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Left Ventricular Structure, Tissue Composition, and Aortic Distensibility in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications

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Alterations in myocardial structure, function, tissue composition (e.g., fibrosis) may be associated with metabolic syndrome (MetS). This study aimed to determine the relation of MetS and its individual components to markers of cardiovascular disease in patients with type 1 Diabetes Mellitus (T1DM). A total of 978 subjects of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications T1DM cohort (age: 49 ± 7 years, 47% female, DM duration 28 ± 5 years) underwent cardiovascular magnetic resonance. In a subset of 200 patients, myocardial tissue composition was measured with cardiovascular magnetic resonance T1 mapping after contrast administration. MetS was defined as T1DM plus 2 other abnormalities based on the American Heart Association/National Cholesterol Education Program criteria. MetS was present in 34.1% of subjects. After adjustment for age, height, scanner, study cohort, gender, smoking, mean glycated hemoglobin levels, history of macroalbuminuria and end-stage renal disease, left ventricle mass was greater by 12.3 g, end-diastolic volume was higher by 5.4 ml, and mass to end-diastolic volume ratio was higher by 5% in patients with MetS versus those without MetS ($p < 0.001$ for all). Myocardial T1 times were lower by 29 ms in patients with MetS than those without ($p < 0.001$). Elevated waist circumference showed the strongest associations with left ventricle mass (+10.1 g), end-diastolic volume (+6.7 ml), and lower myocardial T1 times (+31 ms) in patients with MetS compared with those without ($p < 0.01$). In conclusion, in a large cohort of patients with T1DM, 34.1% of subjects met MetS criteria. MetS was associated with adverse myocardial structural remodeling and change in myocardial tissue composition. **(Am J Cardiol 2022;174:158−165)**

Introduction

Metabolic syndrome (MetS) is a cluster of interrelated factors and is associated with cardiovascular disease. The core components of MetS are hypertension, central obesity, impaired glucose tolerance/diabetes mellitus (DM), and hyperlipidemia.[1] The value of the MetS to identify high cardiometabolic risk in DM is unclear.[2] In a cohort of patients with type 1 DM (T1DM) who developed MetS and obesity, the patients were more likely to have an increased carotid artery intima-media thickness, and, by inference, be at a higher risk of atherosclerosis and cardiovascular disease.[3,4] The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study evaluated the association between MetS and cardiovascular function using cardiac magnetic resonance (CMR), and to assess whether the MetS definition predicts these associations better than its individual components.

Methods

The DCCT/EDIC study has been described in detail.[5,6] In 1983−1989, a total of 1,441 patients (aged 13 to 39 years) with T1DM were recruited to compare the effects of

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intensive insulin therapy with conventional therapy on long-term complications. At baseline, all patients were free of cardiovascular disease, hypertension, and hypercholesterolemia. After the DCCT, the EDIC study (1994-present) was designed as an observational follow-up study of the DCCT cohort. A total of 96% (1,375) of the surviving 1,428 participants joined EDIC, and 1,301 participants were active in EDIC years 14 to 16 (2007−2009) at the time of the CMR examination. The study was approved by the institutional review boards of all participating centers, and all subjects gave written informed consent.

During DCCT/EDIC, participants underwent medical history, physical examination, and laboratory testing for fasting lipid levels, serum creatinine, urinary albumin excretion rate (AER), glycated hemoglobin (HbA1c) values, and other risk factors for cardiovascular disease (CVD) regularly.[5,6] Weighted mean laboratory values over the study duration were computed with weights proportional to the time interval between values owing to differences in frequency of measurement during DCCT/EDIC.

The MetS was defined according to the American Heart Association updated National Cholesterol Education Program criteria[7] with minor modifications as DM plus 2 other abnormalities: waist circumference ≥88 cm in women and ≥102 cm in men, triglycerides ≥150 mg/100 ml in men and women, high-density lipoprotein (HDL) cholesterol <50 mg/100 ml in women and <40 mg/100 ml in men, blood pressure ≥130/85 mm Hg or use of any antihypertensive medication. Lipid-lowering medication was not included in the criteria.

