6 $\pm$ 5.7 kg/m^2, median diabetes duration 7 years [interquartile range 1–8], and mean HBA_{1c} of 7.5 $\pm$ 1.2%) and 20 control subjects (9 male, mean age 54 $\pm$ 10 years, BMI 28.6 $\pm$ 2.8 kg/m^2) were studied. Patients had age, sex, weight, resting heart rate, and BP similar to those of control subjects. As expected, diabetes was associated with higher fasting blood glucose, HBA_{1c}, free fatty acids, and triglyceride levels and lower HDL cholesterol. About 74% of the patients with diabetes were taking statin therapy; hence the lower total cholesterol and LDL cholesterol levels were detected in patients compared with control subjects. Urine albumin-to-creatinine ratio and urine albumin results were recorded for 32 patients with T2DM in the study, and all were within normal limits. Coronary Computed Tomographic Angiography Of the 46 patients with T2DM, significant CAD was excluded by CCTA in 76%; the remaining 11 patients did not consent to having CCTA.

Effect of Diabetes on LV Geometry and Function

In agreement with previous reports, diabetes was associated with concentric LV remodeling. Although LV mass was not significantly different between patients with T2DM and control subjects (P = 0.183), LV end-diastolic volume was 16% smaller in patients with T2DM (P = 0.004). As a result, T2DM was associated with increased LVMVR by 31% (0.97 $\pm$ 0.17 vs. 0.74 $\pm$ 0.14 g/mL; $P <$ 0.001) (Fig. 1*A* and Table 2), suggesting significant concentric remodeling. Importantly, this concentric remodeling was not correlated with BP, which was within normal limits in both groups (R = $-$0.002; P = 0.989).

Despite normal LV ejection fraction, midventricular peak systolic circumferential strain was impaired in patients with T2DM (14.5 $\pm$ 3.5% vs. 18.3 $\pm$ 2.6% in controls; $P < 0.001$; Fig. 1*B*), indicating subtle contractile dysfunction. The differences in diastolic strain rate between the patients with T2DM and control subjects did not reach statistical significance, but there was a strong trend (60 $\pm$ 24 s^{-1} in patients with T2DM vs. 65 $\pm$ 13 s^{-1} in control subjects; P = 0.057). LVMVR showed a negative correlation with peak systolic circumferential strain (R = $-$0.430; $P < 0.001$), but not with diastolic strain rates (R = $-$0.121; P = 0.341). The echocardiographic assessment of mitral inflow E-to-A ratio was significantly lower in patients with T2DM (0.99 $\pm$ 0.25 vs. 1.17 $\pm$ 0.38 in control subjects; P = 0.038). In keeping with the dissociation of diastolic strain rates and myocardial triglycerides, there was no significant correlation between the mitral inflow E-to-A ratio and myocardial triglycerides (R = $-$0.135; P = 0.393).

Cardiac Steatosis, Myocardial Energetics, Concentric Remodeling, and Strain

As described before, diabetes was associated with an almost twofold increase in myocardial triglycerides (1.13 $\pm$ 0.78% in patients with T2DM vs. 0.64 $\pm$ 0.52% in control subjects; P = 0.017; Fig. 1*C*) and also was associated with an ~18% reduction in the myocardial PCr-to-ATP ratio (1.68 $\pm$ 0.28 in patients with T2DM vs. 2.05 $\pm$ 0.34 in control subjects; $P < 0.001$; Fig. 1*D*). When investigating all study subjects, there was a positive correlation between the myocardial triglyceride content and concentric LV remodeling (R = 0.41; P = 0.003) and a negative correlation between myocardial energetics and LVMVR (R = $-$0.30;

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Table 1—Clinical and biochemical characteristics and echocardiographic features

