Metabolic Syndrome Is Associated With Impaired Diastolic Function Independently of MRI-Derived Myocardial Extracellular Volume: The MESA Study

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The relationship of metabolic syndrome (MetS) and insulin resistance (one of its key pathophysiological mediators) with diastolic dysfunction and myocardial fibrosis is not well understood. This study aimed to evaluate the association of MetS with diastolic function and myocardial extracellular matrix (ECM) using cardiac MRI (CMRI) in a large community-based population. This cross-sectional analysis included 1,582 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) with left ventricular ejection fraction ≥50% and no history of cardiac events. Diastolic function was assessed using tagged CMRI parameters including end-diastolic strain rate (EDSR) and strain relaxation index (SRI). ECM was evaluated using extracellular volume (ECV) quantification. Participants' mean age was 67.4 ± 8.6 years, and 48.1% were males. MetS was present in 533 individuals (33.7%), and type 2 diabetes in 250 (15.8%). In the multivariable analyses, MetS (irrespective of the presence of type 2 diabetes) and higher insulin resistance were associated with impaired diastolic function (higher SRI and lower EDSR), independent of ECV. In conclusion, MetS, irrespective of the presence of type 2 diabetes, was independently associated with impaired diastole. These functional myocardial changes seem to result from intrinsic cardiomyocyte alterations, irrespective of the myocardial interstitium (including fibrosis).

Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors that reached epidemic proportions during the last two decades. Approximately 20–40% of the adult populations of U.S. and Europe have MetS (1).

Insulin resistance and inflammation play a key role in the pathophysiology of MetS, contributing to a prothrombotic and oxidative state that increases the risk of cardiovascular disease due to microvascular and macrovascular damage (2). This metabolic dysfunctional status is associated with the deterioration of cardiac structure and function, also known as "insulin-resistant cardiomyopathy" (3). Furthermore, myocardial fibrosis plays a pivotal role in cardiac remodeling in hypertensive and advanced diabetic heart disease (4), being associated with diastolic dysfunction (5). However, the relationships of MetS and insulin resistance with left ventricular (LV) myocardial fibrosis and diastolic dysfunction have not been well characterized in population studies (5).

New cardiac MRI (CMRI) techniques allow an accurate evaluation of both cardiac structure and function in populations (6,7). First, extracellular volume (ECV) quantification offers noninvasive assessment of changes in the myocardial extracellular matrix (ECM), including fibrosis and steatosis (8). Indeed, ECV quantification is derived from data obtained from magnetic resonance parameter T1 (the longitudinal relaxation time) without a contrast agent and postcontrast, both from myocardium and blood, as well as from hematocrit data. ECV is a marker of myocardial tissue remodeling and a physiologically intuitive unit of measurement. Recently, "synthetic" ECV calculation was described and shown to be associated with cardiovascular

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outcomes, overcoming the need for blood sampling in order to have the hematocrit data (9). Moreover, tagged CMRI measurements of diastolic function, such as end-diastolic strain rate (EDSR) and strain relaxation index (SRI), were recently described as predictors of heart failure in a population free of cardiovascular disease (7).

This study aimed to: *1*) evaluate the relationship between MetS and insulin resistance with LV diastolic function in a large community-based cohort using CMRI and *2*) assess whether this association is dependent on myocardial ECM.

RESEARCH DESIGN AND METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, population-based, epidemiological study started in 2000 and aiming to investigate the prevalence and progression of subclinical cardiovascular disease in a multiethnic cohort (Caucasian, African American, Hispanic, Chinese American) of 6,814 individuals. The study protocol was approved by the institutional review boards of participating institutions. The characteristics of subjects enrolled in the MESA have been described previously (10).

From all individuals who underwent evaluation as part of the MESA "Exam 5" (the fifth round of examinations of the MESA study), which happened from 2010 to 2012, participants with prior clinical cardiac events (myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina if followed by revascularization, and cardiac death) (n = 459), LV ejection fraction <50% (n = 133), unknown MetS status (n = 2,024), and positive or unknown late gadolinium enhancement during CMRI (n = 2,660) were excluded from the analysis. The final sample size was composed of 1,582 individuals, with data available on myocardial tagging and synthetic ECV quantification. The characteristics of the participants are described in Table 1.