The events of retinopathy, nephropathy, and neuropathy since DCCT entry to the CMR examination were obtained. Clinical myocardial infarction (MI) events (nonfatal MI) were adjudicated by the EDIC Mortality and Morbidity Review Committee. Silent MIs were identified based on serial changes in Minnesota codes during DCCT/EDIC as reported previously.[8] Retinopathy was defined as any proliferative diabetic retinopathy or worse. Nephropathy included sustained microalbuminuria, defined as urinary AER ≥30 mg/24 hours at any 2 consecutive visits, macroalbuminuria, defined as AER≥300 mg/24 hours at any visit, or end-stage renal disease (ESRD). Neuropathy included cardiac autonomic neuropathy and confirmed clinical neuropathy.

Of 1,301 active participants, 1,028 underwent CMR examination according to a standard protocol at 27 centers as previously described[9] (Figure 1). Briefly, left ventricle (LV) parameters were determined from short-axis steady-state free-precession cine images with temporal resolution 30 to 50 ms. Ascending aortic (AA) distensibility was calculated as (maximum area-minimum area)/[(minimum area) × Δ P], where Δ P is the pulse pressure (the difference between mean systolic and diastolic blood pressure in the scanner).[10] The AA maximum and minimum areas were obtained from electrocardiogram gated phase-contrast cine images. Reread of 100 CMR scans revealed an intraclass correlation range from 0.917 to 0.978.

A subset of 200 participants had CMR acquisitions that were technically sufficient to allow T1 mapping as a measure of myocardial tissue composition (Figure 1).[11] Myocardial T1 values were derived from a single mid-ventricular slice location using true fast imaging with steady-state precession (FISP) Look-Locker sequence on Siemens 1.5-T scanners after 0.15 to 0.2 mmol/kg gadopentetate dimeglumine administration in participants who had an estimated glomerular filtration rate value <60 ml/min/1.73 m^2 at any time during EDIC. As this method depends on acquisition and patient parameters such as gadolinium dose, differing glomerular filtration rates, and patient-specific delay times, therefore, comparison of T1 times between different patients is challenging. A pixel by pixel fit to a 3-parameter model[12] was performed to account for variations between patients and to allow for comparison of T1 data, and only pixels where the chi-square test for goodness of fit[13] was significant with a level of significance $\alpha = 0.05$ were included in the final average T1 value. The reported myocardial T1 values were normalized to a standard dose of 0.2-mmol/kg gadolinium chelate after a

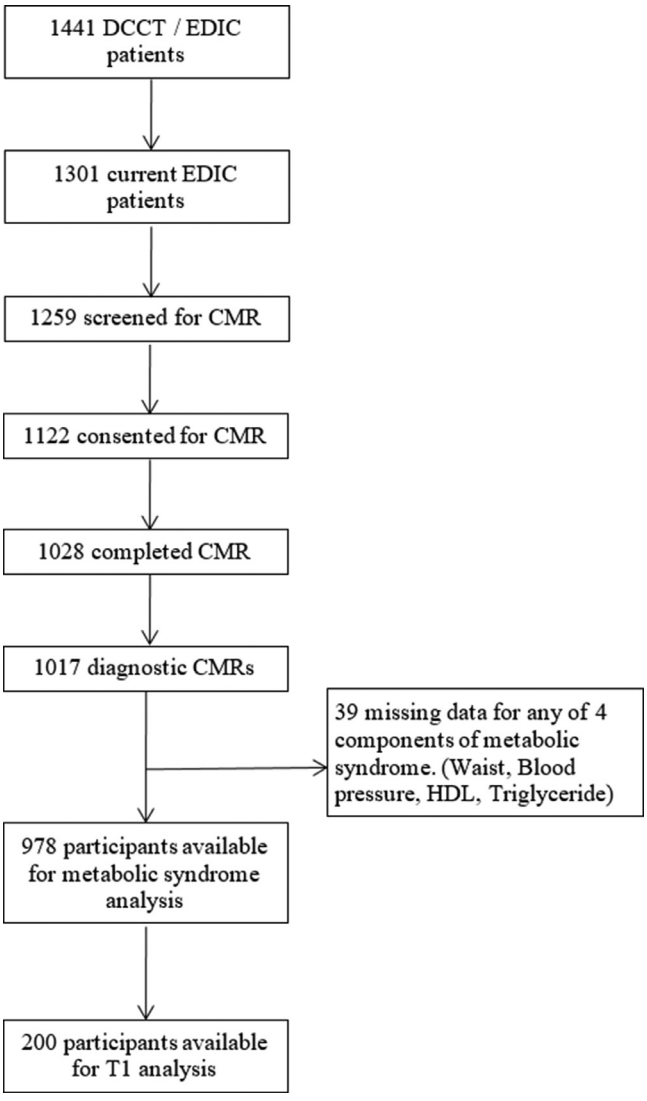

Figure 1. Flow chart of DCCT/EDIC patients who completed CMR and had metabolic syndrome data. CMR= cardiac magnetic resonance; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; HDL = high-density lipoprotein.