Variables	Control subjects (n = 20)	Patients with T2DM (n = 46)	P value
Age, years	54 ± 10	55 ± 9	0.583
BMI, kg/m^2	28.6 ± 2.8	29.6 ± 5.7	0.463
Male sex, %	45	50	0.714
Diabetes duration, years (IQR)	—	7 (1–8)	
Heart rate, bpm	66 ± 13	68 ± 8	0.377
Systolic blood pressure, mmHg	128 ± 12	129 ± 8	0.583
Diastolic blood pressure, mmHg	74 ± 8	76 ± 7	0.311
Plasma fasting glucose, mmol/L	4.9 ± 0.5	8.9 ± 3.1	<0.001
Glycated hemoglobin, % (mmol/mol)	5.4 ± 0.3 (37 ± 3)	7.5 ± 0.2 (57 ± 15)	<0.001
Plasma triglycerides, mmol/L	1.59 ± 0.68	1.60 ± 0.78	0.931
Plasma free fatty acids, mmol/L	0.38 ± 0.23	0.61 ± 0.36	0.017
Total cholesterol, mmol/L	5.6 ± 0.9	3.9 ± 0.9	<0.001
HDL, mmol/L	1.53 ± 0.61	1.18 ± 0.29	0.005
LDL, mmol/L	3.41 ± 0.53	2.04 ± 0.74	<0.001
Creatinine, mmol/L	72 ± 19	65 ± 17	0.228
Hematocrit, %	41 ± 4	42 ± 3	0.501
Urine albumin, mg/L (n = 32)	—	16 ± 30	
Urine albumin-to-creatinine ratio, mg/mmol (n = 32)	—	1.7 ± 3	
Medications, n (%)			
Metformin	—	41 (89)	
Sulphonylurea	—	14 (30)	
Aspirin	—	5 (11)	
Statin	—	34 (74)	
ACE-I	—	12 (26)	
Echocardiographic features			
Mitral in-flow E-to-A ratio	1.17 ± 0.38	0.99 ± 0.25	0.038

Values are means ± standard deviations or percentages unless otherwise indicated. ACE-I, angiotensin-converting enzyme inhibitor; E-to-A ratio, transmitral early-to-late diastolic velocity ratio; IQR, interquartile range.

$P < 0.020$). Stepwise multivariable regression revealed myocardial triglyceride (β = 0.473; P = 0.001) to be the only independent predictor of concentric remodeling (overall R^2 of the model = 0.304; P = 0.001). Furthermore, myocardial triglycerides also negatively correlated with systolic strain (R = −0.40; P = 0.003), and it was also the only independent predictor of systolic strain (β = −0.400; P = 0.003) on stepwise multivariable regression analysis. However, there was no correlation between diastolic strain rate and steatosis (R = 0.158; P = 0.263). Figure 2 shows representative examples of cardiac ^{31}P-MRS, ^{1}H-MRS, and cine images in a control and a patient with T2DM.

T1 Mapping, ECV Quantification, and LGE

There was no significant difference in native myocardial T1 values between the patients with T2DM and the control subjects (1,194 ± 32 ms in patients with T2DM vs. 1,184 ± 28 ms in control subjects; P = 0.23). Similarly, ECV did not differ between the groups (29 ± 2% in patients with T2DM vs. 29 ± 3% in control subjects; P = 0.773), suggesting the absence of interstitial fibrosis. Upon visual assessment of the LGE images, no areas of enhancement indicative of scarring in either ischemic or nonischemic patterns were identified in any of the participants.

