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ORIGINAL RESEARCH

Association of Insulin Resistance and Glycemic Metabolic Abnormalities With LV Structure and Function in Middle Age

The CARDIA Study

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ABSTRACT

OBJECTIVES This study sought to investigate how cumulative exposure to glycemic abnormalities and trajectories of insulin resistance (IR) relate to left ventricular (LV) remodeling and function during young to middle adulthood.

BACKGROUND Cumulative exposure to glycemic abnormalities and trajectories of IR may adversely influence LV remodeling and function over a 25-year period in subjects who were young adults, predisposing individuals to heart failure later in life.

METHODS In the CARDIA (Coronary Artery Risk Development in Young Adults) Year 25 examination, 3,179 participants were identified with information on glucose metabolism; these participants were stratified into 4 subgroups: group 1 normal glucose tolerance (NGT), group 2 impaired glucose tolerance (IGT) or impaired fasting glucose, group 3 late diabetes mellitus (DM) (DM diagnosed at year 15 or later), and group 4 early DM (DM diagnosed at year 0 to year 15). Among the subgroup without DM, 3 trajectory groups of change in the homeostasis model assessment of IR were identified: low IR, moderate IR, and high IR. LV mass, relative wall thickness, LV ejection fraction (LVEF), longitudinal systolic strain (Ell), and early diastolic strain rate (Ell_SRe) at year 25 were assessed by echocardiography. Clinically relevant systolic and diastolic dysfunction were defined as LVEF <50% for systolic dysfunction, and E/e′ ≥13 for diastolic dysfunction.

RESULTS The early DM group had less favorable LV mass (coefficient = 11.04; $p < 0.001$), LVEF (coefficient = −2.72; $p < 0.05$), Ell (coefficient = 1.53; $p < 0.001$), and Ell_SRe (coefficient = −0.09; $p < 0.05$) than did the NGT group. Being in the early DM group and having high hemoglobin A_{1c} were independently associated with greater odds of having systolic dysfunction (odds ratio = 5.44; $p < 0.005$) compared with the NGT group. High IR was associated with worse relative wall thickness (coefficient = 0.019; $p < 0.0001$) and worse Ell, E′, and Ell_SRe, depending on obesity level.

CONCLUSIONS Cumulative exposure to DM or higher IR beginning in early adulthood adversely impacts LV remodeling and function at middle age. (J Am Coll Cardiol Img 2017;10:105–14) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

BMI = body mass index

CVD = cardiovascular disease

DM = diabetes mellitus

Ecc = circumferential peak strain

Ecc_SRe = circumferential peak early diastolic strain rate

Ell = 4-chamber longitudinal peak strain

Ell_SRe = 4-chamber longitudinal peak early diastolic strain rate

HbA_{1c} = hemoglobin A_{1c}

HF = heart failure

HOMA = homeostasis model assessment

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

IR = insulin resistance

LV = left ventricular

LVEF = left ventricular ejection fraction

LVEDV = left ventricular end-diastolic volume

LVMI = left ventricular mass index

NGT = normal glucose tolerance

STE = speckle-tracking echocardiography

WHR = waist-to-hip ratio

Cardiovascular disease (CVD) and left ventricular (LV) structure and function are related to chronic risk exposure (1,2). LV remodeling (high LV mass or high LV wall thickness) has been associated with CVD and LV dysfunction (3,4). We recently reported that obesity was associated with adverse LV remodeling and impaired LV systolic and diastolic function (5,6). In cross-sectional analyses and short-term longitudinal analyses involving older adults, the state of glycemic dysregulation (diabetes mellitus [DM], impaired fasting glucose [IFG], impaired glucose tolerance [IGT]) and insulin resistance (IR), assessed as the relationship of insulin secretion to measured glucose, affect LV structure and function (5,7). Dysglycemia and IR can both occur in lean or obese individuals. There is limited information on how long-term exposure to glycemic abnormality and IR contribute to LV structure and LV function in middle adulthood independent of obesity.

Two-dimensional (2D) speckle-tracking echocardiography (STE)-derived cardiac tissue deformation parameters might be more sensitive and could be early indicators of cardiac dysfunction compared with traditional echocardiographic assessment (8). DM and high IR are both independent predictors of heart failure (HF) (9). Long duration of exposure to DM and high IR among young adults might both convey greater lifetime risks for developing HF. The duration of glycemic abnormality and IR in relation to early markers of myocardial dysfunction, however, have not been studied during the transition from young adulthood to middle age.