contrast delay time of 15 minutes and an estimated glomerular filtration rate of ≅ 90 ml/min/1.73 m^2.[12]

Clinical characteristics and diabetic complications of DCCT/EDIC participants were presented as mean ± SD or percentage by participants with and without MetS. MetS groups were compared using Wilcoxon rank sum tests for quantitative variables and chi-square tests or the Fisher exact test for categorical variables. The distribution of MetS components by gender, treatment group (intensive vs conventional), age (≤40, 40 to 50, >50 years), weighted HbA1c levels (≤7.5, 7.5 to 9.0, >9.0%) was compared using Cochran-Armitage trend test.

The association of MetS and its individual components with CMR indexes was assessed using multiple linear regression models. Basic models were adjusted for age, gender, study cohort, height, and machine type except for myocardial T1 value, in which machine was not included (all in Siemens scanners). Multivariable models for CMR parameters were also adjusted for current smoker, mean HbA1c, and history of nephropathy /ESRD; the model for myocardial T1 time was also adjusted for mean HbA1c and LV mass indexed to height.[1,6]

The distribution of AA distensibility was skewed. A natural log transformation was therefore used to obtain homoscedastic and approximately normally distributed residuals.

Additional separate models, which included 4 components of the MetS classification with each of the 9 cardiac parameters and MetS definition as a binary covariate (presence or absence of classification of MetS), were used for comparison.

All analyses were performed using Statistical Analysis System (SAS) software (version 9.3; SAS Institute, Cary, NC). P values <0.05 were considered statistically significant.

Results

Of 1,017 participants who had diagnostic cine CMR, 978 had available MetS data and were included in the analysis. Of 978 subjects, 846 had ascending aorta distensibility measurements, and 200 had T1 mapping CMR. At the time of CMR, the overall prevalence of MetS was 34.1%, without a significant difference by gender (32.8% for women vs 35.1% for men; p = 0.4).

Patients with MetS were slightly older (by+1 y; p = 0.02), more likely to have ever smoked (by+7.1%; p = 0.02), and had higher HbA1c levels (by+0.3%; p <0.0001) than those without MetS. Consistent with the definition of MetS, the body mass index, triglycerides, systolic and diastolic blood pressures were higher, and HDL cholesterol was lower in patients with MetS (p <0.0001 for all). Diabetic complications were more common in patients with MetS than those without including the cumulative incidence of all cardiovascular disease events (9.6% vs 4.8%; p = 0.004), retinopathy (27% vs 17.5%; p = 0.0005), nephropathy (macroalbuminuria and ESR: 15.9% vs 6.5%; p <0.0001); and the prevalence of autonomic neuropathy 39.6% vs 26.9%; p <0.0001) (Table 1).

Table 1
Clinical characteristics and diabetic complications by metabolic syndrome at the time of cardiac magnetic resonance imaging, 2007−2009, EDIC years 14 to 16