DISCUSSION

Concentric LV remodeling is an adverse prognostic marker of cardiovascular events (34) and is linked to contractile dysfunction (35). Using CMR and MRS, we show here that diabetes, in the absence of hypertension, is associated with concentric LV remodeling, and we confirm the findings of previous studies, showing pronounced cardiac steatosis (13) and decreased energetics (14,36) in patients with T2DM. We also show that, despite normal LV ejection fraction, peak systolic strain was significantly impaired in patients with diabetes, indicating a subtle contractile dysfunction, which was negatively correlated with both reduced myocardial energetics and concentric LV remodeling. Importantly, we show here for the first time that the degree of myocardial triglyceride accumulation is predictive of concentric LV remodeling and cardiac contractile function in patients with T2DM. The correlation of myocardial concentric remodeling with myocardial

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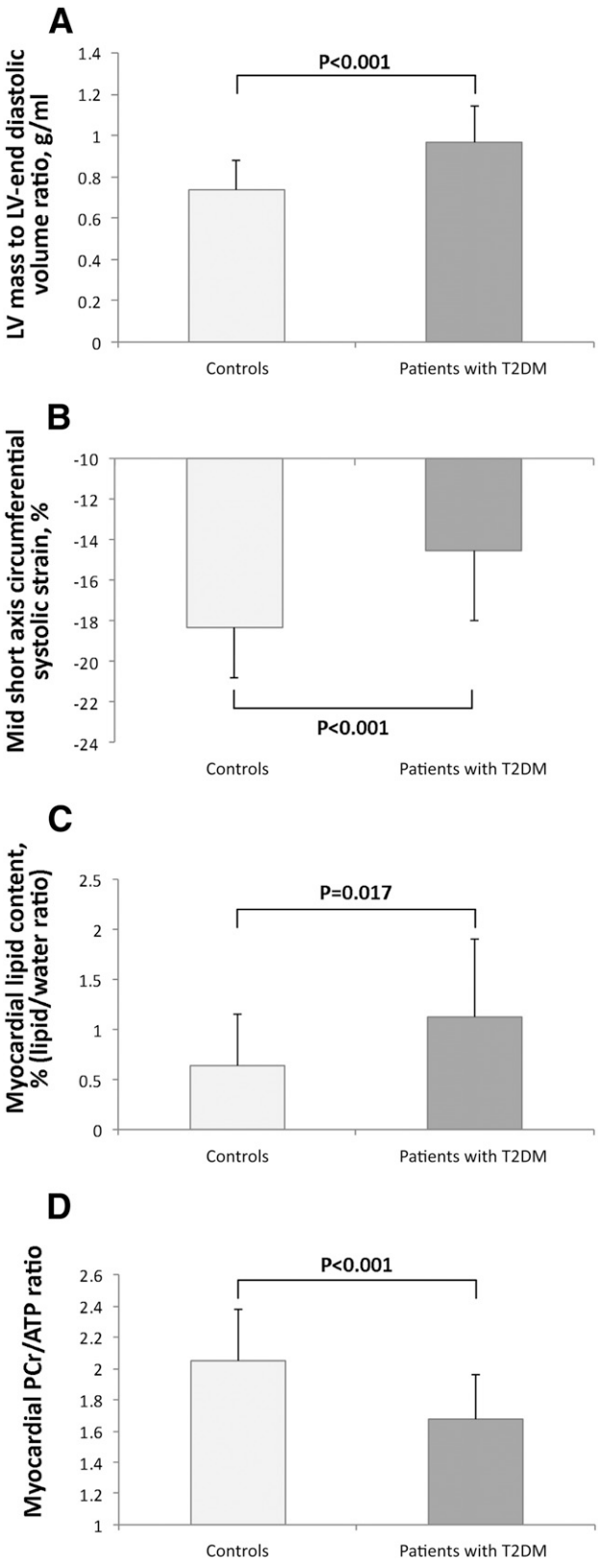

Figure 1—Differences in cardiac geometry and function between patients with T2DM and control subjects: LV mass–to–LV end diastolic volume (EDV) ratio (grams/milliliter) (*A*), systolic strain (percentage) (*B*), myocardial triglyceride content (percentage) (*C*), and myocardial energetics (PCr-to-ATP ratio) (*D*).