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We hypothesized that both a long duration of exposure to glycemic abnormalities (presence of DM or IFG/IGT) and trajectory patterns of greater IR over 25 years would be associated with adverse LV remodeling and worse LV function. We investigated whether the association of glucose control among diabetic people is associated with LV remodeling and dysfunction at midlife and whether IR trajectory patterns are related to LV remodeling and dysfunction independent of obesity.

METHODS

PARTICIPANTS. The CARDIA (Coronary Artery Risk Development in Young Adults) study is a multicenter prospective investigation that enrolled 5,115 African-American and white men and women 18 to 30 years of age from 4 U.S. field centers in 1985 to 1986 (year 0) and followed them prospectively in 7 subsequent examinations (10). The institutional review board at each of the study sites approved the study protocols, and written informed consent was obtained from all participants. We used 2 cohorts, as follows.

Glycemic abnormalities and IR cohorts. Participants were re-examined across 6 examinations, including baseline (year 0) and years 7, 10, 15, 20, and 25. Of the 5,115 who attended the year 0 examination, 1,617 were excluded for not attending the year 25 (2010 to 2011) examination. Further exclusions were for the following reasons: 24 who did not have an echocardiogram, 192 women who were pregnant at the year 0 to 25 examination, and 103 for whom covariate data were missing, which left 3,179 to be categorized into 4 glucose status groups (normal glucose tolerance [NGT], IFG or IGT, DM for >10 years, DM for <10 years). After the exclusion of those with DM and those missing 4 or more homeostasis model assessment of IR (HOMA-IR) measurements, an IR trajectory cohort comprising the remaining 2,707 participants was used for analysis of the separate impact of IR on cardiac function.

COVARIATES. Standardized protocols were used to measure height, weight, body mass index (BMI), heart rate, blood pressure, lipids, glucose, smoking, educational level, physical activity, and waist-to-hip ratio (WHR) (10). Glucose was assayed at baseline with the hexokinase UV method by American Bio-Science Laboratories (Van Nuys, California) and by hexokinase coupled to glucose-6-phosphate dehydrogenase (Merck Millipore, Billerica, Massachusetts) at years 7, 10, 15, 20, and 25. The presence of DM was assessed at each examination based on a combination of medication use for DM (every examination), fasting plasma glucose ≥126 mg/dl (years 0, 7, 10, 15, 20, and 25), 2-h glucose ≥200 mg/dl (years 10, 20, and 25) by oral glucose tolerance test, or hemoglobin A_{1c} (HbA_{1c}) ≥6.5% (years 20 and 25). IGT was defined as

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fasting plasma glucose <126 mg/dl and 140 mg/dl ≤2-h glucose (by oral glucose tolerance test) <200 mg/dl. IFG was defined as 100 mg/dl ≤ fasting plasma glucose <126 mg/dl. Incident cases of DM, IFG, and IGT were computed if the criteria for DM/dysglycemia were ever met over the period from year 0 to year 25 (11). Insulin measurements were determined by radioimmunoassay (Linco Research, St. Charles, Missouri) at baseline and at years 7, 10, 15, and 20, as well as by an Elecsys sandwich immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) at year 25. HbA_{1c} was classified into 2 groups: high and low HbA_{1c} among DM groups, stratified by high (HbA_{1c} >7.0%) and low (HbA_{1c} ≤7.0%), based on the average HbA_{1c} of year 20 and year 25 examinations. As a surrogate index of IR, HOMA-IR was calculated (12).

DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT. Doppler echocardiography and 2D-guided M-mode echocardiography were performed with an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by trained sonographers using standardized protocols across all field centers (13). Experienced sonographers made measurements from digitized images using a standard software off-line image analysis system (Digisonics, Houston, Texas). LV end-diastolic volume (LVEDV), LV end-systolic volume, and LV ejection fraction (LVEF) were measured from the apical 4-chamber view based on the American Society of Echocardiography recommendations (14). LV mass was derived from the Devereux formula and indexed to body surface area (left ventricular mass index [LVMI]) (14). Relative wall thickness was calculated as the ratio (LV posterior wall thickness at end diastole × 2)/LV internal dimension at end diastole (14). Peak velocities from the early phase of the mitral inflow (E) were measured from pulsed Doppler echocardiography recordings of transmitral flow. Using tissue Doppler imaging, early peak diastolic mitral annular velocity (e′) was measured at the septal and lateral mitral annulus (15). The e′ was calculated from the average of the septal and lateral mitral annulus. E/e′ ratio was calculated as an index of LV filling pressures (15).