Variable	Metabolic Syndrome		p Value*
	Yes	No	
	n = 333	n = 645	
Clinical characteristics			
Female	45.4%	47.9%	0.4469
Intensive	51.7%	49.5%	0.5155
Primary cohort	47.8%	50.7%	0.3819
Attained age(years)	50 ± 7	49 ± 7	0.0188
Attained duration of IDDM(years)	27.7 ± 4.8	27.5 ± 4.9	0.5243
Smoking during DCCT/EDIC (ever)	34.5%	27.4%	0.0216
Body Mass Index(kg/m^2)	31.8 ± 4.8	26.2 ± 3.4	<0.0001
Mean Systolic blood pressure(mm Hg)†	122 ± 8	116 ± 8	<0.0001
Mean Diastolic blood pressure(mm Hg)†	76 ± 5	73 ± 5	<0.0001
Hypertensive	74.5%	37.7%	<0.0001
Anti-Hypertensive medication	66.7%	28.2%	<0.0001
Mean hemoglobin A1c(%)†	8.2 ± 1.0	7.9 ± 0.9	<0.0001
Mean HDL cholesterol(mg/100 ml)†	50 ± 12	57 ± 12	<0.0001
Mean LDL cholesterol (mg/100 ml)†	115 ± 20	107 ± 20	<0.0001
Mean Triglyceride(mg/100 ml)†	104 ± 49	73 ± 29	<0.0001
Hypercholesterolemia	77.8%	56.7%	<0.0001
Lipid-lowering medication	72.1%	50.1%	<0.0001
AER≥30 mg/24 h or ESRD(sustained)	33.9%	23.0%	0.0002
AER≥300 mg/24 h or ESRD(ever)	15.9%	6.5%	<0.0001
Heart Rate(beats per minute)	73 ± 12	67 ± 11	<0.0001
Diabetic complications ‡	n (%)	n (%)	
Cardiovascular disease §			
Nonfatal Acute MI (clinical or silent)	19(5.7)	14(2.2)	0.0037
Retinopathy			
PDR or worse	90(27.0)	113(17.5)	0.0005
Nephropathy			
Macroalbuminuria / ESRD ¶	53(15.9)	42(6.5)	<0.0001
Sustained microalbuminuria / ESRD **	113(33.9)	148(23.0)	0.0002
Neuropathy ††			
Autonomic neuropathy ‡‡	128(39.6)	166(26.9)	<0.0001
Peripheral neuropathy§§	113(36.0)	156(25.5)	0.0009

* p value, comparison between patients with metabolic syndrome and nonmetabolic syndrome, is based on chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables except for cardiovascular disease.

† Mean was obtained from DCCT baseline through EDIC before CMR.

‡ The cumulative incidence of retinopathy, nephropathy, and CVD since DCCT entry to the CMR examination, and the prevalence of neuropathy shortly before the CMR examination.

§ CVD includes nonfatal myocardial infarction, silent myocardial infarction, revascularization, confirmed angina, nonfatal cerebrovascular event, CHF (congestive heart failure) (from EDIC year 13), and cardiovascular death. P values obtained from the log-rank test of the event times.

¶ AER ≥300 mg/24 hour or ESRD.

** AER ≥30 mg/24 hour consecutive 2 visits or ESRD.

†† Neuropathy data were obtained once at EDIC year 13/14.

‡‡ N is 323 and 618 for each category of participants, respectively.

§§ N is 314 and 611 for each category of participants, respectively.

AER = albumin excretion rate; CMR = cardiac magnetic resonance; CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; ESRD = end-stage renal disease; HDL = high-density lipoprotein; IDDM = insulin-dependent diabetes mellitus; LDL = low-density lipoprotein; MI = myocardial infarction.

Table 2
Least square means (LSM) of cardiac parameters by gender and metabolic syndrome

Parameter	Females			Males		
	Metabolic Synd. LSM(95% CI)	No Metabolic Synd. LSM(95% CI)	p Value	Metabolic Synd. LSM(95% CI)	No Metabolic Synd. LSM(95% CI)	p Value
n	151	309		182	336	
End-diastolic volume(ml)	133(129−137)	128(125−131)	0.0293	146(142−50)	141(138−144)	0.0264
End systolic volume(ml)	50(47−52)	48(46−50)	0.3715	59(56−61)	56(54−58)	0.0247
Stroke volume(ml)	84(81−86)	80(78−82)	0.0125	87(85−90)	85(83−87)	0.1995
Cardiac output(L/min)	6.1(5.9−6.3)	5.6(5.4−5.7)	<0.0001	6.4(6.2−6.6)	5.8(5.7−6.0)	<0.0001
LV mass(g)	132(128−136)	120(117−123)	<0.0001	162(158− 66)	147(144−149)	<0.0001
Ejection fraction(%)	63(62−64)	63(62−64)	0.3277	60(59−61)	60(60−62)	0.3835
LVM/EDV(g/ml)	1.01(0.98−1.03)	0.94(0.92−0.96)	<0.0001	1.13(1.10−1.15)	1.05(1.03−1.08)	<0.0001
N	129	262		152	303	
Log AD(mm Hg^{-1})	0.55(0.46−0.63)	0.66(0.60−0.73)	0.0179	0.61(0.53−0.69)	0.64(0.58−0.70)	0.5483
N	24	58		41	77	
Myocardial T1 time(ms)	412(391−433)	453(439−467)	0.0014	46 (447−479)	485(473−497)	0.0296

Models adjusted for machine type, age, study cohort, height, metabolic syndrome, and interaction of (gender metabolic syndrome).