triglyceride accumulation and peak systolic strain in the hearts of patients with diabetes suggests a link between these; however, the causality of these relationships needs to be investigated in future studies. From these initial cross-sectional studies, we clearly cannot determine whether the observed correlations between myocardial triglyceride and LVMVR and function are causal. Myocardial steatosis has been shown to be modifiable (37,38), and this provides the potential for novel therapies aimed at reducing concentric LV remodeling and improving cardiac function in diabetes. Finally, because no significant difference in ECV and native (precontrast) T1 mapping was found between the patients with T2DM and control subjects, it is unlikely that interstitial fibrosis plays a significant role in the pathogenesis of concentric LV remodeling in this population with well-controlled, stable T2DM. This suggests that the process of concentric remodeling is not limited to patients with poorly controlled diabetes, or those with renal dysfunction (17), and occurs in the absence of significant systemic hypertension.

Microalbuminuria is strongly associated with risk for cardiovascular disease, but the nature of this link remains controversial and poorly understood (39). In this study, in patients with stable T2DM who were free of CAD, no association between urine albumin excretion and LV remodeling, contractile dysfunction, cardiac energetics, or steatosis was observed.

The population with diabetes assessed in this study comprises highly selected patients with only stable T2DM and no other significant comorbidities. Although this has the advantage of better demonstrating the pathophysiological relationships between T2DM and cardiovascular remodeling, it does reduce the broader applicability to "real-world" populations in which additional comorbidities are commonplace. Given the fact that we showed significant abnormalities in myocardial energetics, myocardial triglyceride deposition, myocardial geometry, and peak systolic strain in a population with stable diabetes, similar or amplified findings may potentially be expected in patients with diabetes with more advanced cardiovascular disease or other significant comorbidities such as hypertension. Future studies are needed to confirm this. Furthermore, whether the subtle changes in cardiac geometry, energetics, and lipid deposition predict adverse cardiovascular outcomes in a diabetes cohort remains to be definitively demonstrated by longitudinal studies.

The LVMVR is calculated by dividing the LV mass by the LV end diastolic volume, as an index of wall thickness to cavity size. LVMVR lacks a well-defined normal reference range; therefore age- and sex-matched healthy volunteers without coexistent CAD, hypertension, aortic stenosis, or other forms of heart disease were recruited and scanned contemporaneously. LVMVR in this group was 0.74 $\pm$ 0.10 g/mL and consistent with previous larger studies of $>$700 healthy volunteers carried out in our center (26). The LVMVR in the control group in this small cross-sectional study is, however, lower than the average demonstrated in the Multi-Ethnic Study of

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Table 2—LV geometry and function

	Control subjects (n = 20)	Patients with T2DM (n = 46)	P value
LV end-diastolic volume, mL	148 ± 34	124 ± 27	0.004
LV end-systolic volume, mL	43 ± 16	37 ± 13	0.351
LV stroke volume, mL	104 ± 21	86 ± 21	0.055
LV ejection fraction, %	71 ± 5	70 ± 7	0.586
LV wall thickness, mm	9.6 ± 1.3	10.4 ± 1.8	0.047
LV mass, g	109 ± 31	120 ± 28	0.183
LV mass index, g/m^2	53.1 ± 15.9	60.2 ± 11.6	0.05
LVMVR, g/mL	0.74 ± 0.14	0.97 ± 0.17	<0.001
Peak circumferential diastolic strain rate, s^{-1}	65 ± 13	60 ± 24	0.057
Native myocardial T1 value, ms	1,184 ± 28	1,194 ± 32	0.23
Extracellular volume fraction, %	29 ± 3	29 ± 2	0.773

Values are means ± standard deviations.

Atherosclerosis (MESA). This is likely because the MESA population of >5,000 participants did not exclude subjects with hypertension, impaired fasting glucose, diabetes, smoking, and other causes of concentric hypertrophy (40). In addition, participants in MESA were, on average, 6–8 years older than the participants in our study, and only ~10% had diabetes, making comparisons with this larger population-based study more difficult (40).