2D STE ANALYSIS. STE images for myocardial strain and strain rate measurements were analyzed on a 16-segment basis for LV mid-wall layer with Wall Motion 2D Tracking software (Toshiba Medical Systems) (6,13). Three cardiac cycles from each view were recorded for off-line analyses. The average frame rate was 46.2 frames/s with a mean heart rate of <70 beats/min (16). Longitudinal strain and strain rate curves were assessed from 4-chamber views. Circumferential strain and strain rate were assessed from the short-axis view at the midventricular level. Global strain values were calculated as the average of segmental peak strains. Global strain rate values were also calculated from the average of segmental peak values for each phase (in s^{-1}). The STE image set in each view was excluded if more than 3 segments were improperly tracked. STE indexes of systolic cardiac deformation included 4-chamber longitudinal peak strain (Ell) and circumferential peak strain (Ecc). The diastolic STE indexes were peak early diastolic strain rate in the 4-chamber longitudinal (Ell_SRe) and circumferential (Ecc_SRe) views.

STATISTICAL ANALYSIS. Descriptive statistics are displayed as mean ± SD for continuous variables and group proportions for categorical variables. Glycemic abnormalities were categorized into 4 groups over 6 examinations (year 0 to year 25 examination): group 1 NGT: no DM and no IGT/IFG; group 2 IGT/IFG: IGT/IFG but no DM at any point; group 3 late DM: DM diagnosed at year 15 or later; and group 4 early DM: DM diagnosed by year 15. Multivariable linear regression models investigated the association of glycemic abnormality with LV structure and function at year 25. Multivariable models were adjusted for demographics and CVD risk factors: model adjusted for age, sex, race, physical activity, educational level, alcohol intake, systolic blood pressure, antihypertension medications, smoking status, and heart rate at year 25. An analysis of variance was used to compare LV structure and function across DM groups, stratified as high (HbA_{1c} >7.0%) and low (HbA_{1c} ≤7.0%), based on the average HbA_{1c} of year 20 and year 25, with adjustment for age, sex, race, and BMI at year 25 examination. As an alternative approach, clinically relevant systolic and diastolic dysfunction at year 25 were defined as LVEF <50% for systolic dysfunction and E/e′ ≥13 for diastolic dysfunction (15). Strain above the 90th percentile was chosen as abnormal. The cutpoint was −12.0 for Ell and 0.51 for Ell_SRe. We explored the relationship between glycemic abnormality groups over 25 years and clinically relevant systolic dysfunction at year 25 using multivariate logistic regression analysis, reporting odds ratio (ORs) and 95% confidence interval (CI). In multivariate logistic regression models, glycemic abnormality groups were adjusted for the same variables used in the multivariate linear regression analysis models, as described previously, but with the addition of WHR.

For the trajectory analysis, HOMA-IR was logarithmically transformed to approximate normality. Distinct HOMA-IR trajectories (measured at 6 follow-up examinations over 25 years) were identified over 25 years with the PROC TRAJ procedure (SAS version 9.4 for Windows, SAS Institute Inc., Cary, North Carolina). Trajectories derived via maximum likelihood and Bayesian information criterion were used

TABLE 1 Participant Characteristics in Glycemic Abnormality at the CARDIA Year 25 Examinations (N = 3,179)