AD = aortic distensibility; CI = confidence interval; LV = left ventricle; LVM/EDV = left ventricular mass to end-diastolic volume ratio; Synd. = syndrome.

In the individual MetS components, other than DM, hypertension had the highest prevalence, followed by the large waist circumference. Including DM, 43% of participants had 2 components of MetS, 25% had 3 components, 7.3% of patients had 4 components, and only 0.2% had all 5 components. In patients with MetS, the most frequent combination of different components was DM, hypertension, and elevated waist circumference (17%) (Supplementary Table 1).

The number of subjects with MetS were significantly higher with older age (≤40, 40 to 50, >50 y) and HbA1c levels (≤7.5, 7.5 to 9.0, >9.0%) (p for trend = 0.003 and <0.0001, respectively) (Supplementary Table 2). Of the individual components, hypertension and abdominal obesity became more common with increasing age, and only hypertension was more common with increasing HbA1c levels.

Left ventricular (LV) mass, end-diastolic volume, and cardiac output was higher in patients with MetS than those without MetS in both genders in minimally adjusted models (e.g., LV mass: 132 vs 120 g in women, 162 vs 147 g in men, respectively) (Table 2). Aortic distensibility was significantly lower, and stroke volume was higher in patients with MetS in females. There was no significant difference in ejection fraction between patients with and without MetS (Table 2). The differences between those with versus without MetS were similar in males and females.

In multivariable models that were additionally adjusted for gender, smoking, mean HbA1c levels, history of macroalbuminuria, and ESRD, LV mass was greater by 12.3 g, end-diastolic volume was higher by 5.4 ml, and mass to end-diastolic volume ratio was higher by 5% in patients with MetS versus those without MetS (p <0.001 for all). After the adjustments, stroke volume and cardiac output also remained positively associated with MetS (Table 3). The association between AA distensibility and MetS was nonsignificant after these additional adjustments.

In individual components of MetS, elevated waist circumference showed the strongest associations with LV indexes of LV mass, end-diastolic volume, stroke volume,

Table 3
Individual multivariate models: metabolic syndrome on cardiac parameters by CMR

Left Ventricular Parameters	Metabolic Syndrome (Yes vs No)			
	Semi-Partial R^2 (%)	Mean Difference	SE	p Value
End-diastolic mass(g)	2.94	12.30	1.52	<0.0001
End-diastolic volume(ml)	0.67	5.38	1.59	0.0008
End-systolic volume(ml)	0.41	2.36	0.99	0.0174
Stroke volume(ml)	0.58	3.02	1.03	0.0036
Cardiac output(L/min)	3.00	0.51	0.08	<0.0001
Mass: volume ratio	1.91	0.05	0.01	<0.0001
Ejection fraction(%)	0.0001	0.01	0.43	0.9733
Log (AD)(mm $Hg^{-1} \times 10^{-3}$)	0.08	−0.03	0.03	0.3277
Myocardial T1 time(ms)		−29.42	7.92	0.0003

Models, except myocardial T1 time, were adjusted for age, gender, study cohort, height, machine type, current smoker, mean HbA1c during DCCT/EDIC, history of nephropathy, or ESRD. The model for myocardial T1 time was adjusted for age, gender, study cohort, mean HbA1c during DCCT/EDIC, and LV mass indexed to height.[1,6] The adjusted mean difference equals the coefficient estimate in the model.

AD = aortic distensibility; CMR = cardiac magnetic resonance; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; ESRD = end-stage renal disease; HbA1c = glycated hemoglobin; SE = standard error.

and cardiac output (Table 4). Elevated blood pressure had the strongest individual associations with mass:volume ratio and AA distensibility.