Relationship Between LV Geometric Remodeling and Cardiac Steatosis in the Hearts of Patients With Diabetes

Ectopic lipid deposition in the hearts of patients with diabetes is a well-documented process, and noninvasive studies using ^{1}H-MRS have reported elevated levels of cardiac triglyceride in human diabetes (13). However, the link between cardiac steatosis and diabetes, above and beyond that observed in obesity, and its potential role in concentric LV remodeling within diabetes, has not been explored in humans. This study now demonstrates that diabetes per se is linked to significant cardiac steatosis, and we show a correlation between myocardial triglycerides and concentric LV remodeling, suggesting a link between the two; however, the causality of this relationship needs to be investigated in future studies.

The importance of cardiac steatosis in the pathophysiology of concentric LV remodeling has been assessed in experimental models. In diabetes, where fatty acid supply exceeds the oxidative capacity of the heart, this leads to the diversion of lipids away from oxidative processes and toward nonoxidative processes with the production of lipotoxic intermediates such as ceramide and diacylglycerol (41). These lipotoxic intermediates have been shown to activate signaling pathways affecting ATP production, insulin sensitivity, myocellular contractility, and apoptosis (41). It has also been demonstrated recently that cardiac steatosis potentiates the effects of angiotensin 2 on the heart (42). Given the fact that angiotensin 2 is a potent hypertrophic stimulus and that both angiotensin 2 receptor density and mRNA expression are elevated in the heart of patients with diabetes (43), this is likely to be an important driver for hypertrophy. In addition, animal models of overexpression of fatty acid transporters and increases in triglyceride synthesis both result in severe cardiac steatosis and concentric LV hypertrophy (9,36). This provides a mechanistic link between cardiac steatosis, lipotoxicity, and concentric LV remodeling in diseases of upregulated fatty acid metabolism such as diabetes. Importantly, successful reduction of myocardial steatosis with GLP-1 receptor agonists (37) and mineralocorticoid receptor blockers (38) both have been shown to reverse concentric LV remodeling.

Here we demonstrate that myocardial steatosis is a predictor of concentric LV remodeling and subclinical contractile dysfunction in patients with T2DM. This supports the notion that the development of concentric LV remodeling in T2DM may be mechanistically linked to cardiac steatosis and that cardiac lipotoxicity represents a component of this process; however, an observational study such as ours cannot clearly identify the mechanisms responsible, and future studies will need to investigate this. If a causal link is proven, it would suggest that therapies and interventions aimed at reducing myocardial triglycerides may promote beneficial reverse remodeling in humans.

LV Concentric Remodeling and Myocardial Energetics

A healthy heart is able to metabolize a range of substrates to fulfill the demand for ATP production. Depending on the availability of substrates and the physiological conditions, the heart switches its metabolic preference among substrates. This flexibility is lost in diabetes, and myocardial substrate selection is shifted almost exclusively to fatty acid metabolism (43). This overuse of fatty acids results in a reduced ATP yield and a loss of mitochondrial efficiency (43). The interplay between myocardial energetic