Table 1—Participants' characteristics

	Total (N = 1,582)
Age, years	67.4 ± 8.6
Male sex, *n* (%)	761 (48.1)
Ethnicity, *n* (%)	
Caucasian	706 (44.6)
Chinese	163 (10.3)
African American	375 (23.7)
Hispanic	338 (21.4)
eGFR (MDRD, mL/min/1.73 m^2)	84.9 ± 18.7
BMI, kg/m^2	28.4 ± 5.2
Waist circumference, cm	98.5 ± 13.4
Body weight, kg	78.4 ± 16.5
Height, cm	166.1 ± 9.7
Heart rate, bpm	64.2 ± 10.0
Cigarette smoking, *n* (%)	
Never	693 (44.0)
Former	770 (48.8)
Current	113 (7.2)
SBP, mmHg	121.9 ± 19.1
DBP, mmHg	68.5 ± 9.6
HDL-C, mg/dL	55.1 ± 16.3
Triglycerides, mg/dL	110.3 ± 61.8
Total cholesterol, mg/dL	184.5 ± 36.2
Fasting glucose, mg/dL	100.1 ± 24.3
$\log_2$(HOMA-IR)	3.4 ± 1.0
MetS, *n* (%)	533 (33.7)
Increased waist circumference, *n* (% of MetS)	472 (88.6)
Triglycerides ≥150 mg/dL or receiving fibrates, *n* (% of MetS)	233 (43.7)
Decreased HDL-C or taking niacin, *n* (% of MetS)	290 (54.4)
SBP ≥130 or DBP ≥85 mmHg, *n* (% of MetS)	464 (87.1)
IFG or type 2 diabetes, *n* (% of MetS)	390 (73.2)
Presence of MetS but no type 2 diabetes, *n* (%)	350 (22.1)
Type 2 diabetes, *n* (%)	250 (15.8)
LV ejection fraction, %	62.5 ± 6.1
LVEDVi, mL/m^2	65.0 ± 12.7
LVMi, g/m^2	65.4 ± 12.1
LV mass-to-volume ratio, mL/g	1.0 ± 0.2
Antihypertensive medication, *n* (%)	758 (47.9)

Values are reported as the mean ± SD, unless otherwise indicated. DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEDVi, indexed LV end-diastolic volume; LVMi, indexed LV mass; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure.

Definition of MetS and Insulin Resistance

MetS was defined according to the 2005 definition of the American Heart Association/National Cholesterol Education Panel (i.e., if three or more of the following were present): *1*) abdominal obesity based on waist circumference ≥88 cm (35 inches) for women and ≥102 cm (40 inches) for men (≥80 cm and ≥90 cm for Asian American females and males, respectively); *2*) HDL cholesterol (HDL-C) <1.0 mmol/L (40 mg/dL) for men or <1.3 mmol/L (50 mg/dL) for women or receiving treatment to increase HDL-C levels; *3*) fasting triglyceride measurements ≥1.7 mmol/L (150 mg/dL) or receiving treatment to reduce triglyceride levels; *4*) blood pressure of ≥130 mmHg systolic or ≥85 mmHg diastolic, or receiving antihypertensive treatment; or *5*) impaired fasting glucose (IFG) defined as a fasting glucose level of 5.55–6.99 mmol/L (100–125 mg/dL) or type 2 diabetes (fasting plasma glucose of ≥7.0 mmol/L [≥126 mg/dL]) (1).

BMI was calculated as weight divided by the square of height (in kilograms per square meter). Resting blood pressure was measured three times in the seated position using a Dinamap PRO-100 Sphygmomanometer (Critikon; Wipro GE Healthcare, Waukesha, WI). Fasting blood glucose was assessed using Vitros analyzer (Johnson & Johnson Ortho-Clinical Diagnostics, Rochester, NY), and fasting insulin with the Elecsys assay (electrochemiluminesce

immunoassay; Roche Diagnostics, Mannheim, Germany). Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation (11).

Insulin resistance was calculated for patients not taking insulin or hypoglycemic agents (N = 1,069) using the HOMA of insulin resistance (HOMA-IR) (fasting glucose [in milligrams per deciliter] × fasting insulin [in milliunits per liter]/405) (12).

CMRI

Images were acquired using 1.5-T MRI scanners using electrocardiogram-triggered segmented k-space fast spoiled gradient-echo pulse sequences during breath-holds. Torso phase array coils were used for signal reception. CMRI myocardial horizontal and vertical tagging were performed on three LV short-axis slices (base to apex) by nonselective radiofrequency pulses separated by a spatial modulation of magnetization-encoding gradients. Parameters for imaging and analysis methods have been previously described (13). LV volume and mass were indexed according to body surface area.

Additional information on the analyses of ECV using T1 mapping and diastolic function using myocardial tagging is included as Supplementary Data.

Statistical Analysis

Summary statistics were presented as the mean ± SD for continuous variables and as percentages for categorical variables.