	n	NGT (n = 1,485)	n	IGT/IFG (n = 1,241)	n	Late DM (n = 368)	n	Early DM (n = 85)	p for Trend
Age, yrs	1,485	49.8 ± 3.7	1,241	50.5 ± 3.5	368	50.6 ± 3.7	85	51.2 ± 3.1	<0.0001
Female	1,485	961 (64.7)	1,241	503 (40.5)	368	198 (53.8)	85	48 (56.5)	<0.0001
White	1,485	832 (56.0)	1,241	707 (57.0)	368	115 (31.3)	85	38 (44.7)	<0.0001
Weight, kg	1,485	81.3 ± 19.8	1,241	90.3 ± 20.2	368	103.7 ± 25.6	85	94.3 ± 21.1	<0.0001
BMI, kg/m^2	1,485	28.5 ± 6.6	1,241	30.4 ± 6.6	368	35.8 ± 8.4	85	32.5 ± 6.3	<0.0001
BMI ≥30 kg/m^2 (obesity)	1,485	485 (32.7)	1,241	572 (46.1)	368	278 (75.5)	85	51 (60.0)	<0.0001
Waist circumference, cm	1,485	89.1 ± 14.2	1,241	97.0 ± 14.4	368	107.9 ± 16.2	85	102.1 ± 16.9	<0.0001
Hip circumference, cm	1,485	108.3 ± 13.5	1,241	110.6 ± 13.1	368	119.1 ± 17.3	85	114.7 ± 13.7	<0.0001
Waist-to-hip ratio	1,485	0.82 ± 0.08	1,241	0.88 ± 0.08	368	0.91 ± 0.09	85	0.89 ± 0.09	<0.0001
Heart rate, beats/30 s	1,485	32.5. ± 4.9	1,241	33.5 ± 5.6	368	35.5 ± 5.6	85	35.2 ± 6.2	<0.0001
Systolic blood pressure, mm Hg	1,485	115.8 ± 14.6	1,241	120.5 ± 14.8	368	124.5 ± 17.4	85	121.3 ± 16.9	<0.0001
Diastolic blood pressure, mm Hg	1,485	72.1 ± 10.7	1,241	75.2 ± 10.5	368	78.1 ± 10.6	84	73.8 ± 10.5	<0.0001
Hypertension	1,485	352 (23.7)	1,241	438 (35.3)	368	267 (72.6)	84	53 (63.1)	<0.0001
Smoking status									0.03
Current smoker		222 (15.0)		227 (18.3)		79 (21.5)		11 (12.9)	
Former smoker		328 (22.1)		268 (21.6)		81 (22.0)		20 (23.5)	
Never smoker		935 (63.0)		746 (60.1)		208 (56.5)		54 (63.5)	
Antihypertensive medication	1,485	250 (16.8)	1,241	326 (26.3)	368	233 (63.3)	85	48 (56.5)	<0.0001
Educational level ≤12 yrs	1,485	282 (19.0)	1,241	296 (23.9)	368	110 (29.9)	85	21 (24.7)	<0.0001
Physical activity, EU	1,485	351 ± 276	1,241	352 ± 283	368	278 ± 248	85	298 ± 284	0.0002
Fasting glucose, mg/dl	1,421	88.2 ± 6.3	1,197	98.7 ± 9.0	356	139.9 ± 55.2	81	140.7 ± 75.3	<0.0001
Fasting insulin, μU/ml	1,413	8.5 ± 5.8	1,191	12.0 ± 8.1	355	18.8 ± 11.8	76	16.0 ± 30.2	<0.0001
HbA_{1c}, %	1,446	5.38 ± 0.35	1,215	5.56 ± 0.38	357	7.27 ± 1.75	83	7.40 ± 2.27	<0.0001
Total cholesterol, mg/dl	1,478	192.7 ± 35.0	1,239	195.0 ± 37.3	368	186.1 ± 41.5	84	185.7 ± 42.0	0.001
CRP, mg/dl	1,475	2.58 ± 6.41	1,237	3.23 ± 5.80	368	5.73 ± 6.99	84	3.43 ± 6.00	<0.0001
Log CRP, mg/dl	1,475	0.19 ± 1.18	1,237	0.43 ± 1.18	368	1.11 ± 1.19	84	0.50 ± 1.15	<0.0001
HOMA-IR	1,413	1.87 ± 1.33	1,191	2.97 ± 2.12	355	6.52 ± 4.89	76	5.14 ± 7.04	<0.0001
Log HOMA-IR	1,413	0.41 ± 0.65	1,191	0.86 ± 0.69	355	1.62 ± 0.75	76	1.16 ± 0.98	<0.0001
LVEF, %	1,406	61.6 ± 6.7	1,149	61.3 ± 7.2	314	60.5 ± 8.6	73	58.3 ± 9.8	0.004
LVMI, g/m^2	1,378	80.9 ± 20.1	1,086	85.6 ± 21.1	309	87.5 ± 22.8	74	94.5 ± 28.7	<0.0001
RWT	1,379	0.34 ± 0.07	1,082	0.35 ± 0.07	308	0.37 ± 0.08	74	0.36 ± 0.08	<0.0001
LVM/LVEDV ratio	1,314	1.51 ± 0.46	1,024	1.58 ± 0.50	276	1.70 ± 0.56	65	1.73 ± 0.55	<0.0001
e′, cm/s	1,460	10.9 ± 2.3	1,217	10.4 ± 2.2	356	9.4 ± 2.1	82	9.6 ± 2.7	<0.0001
E/e′ ratio	1,451	7.63 ± 2.17	1,211	7.70 ± 2.23	351	8.99 ± 2.66	79	8.79 ± 2.99	<0.0001
Ell, %	1,319	−15.5 ± 2.4	1,093	−14.9 ± 2.3	291	−14.1 ± 2.5	68	−13.5 ± 2.9	<0.0001
Ecc, %	1,362	−15.5 ± 2.7	1,096	−15.3 ± 2.8	297	−14.8 ± 3.2	71	−14.2 ± 3.3	<0.0001
Ell_SRe, s^{-1}	1,316	0.86 ± 0.25	1,089	0.79 ± 0.24	287	0.75 ± 0.26	67	0.73 ± 0.26	<0.0001
Ecc_SRe, s^{-1}	1,359	0.81 ± 0.32	1,095	0.80 ± 0.32	297	0.75 ± 0.35	71	0.72 ± 0.29	0.006