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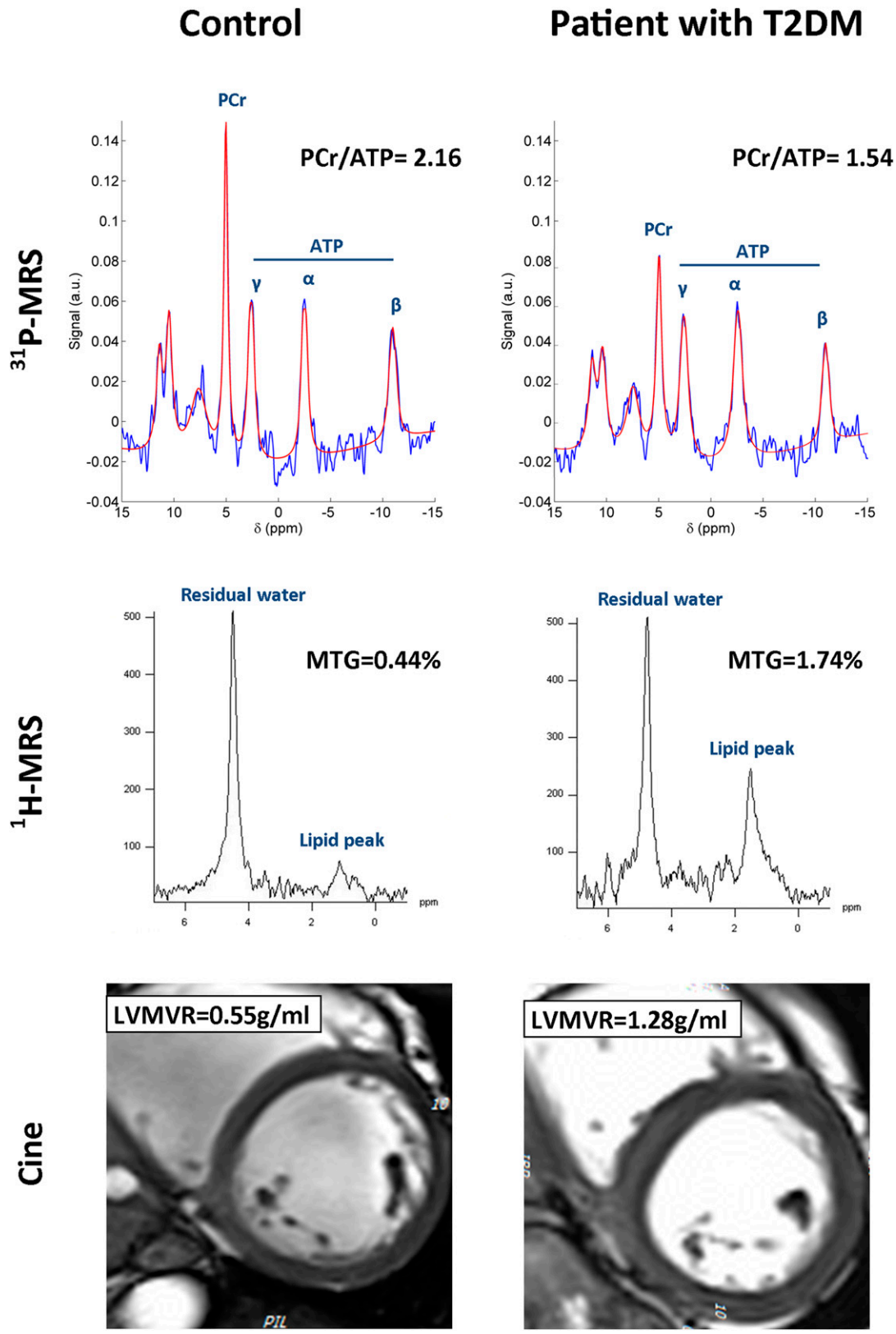

Figure 2—Representative examples of cardiac ^{31}P-MRS, ^{1}H-MRS, and cine imaging in a control subject and a patient with T2DM. Top panels: normal control ^{31}P-MRS (PCr-to-ATP ratio [Pcr/ATP] = 2.16) vs. a patient with T2DM (PCr/ATP = 1.54). Middle panels: normal control ^{1}H-MRS (myocardial lipid-to-water ratio = 0.44%) vs. a patient with T2DM (myocardial lipid-to-water ratio = 1.74%). MTG, myocardial triglyceride content. Bottom panels: normal control cine image (LVMVR = 0.55 g/mL) vs. a patient with T2DM (LVMVR = 1.28 g/mL).