The subset of subjects with T1 mapping CMR was less hypertensive (by −10.9%; p = 0.006), had lower mean HbA1c levels (by −0.2%; p = 0.004), lower mean total cholesterol levels (by −3 mg/100 ml; p = 0.044), lipid-lowering medication (by −8.3%; p = 0.04), and history of nephropathy and ESRD (by −7.8%; p = 0.0009) than those without T1 mapping (not shown). There was no significant difference in the prevalence of MetS between patients with and without T1 mapping (32.5% vs 34.5%; p = 0.6)

The mean postgadolinium myocardial T1 time (normalized to 15-minute delay) was lower in women than men (440 ± 59 ms vs 478 ±49 ms, respectively; p <0.0001) and in patients with MetS than those without in both genders (412 vs 453 ms in women, p = 0.001; 463 vs 485 in men, p = 0.03, respectively) (Table 2). After adjustment for gender, mean HbA1c levels, and LV mass index, myocardial T1 time was lower by 29 ms in patients with MetS than in those without (p <0.001)(Table 3). In individual components of MetS, waist circumference was the only component that showed significant association with T1 time. This association remained significant after additional adjustments for mean HbA1c levels and LV mass index (−31 ms, p <0.001) (Table 5).

Additional adjusted models (Table 6) (adjusted for age, gender, study cohort, height, and machine type), including the 4 components of the MetS, each as a separate binary covariate, provided a stronger association (larger R^2) with each of the 9 CMR parameters than like models with only a binary covariate to represent the presence or absence of MetS. Furthermore, the adjusted R^2 allowing for 4 versus 1 covariates were likewise greater in the 4 component models for 7 of 8 factors. Thus, the overall classification of MetS did not provide any statistical advantage over the 4 individual components together.

Discussion

Our main conclusions are: (1) MetS is a common finding in patients with T1DM of long-duration (prevalence, 34%), especially at an older age, in patients with poor glycemic control and with microvascular complications of DM. (2) Patients with MetS had adversely altered LV geometry characterized by a higher LV mass, volumes, cardiac output, and mass:volume ratio (index of concentric remodeling) than patients without MetS. Obesity was a strong contributor to these associations. (3) Postgadolinium myocardial T1 time was lower in patients with MetS than in those without. Obesity was the only individual component of MetS associated with altered T1 time. Finally, clustering risk factors under the definition of MetS showed no additional value beyond its individual component risk factors in determining their relations to the myocardial structure.

The prevalence of MetS has been shown to be 20% to 34.7% in the general population[14,15] and 61% to 75% in patients with type 2 DM.[16–18] The definition of MetS is controversial in T1DM because the glucose component is designed to represent insulin resistance. In previous studies, the prevalence of MetS in T1DM was 8% to 45%[19–21] and

Table 4
Basic Models with the effects of 4 individual components of metabolic syndrome (yes/no) on cardiac parameters

Parameter	EDV				ESV				SV				Cardiac Output			
	Semi-Partial R^2 (%)	Estimate	SE	p Value	Semi-Partial R^2 (%)	Estimate	SE	p Value	Semi-Partial R^2 (%)	Estimate	SE	p Value	Semi-Partial R^2 (%)	Estimate	SE	p Value
Elevated blood pressure*	0.12	2.34	1.62	0.1487	0.002	0.15	1.01	0.8798	0.30	2.19	1.05	0.0373	2.19	0.44	0.08	<0.0001
Elevated waist†	0.92	6.48	1.64	<0.0001	0.39	2.38	1.02	0.0198	1.01	4.10	1.06	0.0001	2.77	0.50	0.08	<0.0001
Low HDL‡	0.01	−1.01	2.19	0.6449	0.002	0.21	1.36	0.8759	0.05	−1.23	1.42	0.3877	0.08	−0.12	0.11	0.2959
Elevated triglyceride¶	0.15	−4.30	2.71	0.1130	0.07	−1.70	1.68	0.3125	0.15	−2.60	1.76	0.1402	0.06	0.13	0.14	0.3588
Parameter	LV mass				EF				LV mass/EDV				log(AD)			
	Semi-Partial R^2 (%)	Estimate	SE	p value	Semi-Partial R^2 (%)	Estimate	SE	p value	Semi-Partial R^2 (%)	Estimate	SE	p value	Semi-Partial R^2 (%)	Estimate	SE	p value
Elevated blood pressure*	1.29	8.25	1.59	<0.0001	0.25	0.69	0.44	0.1114	1.71	0.05	0.01	<0.0001	1.69	−0.14	0.03	<0.0001
Elevated waist†	1.88	10.11	1.61	<0.0001	0.04	0.29	0.44	0.5076	0.50	0.03	0.01	0.0194	7.6×10^{-7}	−0.0001	0.03	0.9977
Low HDL‡	0.19	4.32	2.14	0.0440	0.07	−0.51	0.59	0.3826	0.51	0.04	0.02	0.0175	0.02	−0.02	0.05	0.6782
Elevated triglyceride¶	0.04	2.57	2.66	0.3343	0.01	−0.27	0.73	0.7082	0.59	0.05	0.02	0.0108	0.01	−0.02	0.06	0.6910

Models were also adjusted for machine types, age, gender, study cohort, and height.