Values are mean ± SD or n (%). Comparisons across categorical glycemic abnormality groups were by Student *t* test from an analysis of variance for continuous variables and by Wald chi-square test for categorical variables. Normal indicates no DM and no IGT/IFG; IGT/IFG indicates IGT/IFG at some point; late DM indicates DM year 15 or later; and early DM indicates DM year 0 or year 10.

BSA = body surface area; BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; CRP = C-reactive protein; DM = diabetes mellitus; e′ = peak early diastolic mitral annular velocity; Ecc = circumferential peak systolic strain; Ecc_SRe = circumferential peak early diastolic strain rate; E/e′ = ratio of early peak diastolic mitral velocity/peak early diastolic mitral annular velocity; Ell = longitudinal peak systolic strain; Ell_SRe = longitudinal peak early diastolic strain rate; EU = exercise unit; HbA_{1c} = hemoglobin A_{1c}; HOMA-IR = homeostasis model assessment of insulin resistance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVM = left ventricular mass; LVMI = left ventricular mass index; NGT = normal glucose tolerance; RWT = relative wall thickness.

to determine the number of trajectory groups up to a maximum of 3 groups. Individuals were classified into the following 3 trajectory groups: low IR, those with persistently low log(HOMA-IR) (n = 915); moderate IR, those with moderate log(HOMA-IR) with or without some increase over 25 years (n = 1,226); and high IR, those with persistently high log(HOMA-IR) with or without an increase (n = 566). A multivariable linear regression model was used to evaluate mean values of covariate-adjusted LV measures across HOMA-IR trajectory groups: model adjusted for sex, race, age (years), physical activity (exercise unit), educational level (years), alcohol intake (ml/day), systolic blood pressure (mm Hg), antihypertension medications (yes/no), smoking status (current vs. never or former), heart rate, BMI category (normal: BMI <25.0 kg/m^2; overweight: 25 kg/m^2 ≤BMI <30 kg/m^2, obese: 30 kg/m^2 ≤BMI) at year 25, and interaction between HOMA-IR trajectory groups and BMI category. A 2-sided p value of

<0.05 was considered for statistical significance. All statistical analyses were performed with SAS version 9.4 for Windows (SAS Institute Inc.).

RESULTS

LONGITUDINAL RELATIONSHIPS BETWEEN GLYCEMIC ABNORMALITY AND LV STRUCTURE AND FUNCTION BETWEEN CARDIA YEAR 0 AND YEAR 25 EXAMINATIONS. We first performed analyses on the full cohort stratified by glycemic abnormality status. Cohort characteristics and echocardiographic characteristics are shown in **Table 1** (Online Table 1). NGT status was maintained by 1,485 participants (47%), and 453 participants (14%) developed DM; the remainder had borderline dysglycemia. Regarding treatment for DM, of the 453 participants with DM at the year 25 examination, 244 were undergoing treatment, and of those, 64 were taking insulin. At year 25, the late-onset DM group (duration of DM ≤10 years) was more often characterized by hypertension, current smoking, use of antihypertensive medications, and low educational level. That group had greater BMI, waist circumference, fasting insulin, C-reactive protein, and HOMA-IR and worse LV diastolic indexes such as e′ and E/e′ ratio compared with other groups. The early-onset DM group (duration of DM >10 years) had the highest LVMI and LV mass/LVEDV ratio despite having lower blood pressure and BMI than did the late-onset group. The latter group also had the lowest LV function echocardiographic profiles.