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status and geometric changes in diabetes has not previously been explored. Here we report that, in the context of well-controlled diabetes, myocardial energetics, in the form of PCr-to-ATP ratios, are impaired and are linked to concentric remodeling.

Limitations

Of the 46 patients with T2DM, 11 patients (24%) did not consent to have CCTA performed, and as such it is possible that occult CAD could be present in this minority of patients. Insulin was not measured in the control group. Although diabetes was excluded based on fasting glucose measurements, this does preclude the investigation of the role of insulin resistance in the pathogenesis of cardiac steatosis. In addition, urine albumin concentrations were recorded for only ~69% (n = 32) of the patients with T2DM.

Conclusion

When compared with BMI-matched control subjects, patients with well-controlled T2DM exhibit LV concentric remodeling in the absence of arterial hypertension. This concentric remodeling is associated with cardiac steatosis, impaired myocardial energetics, and subclinical systolic dysfunction. Since myocardial steatosis is independently predictive of concentric remodeling and cardiac systolic strain, it may play an important role in adverse geometric remodeling in T2DM. Importantly, because myocardial triglyceride content is modifiable, strategies aimed at reversing myocardial steatosis may be beneficial in reversing LV remodeling and may potentially improve contractile function and prognosis in patients with diabetes.

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Author Contributions. E.L. contributed substantially to the conception and design of the study, acquired and analyzed the data, and drafted the manuscript. M.M. and R.A. acquired data and critically revised the manuscript. S.K.P. contributed substantially to data analyses. J.M.F. acquired data. C.T.R. and J.E.S. acquired and analyzed data, and critically revised the manuscript. W.T.C. and N.S. acquired and analyzed data. T.D.K. designed the study and critically revised the manuscript. K.C. critically revised the manuscript. O.J.R. contributed to statistical analyses and drafted the manuscript. S.N. conceived, designed, and coordinated the study, and drafted the manuscript. All authors read and approved the final manuscript. E.L. 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.

References

1. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes 1974;23:105–111
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035–2038
3. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 2000;101:2271–2276
4. Bella JN, Devereux RB, Roman MJ, et al. Separate and joint effects of systemic hypertension and diabetes mellitus on left ventricular structure and function in American Indians (the Strong Heart Study). Am J Cardiol 2001;87:1260–1265
5. Gjesdal O, Bluemke DA, Lima JA. Cardiac remodeling at the population level–risk factors, screening, and outcomes. Nat Rev Cardiol 2011;8:673–685
6. Bluemke DA, Kronmal RA, Lima JAC, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) Study. J Am Coll Cardiol 2008;52:2148–2155
7. Dweck MR, Joshi S, Murigu T, et al. Left ventricular remodeling and hypertrophy in patients with aortic stenosis: insights from cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:50
8. Gao H, Feng XJ, Li ZM, et al. Downregulation of adipose triglyceride lipase promotes cardiomyocyte hypertrophy by triggering the accumulation of ceramides. Arch Biochem Biophys 2015;565:76–88
9. Glenn DJ, Cardema MC, Ni W, et al. Cardiac steatosis potentiates angiotensin II effects in the heart. Am J Physiol Heart Circ Physiol 2015;308:H339–H350
10. Glenn DJ, Wang F, Nishimoto M, et al. A murine model of isolated cardiac steatosis leads to cardiomyopathy. Hypertension 2011;57:216–222
11. Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. Magn Reson Med 2003;49:417–423
12. Nelson MD, Victor RG, Szczepaniak EW, Simha V, Garg A, Szczepaniak LS. Cardiac steatosis and left ventricular hypertrophy in patients with generalized lipodystrophy as determined by magnetic resonance spectroscopy and imaging. Am J Cardiol 2013;112:1019–1024
13. McGavock JM, Lingvay I, Zib I, et al. Cardiac steatosis in diabetes mellitus: a ^{1}H-magnetic resonance spectroscopy study. Circulation 2007;116:1170–1175
14. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. Circulation 2003;107:3040–3046
15. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation 1997;96:2190–2196
16. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83:1849–1865
17. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30:595–602
18. van Heerebeek L, Hamdani N, Handoko ML, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation 2008;117:43–51
19. White SK, Sado DM, Fontana M, et al. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. JACC Cardiovasc Imaging 2013;6:955–962
20. Liu S, Han J, Nacif MS, et al. Diffuse myocardial fibrosis evaluation using cardiac magnetic resonance T1 mapping: sample size considerations for clinical trials. J Cardiovasc Magn Reson 2012;14:90
21. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553
22. Rider OJ, Tayal U, Francis JM, et al. The effect of obesity and weight loss on aortic pulse wave velocity as assessed by magnetic resonance imaging. Obesity (Silver Spring) 2010;18:2311–2316