* Systolic blood pressure≥130 mm Hg or diastolic blood pressure≥85 mm Hg or any antihypertensive including ACE/ARB for all reasons.

† Female waist ≥88 cm or male waist ≥102 cm.

‡ Female HDL<50 mg/100 ml or male HDL<40 mg/100 ml.

¶ Triglyceride≥150 mg/100 ml.

ACE = Angiotensin-converting enzyme inhibitors; AD = Aortic Distensibility; ARB = Angiotensin receptor blockers; EDV = End-diastolic volume; EF = ejection fraction; ESV = End-systolic volume; HDL = High-density lipoprotein; LV = Left ventricle; SE = Standard error.

Table 5
Multivariate Model of the joint effects of individual components of metabolic syndrome simultaneously on myocardial T1 time

	Normalized T1 (Millisecond) (n=204)		
	Variable R^2	Estimate ± SE	p Value
Age (per 10 years)	0.32	5 ± 6	0.3812
Gender (Female vs Male)	5.99	−33 ± 9	0.0002
Hypertension* (Yes vs No)	0.51	−9 ± 8	0.2682
Elevated Waist Circumference† (Yes vs No)	5.74	−31 ± 8	0.0003
Low HDL‡ (Yes vs No)	0.26	9 ± 11	0.4335
Elevated Triglyceride¶ (Yes vs No)	1.06	−21 ± 131	0.1116
Mean HbA1c (per 1%)	0.77	−6 ± 5	0.1742

Model is additionally adjusted for study cohort and LV mass index.
* Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or any antihypertensives.
† Female waist ≥88 cm or male waist ≥102 cm.
‡ Female HDL <50 mg/100 ml or male HDL<40 mg/100 ml.
¶ Triglyceride ≥150 mg/100 ml.
HDL = high-density lipoprotein; LV = left ventricle; SE = standard error.

was 34% in the sixteenth follow-up year of the DCCT/EDIC study. As shown in the Pittsburgh Epidemiology of Diabetes Complications Study, the prevalence of MetS varies from 8% to 21% by various definitions of MetS. None of the MetS definitions was primarily intended to define patients at higher risk of CVD in T1DM, although the American Heart Association/National Cholesterol Education Program criteria are accepted as more appropriate in T1DM[21] and are used in the present study. Despite the large variation in the prevalence of MetS in previous studies, there is a general consensus that hypertension and abdominal obesity are the more frequent components of MetS in the general population and in both types of DM.[15,16,19,21]

The pathophysiologic changes in LV mass in response to MetS have been assessed using echocardiography in different study samples.[15,22,23] These studies have shown higher LV mass and relative wall thickness in patients with MetS than those without MetS. Our results are consistent with these studies, and in addition, we have shown that LV volumes were higher in patients with MetS. The increase in LV mass was greater than LV end-diastolic volume resulting in an elevated mass:volume ratio (an index of concentric remodeling). LV hypertrophy and concentric remodeling have been shown to be associated with incident heart failure, and coronary heart disease.[24] Intensive DM therapy of T1DM has been reported to reduce DM complications; however, it can be associated with excess weight gain and central obesity. In DCCT, excess weight gain was associated with greater intima-media thickness of carotid arteries and greater coronary artery calcium scores.[25] These findings and concentric remodeling shown in the present study may contribute to increased risk of CVD in MetS.