Subgroups according to the presence of MetS and type 2 diabetes were defined as follows: 1) absence of both MetS and type 2 diabetes; 2) presence of MetS and the absence of type 2 diabetes; and 3) presence of type 2 diabetes, irrespective of the presence or absence of MetS. To verify a progressive increase in insulin resistance from subgroup 1 toward subgroup 3, a comparison of HOMA-IR (base-2 log transformed) between the subgroups was performed.

A t test and one-way ANOVA (with Bonferroni post hoc analysis) were used to test continuous variables in two or more than two subgroups. A χ^2 test was used for comparisons with categorical variables.

Multivariable linear regression analysis was used to assess the association of MetS and insulin resistance with diastolic function and ECV using the following two models: model 1, adjusting for age, sex, ethnicity, smoking status, and antihypertensive medication; and model 2, adjusting for all variables included in model 1 plus ECV.

All analyzes were performed using Stata version 14.0 (StataCorp, College Station, TX). Statistical significance was defined as $P < 0.05$. All reported P values are two tailed.

RESULTS

Participants' Characteristics

The characteristics of the participants are presented in Table 1. The mean age of the final sample was 67.4 ± 8.6 years, and 48.1% were males. MetS was present in 533 individuals

Table 2—CMRI-derived diastolic variables and ECV according to the presence of MetS and type 2 diabetes

	No MetS	MetS+	P value	MetS−/type 2 diabetes−	MetS+/type 2 diabetes−	Type 2 diabetes+	P value
Diastolic parameters							
EDSR, 1/ms	0.115 ± 0.051	0.110 ± 0.054	0.049	0.116 ± 0.051	0.111 ± 0.057	0.106 ± 0.051	0.020
LV TRR, °/cm per ms	−22.231 ± 8.769	−22.099 ± 9.123	0.792	−22.299 ± 8.801	−22.187 ± 9.349	−21.749 ± 8.584	0.709
SRI, ms/%	2.602 ± 1.731	3.103 ± 2.167	<0.001	2.568 ± 1.695	3.139 ± 2.298	3.048 ± 1.960	<0.001
ECV, %	27.024 ± 2.718	26.599 ± 2.749	0.013	27.046 ± 2.731	26.506 ± 2.901	26.763 ± 2.425	0.020

Values are reported as the mean ± SD. An independent t test was used to compare diastolic variables and ECV according to the presence or absence of MetS. One-way ANOVA (with Bonferroni post hoc analysis) was used to compare the three subgroups according to the presence or absence of MetS and type 2 diabetes.

(33.7%), and type 2 diabetes was present in 250 (15.8%). Glycated hemoglobin levels in patients with IFG and type 2 diabetes were 5.9 ± 0.4 and 7.1 ± 1.4, respectively. The mean LV ejection fraction, LV end-diastolic volume index, and LV mass index were 62.5 ± 6.1%, 65.0 ± 12.7 mL/m^2, and 65.4 ± 12.1 g/m^2.

Influence of MetS and Type 2 Diabetes on Diastolic Function

Table 2 presents a comparison of the diastolic variables (EDSR, SRI, and torsion recoil rate [TRR]) and ECV according to MetS and type 2 diabetes status. Individuals with MetS and type 2 diabetes showed a lower EDSR and higher SRI (i.e., worse diastolic function). In the multivariable analyses, MetS was an independent predictor of higher SRI (adjusted β = 0.503; SE = 0.114; $P < 0.001$) and lower EDSR (adjusted β = −0.008; SE = 0.003; $P = 0.012$) irrespective of age, sex, ethnicity, smoking status, and antihypertensive medication (Table 3, model 1). In addition, the presence of MetS (with or without type 2 diabetes) was associated with deteriorated diastolic function (higher SRI and lower EDSR) after adjusting for the previous variables and also ECV (Table 3, model 2), a surrogate for myocardial interstitium changes, including fibrosis. There was no association of MetS and type 2 diabetes with TRR.

Influence of Insulin Resistance on Diastolic Function

When considering the association of insulin resistance with diastolic function variables, the multivariable linear regression analyzes performed showed that $\log_2$(HOMA-IR) was an independent predictor of worse diastolic function, as reflected by lower EDSR (adjusted β = −0.005; SE = 0.002; $P = 0.002$) and higher SRI (adjusted β = 0.254; SE = 0.059; $P < 0.001$), irrespective of age, sex, ethnicity, smoking status and antihypertensive medication. Furthermore, increased insulin resistance was associated with a deteriorated diastolic function even after adjustment for ECV (model 2). There was no association of $\log_2$(HOMA-IR) with TRR (adjusted β = 0.069; SE = 0.198; $P = 0.726$).