LV structure. Because of these findings, comparisons were made among the dysglycemic groups to determine whether dysglycemic status or duration of DM altered the relationships to LV structure. The early DM group compared with the NGT group had a higher LVMI (coefficient: 11.04 g/m^2; $p < 0.001$) and higher LV mass/LVEDV ratio (coefficient: 0.21; $p < 0.005$) (**Table 2**); these relationships were stronger than in the late-onset DM group as well. The relationship persisted after adjustment for WHR (data not shown).

LV systolic and diastolic function. For LV systolic function, the early DM group compared with the NGT group had less favorable LVEF (coefficient: −2.72%; $p < 0.05$), Ell (coefficient: 1.53%; $p < 0.001$), and Ecc (coefficient: 1.12%; $p < 0.05$) (**Table 2**). The magnitudes of the effects were greater for the early DM group than for the late-onset DM group. Attenuated relationships persisted after adjustment for WHR (data not shown).

For LV diastolic function, both late and early DM were independently associated with less favorable e′, E/e′, and Ell_SRe after adjustment for cardiovascular risk factors (**Table 2**). Attenuated relationships persisted after adjustment for WHR (data not shown).

TABLE 2 Relationships of Glycemic Abnormality Over 25 Years to LV Structural and Functional Indexes

Dependent Variables	n	IGT/IFG β Coefficient (SE)	n	Late DM β Coefficient (SE)	n	Early DM β Coefficient (SE)
Structural indexes						
LVMI, g/m^2	1,086	−0.25 (0.89)	309	1.99 (1.56)	74	11.04 (2.76)*
RWT	1,082	0.003 (0.003)	308	0.008 (0.006)	74	0.006 (0.010)
LVM/LVEDV ratio	1,024	0.05 (0.02)†	276	0.12 (0.04)‡	65	0.21 (0.07)‡
Systolic functional indexes						
LVEF, %	1,149	0.36 (0.33)	314	−0.79 (0.57)	73	−2.72 (1.00)†
Ell, %	1,093	0.23 (0.11)†	291	0.66 (0.18)*	68	1.53 (0.32)*
Ecc, %	1,096	−0.06 (0.13)	297	0.38 (0.23)	71	1.12 (0.40)†
Diastolic functional indexes						
e′, cm/s	1,217	−0.03 (0.10)	356	−0.63 (0.17)*	82	−0.67 (0.30)†
E/e′ ratio	1,211	−0.07 (0.10)	351	0.64 (0.17)*	79	0.67 (0.30)†
Ell_SRe, s^{-1}	1,089	−0.03 (0.01)†	287	−0.06 (0.02)‡	67	−0.09 (0.03)†
Ecc_SRe, s^{-1}	1,095	0.01 (0.01)	297	−0.03 (0.03)	71	−0.07 (0.05)

	Intergroup Differences Between Groups With Abnormal Glycemic Control		
	p Value: IGT/IFG vs. Late DM	p Value: IGT/IFG vs. Early DM	p Value: Late DM vs. Early DM
Structural indexes			
LVMI, g/m^2	0.1489	<0.0001	0.0026
RWT	0.3391	0.7574	0.8333
LVM/LVEDV ratio	0.053	0.0206	0.2586
Systolic functional indexes			
LVEF, %	0.0418	0.0022	0.0778
Ell, %	0.0178	<0.0001	0.0147
Ecc, %	0.0535	0.0033	0.0883
Diastolic functional indexes			
e′, cm/s	0.0004	0.0347	0.90
E/e′ ratio	<0.0001	0.0159	0.929
Ell_SRe, s^{-1}	0.112	0.0797	0.4292
Ecc_SRe, s^{-1}	0.0626	0.0564	0.4281