The T1 mapping can detect changes in myocardial tissue composition. Most investigations have focused on the inverse relation between lower postgadolinium T1 time and greater interstitial myocardial fibrosis.[11,26,27] However, increased fat deposition has also been noted in patients with DM,[28,29] resulting in an additional potential contribution to lower T1 times. Notably, in the present study, waist circumference was the only component of MetS to be associated with lower myocardial T1 times. Of the multiple MetS components, elevated waist circumference was also prominent in its association with greater LV mass, end-diastolic volume, and stroke volume. Together, these results contribute to a hypothesis of deranged fatty acid metabolism in DM with the accumulation of triglycerides and adverse effects on myocardial function.[29] Cellular damage eventually results in interstitial myocardial fibrosis, resulting in diastolic dysfunction and concentric remodeling.[30]

There are several limitations of this study. First, subjects in the DCCT/EDIC are relatively healthy. Thus, the prevalence of MetS reported in the present study may be different than in a more general patient population with T1DM and may limit the generalizability of the results. The myocardial T1 mapping CMR was only available in a subset of the whole study population because of technical limitations at

Table 6
R^2/Adjusted R^2 values from adjusted models for the effects of the Metabolic Syndrome definition (yes/no) and its 4 individual components altogether on cardiac parameters

	A (Reduced)	B (Met S)	C (4 Components-Binary)	D (4 Components-Continuous)
	R^2	R^2 / adjusted R^2	R^2 / adjusted R^2	R^2 / adjusted R^2
EDV	41.71	42.29/41.87	42.92/42.33	44.68/44.10
ESV	29.64	30.01/29.50	30.09/29.37	30.77/30.06
SV	32.82	33.30/32.82	34.35/33.67	36.29/5.63
CO	20.29	24.01/23.47	26.41/25.64	28.64/27.91
LV mass	49.51	53.53/53.19	54.08/53.61	57.18/56.73
EF	6.09	6.09/5.41	6.48/5.51	6.27/5.30
LV mass/EDV	7.57	11.15/10.51	12.30/11.39	16.23/15.37
Log AD	22.50	22.88/22.24	24.32/23.40	29.49/28.65
Myocardial T1 time	12.16	17.06/15.36	19.88/16.96	21.55/18.69

Adjusted for machine, age, gender, study cohort, and height.
A. Add MetS (yes/no).
B. Add blood pressure ≥130/85 or antihypertensions, waist ≥88 (female) or 102 (male), HDL <50 (female) or 40 (male), and triglycerides ≥150.
C. Add systolic blood pressure+waist+HDL+ triglycerides as continuous.
AD = aortic distensibility; CO = cardiac output (L/min); EDV = end-diastolic volume; EF = ejection fraction (%); ESV = end-diastolic volume (ml); HDL = high-density lipoprotein; LV = left ventricle; MetS = metabolic syndrome; SV = stroke volume (ml).

the time of the study. The postgadolinium T1 mapping CMR using true FISP Look-Locker sequence was valid at the time of data collection in this study. Native myocardial T1 values are not available in the DCCT/EDIC study.

In conclusion, MetS was present in 34.1% of subjects in a large cohort of long-surviving patients with T1DM. MetS was associated with concentric LV remodeling without change in ejection fraction for both genders. Adverse alteration in myocardial tissue composition may partly explain the underlying mechanism of adverse LV remodeling in MetS. The presence of MetS did not add to the risk of abnormal myocardial structure beyond that of its individual components in this population with T1DM.

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A complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Materials.

A list of the participating radiologists and technologists is shown in the online supplemental material available at Circulation 2011:124:1737-1746.

Industry Contributions

Industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, California), Animas (Westchester, Pennsylvania), Bayer Diabetes Care (North America Headquarters, Tarrytown, New York), Becton Dickinson (Franklin Lakes, New Jersey), CanAm (Atlanta, Georgia), Eli Lilly (Indianapolis, Indiana), Lifescan (Milpitas, California), Medtronic Diabetes Minneapolis, Minnesota), Omron (Shelton Connecticut), OmniPod® Insulin Management System (Bedford, Massachusetts), Roche Diabetes Care (Indianapolis, Indiana), and Sanofi-Aventis (Bridgewater, New Jersey).

Disclosures

Dr. Nazarian reports grants and personal fees from Biosense Webster Software, personal fees from Circle Software, grants from ADAS Software, grants from ImriCor, outside the submitted work; Dr. Bluemke reports consultant fees from Bayer AG, received ≥5 years after conduct of the study; Dr. Lachin reports receiving grants from National Institute of Diabetes, Digestive and Kidney Diseases, during the conduct of the study. The other authors have no conflicts of interest to disclosedeclare.

Data Availability

Data collected for the DCCT/EDIC study through June 30, 2017, are available to the public through the NIDDK Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017−June 2022) will be available within 2 years after the end of the funding cycle.

Trial Registration: clinicaltrials.gov NCT00360815 and NCT00360893.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.036.

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