DISCUSSION

In the current study using a large community-based cohort, adults with MetS without type 2 diabetes, as well as adults with type 2 diabetes, had higher SRI and lower EDSR than individuals without MetS, meaning impaired diastolic function. MetS and type 2 diabetes were not associated with increased myocardial ECM, as assessed by ECV quantification using CMRI. To our knowledge, this is the first study to simultaneously assess myocardial extracellular space (ECV by CMRI) and diastolic dysfunction (EDSR, TRR, and SRI) in relation to presence or absence of MetS and type 2 diabetes.

MetS is reaching epidemic proportions with ~34% of American adults fulfilling MetS criteria (14). A recently published consensus article (15) emphasized that MetS is a complex pathophysiological state, clinically underrecognized, and associated with serious and extensive comorbidity. In this study, we report the first detailed analysis of

Table 3—Linear regression analyses for the association of MetS and type 2 diabetes with LV diastolic function

	SRI						EDSR						LV TRR					
	Univariate		Model 1		Model 2		Univariate		Model 1		Model 2		Univariate		Model 1		Model 2	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Presence of MetS (vs. no MetS)	0.501 (0.110)	<0.001	0.503 (0.114)	<0.001	0.516 (0.137)	<0.001	−0.006 (0.003)	0.049	−0.008 (0.003)	0.012	−0.008 (0.003)	0.004	0.132 (0.499)	0.792	0.131 (0.509)	0.797	0.287 (0.597)	0.631
Comparison between subgroups																		
1) No MetS/no type 2 diabetes		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref
2) MetS with no type 2 diabetes	0.571 (0.129)	<0.001	0.523 (0.139)	<0.001	0.531 (0.155)	0.001	−0.005 (0.003)	0.128	−0.006 (0.003)	0.097	−0.007 (0.003)	0.021	0.112 (0.586)	0.849	0.114 (0.582)	0.845	0.267 (0.676)	0.693
3) Type 2 diabetes	0.480 (0.146)	0.001	0.461 (0.146)	0.002	0.421 (0.177)	0.018	−0.010 (0.004)	0.008	−0.011 (0.004)	0.005	−0.010 (0.003)	0.004	0.550 (0.662)	0.407	0.140 (0.655)	0.831	0.220 (0.781)	0.778

When comparing subgroups according to the presence of MetS and type 2 diabetes, the group with no MetS or type 2 diabetes (subgroup 1) was the reference group. Variables included model 1: age, sex, ethnicity, smoking status, and antihypertensive medication. Variables included in model 2: all from model 1 plus ECV. Ref, reference value.

CMRI-derived diastolic deformation parameters in a large community-based cohort with a prevalence of MetS of ~35%. Our results add value to previously published literature by unraveling subclinical impairment of cardiac diastolic function in patients with MetS, even without the presence of type 2 diabetes (16). Specifically, patients with MetS showed higher SRI, a recently described CMRI-derived diastolic index that reflects the combined influence of impaired cardiac relaxation and abnormal tissue properties and represents an independent predictor of atrial fibrillation and heart failure (7).

Furthermore, HOMA-IR was an independent predictor of EDSR and SRI, showing that increasing insulin resistance is associated with impaired diastolic function. Insulin resistance is central to the pathophysiology of MetS (15) and the concept of "insulin-resistant" cardiomyopathy is emerging and its pathophysiology includes myocardial metabolic deregulation, oxidative stress, and inflammation (3). Indeed, insulin resistance is associated with post-translational modifications of contractile proteins and calcium overload (17), activation of the sympathetic nervous system (18), and cellular injury (19). For example, titin hypophosphorylation might contribute to higher myocardial stiffness without an extracellular increase in myocardial fibrosis. Interestingly, increased myocyte stiffness rather than increased fibrosis has been proposed as the main contributor to diastolic dysfunction in patients with diabetes who have heart failure and preserved ejection fraction (20). Overall, these mechanisms might also be key mediators and triggers for impaired relaxation, myocardial stiffening, and diastolic dysfunction in patients with MetS (21).

The limitations of this study include its cross-sectional design, which prohibits inference about causality. Higher ECV might also be ascribed to other factors than increased myocardial fibrosis, such as increased myocardial inflammation and neovascularization (22). The reference standard for the evaluation of diffuse fibrosis is endomyocardial biopsy, which was not performed in this cohort. Moreover, T1 times and myocardial tagging–derived variables were acquired at the midventricular level and might not represent overall LV mechanics.

In conclusion, using CMRI ECV quantification and myocardial tagging we showed that adults without diabetes with MetS, as well as patients with diabetes, have impaired diastolic function irrespective of myocardial interstitium. Subclinical deleterious changes in cardiac function might help to better stratify patients with MetS and lead to earlier and more aggressive decisions in the management of these patients.

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