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23. American Diabetes Association. Standards of medical care in diabetes–2007. Diabetes Care 2007;30(Suppl. 1):S4–S41
24. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009;3:190–204
25. Baumgartner H, Hung J, Bermejo J, et al.; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23; quiz 101–102
26. Rider OJ, Lewandowski A, Nethononda R, et al. Gender-specific differences in left ventricular remodelling in obesity: insights from cardiovascular magnetic resonance imaging. Eur Heart J 2013;34:292–299
27. Lawton JS, Cupps BP, Knutsen AK, et al. Magnetic resonance imaging detects significant sex differences in human myocardial strain. Biomed Eng Online 2011;10:76
28. Stuber M, Spiegel MA, Fischer SE, et al. Single breath-hold slice-following CSPAMM myocardial tagging. MAGMA 1999;9:85–91
29. Piechnik SK, Ferreira VM, Dall'Armellina E, et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. J Cardiovasc Magn Reson 2010;12:69
30. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138–144
31. Ntusi NA, Piechnik SK, Francis JM, et al. Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis–a clinical study using myocardial T1-mapping and extracellular volume quantification. J Cardiovasc Magn Reson 2014;16:21
32. Purvis LAB, Clarke WT, Biasiolli L, Robson MD, Rodgers CT. *Linewidth constraints in Matlab AMARES using per-metabolite T2 and per-voxel ΔB0*. Concord, CA, ISMRM, 2014, p. 2885
33. Rial B, Robson MD, Neubauer S, Schneider JE. Rapid quantification of myocardial lipid content in humans using single breath-hold 1H MRS at 3 Tesla. Magn Reson Med 2011;66:619–624
34. Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. Am J Cardiol 1996;78:197–202
35. Rosen BD, Edvardsen T, Lai S, et al. Left ventricular concentric remodeling is associated with decreased global and regional systolic function: the Multi-Ethnic Study of Atherosclerosis. Circulation 2005;112:984–991
36. Shivu GN, Phan TT, Abozguia K, et al. Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. Circulation 2010;121:1209–1215
37. Monji A, Mitsui T, Bando YK, Aoyama M, Shigeta T, Murohara T. Glucagon-like peptide-1 receptor activation reverses cardiac remodeling via normalizing cardiac steatosis and oxidative stress in type 2 diabetes. Am J Physiol Heart Circ Physiol 2013;305:H295–H304
38. Ramírez E, Klett-Mingo M, Ares-Carrasco S, et al. Eplerenone attenuated cardiac steatosis, apoptosis and diastolic dysfunction in experimental type-II diabetes. Cardiovasc Diabetol 2013;12:172
39. Damsgaard EM, Frøland A, Jørgensen OD, Morgensen CE. Prognostic value of urinary albumin excretion rate and other risk factors in elderly diabetic patients and non-diabetic control subjects surviving the first 5 years after assessment. Diabetologia 1993;36:1030–1036
40. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266–274
41. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest 2002;109:121–130
42. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BMW. Renin-angiotensin system and cardiovascular risk. Lancet 2007;369:1208–1219
43. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213–3223

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