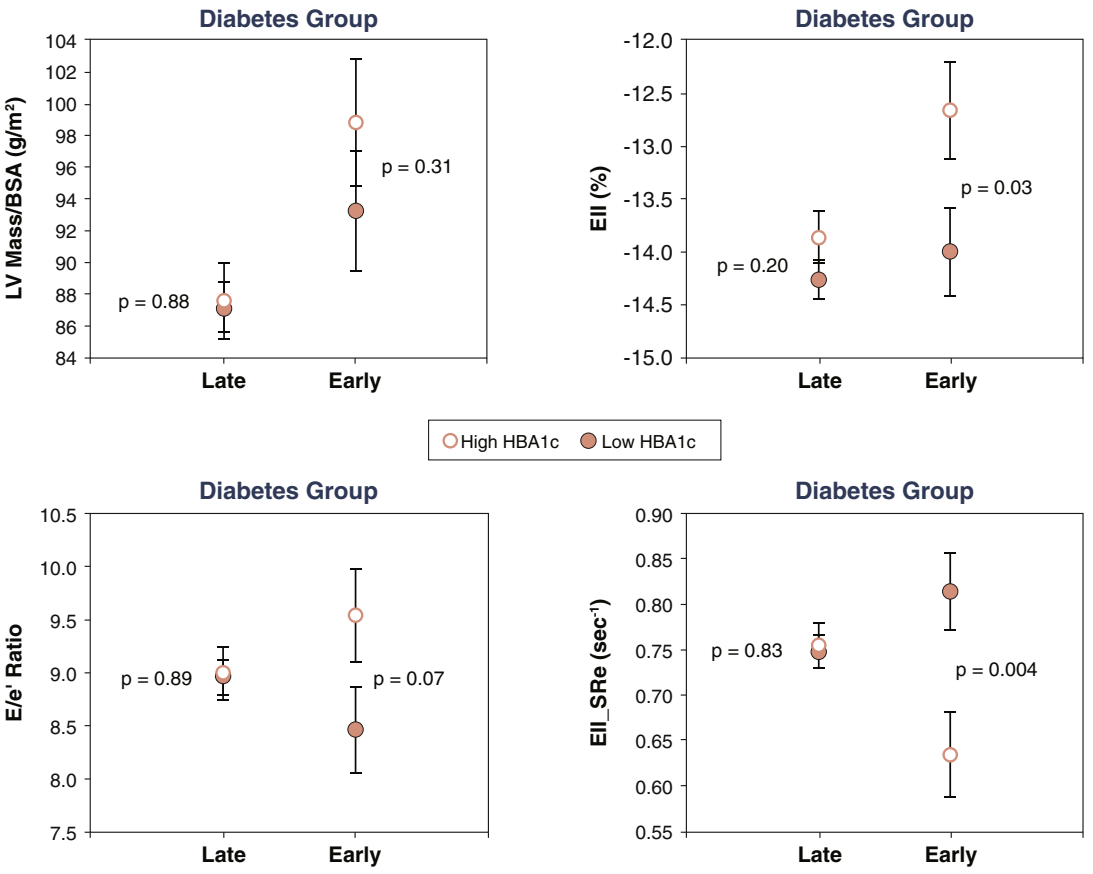
*p < 0.05, †p < 0.005, ‡p < 0.001 (including p < 0.0001) vs. NGT (n ranges from 1,314 to 1,460) as the reference among 4 glycemic abnormality groups. Model: adjusted for age, sex, race, physical activity, educational level, alcohol intake, systolic blood pressure, antihypertension medications, smoking status, and heart rate.

SE = standard error; other abbreviations as in **Table 1**.

Glucose control in relation to LV structure and function. Although those with early-onset DM had higher LVMI, for both the early and late DM groups, there was no difference in LVMI between high HbA_{1c} and low HbA_{1c} groups (**Figure 1**). Those in the early-onset DM group with high HbA_{1c}, however, had worse Ell (systolic function) and a less favorable E/e′ ratio and Ell_SRe (diastolic dysfunction) than those with early-onset DM and with low HbA_{1c} or those with late-onset DM and either high or low HbA_{1c} (**Figure 1**).

LV REMODELING AND LV SYSTOLIC AND DIASTOLIC DYSFUNCTION. As a summary analysis, we calculated the prevalence of echocardiographic abnormalities by glycemic status (**Table 3**). For LV hypertrophy, low LVEF, and adverse speckle tracking parameters (above the 90th percentile for each), prevalence was higher in those with late- and early-onset DM, approximately 2 to 4 times that in the group without

FIGURE 1 LV Structure and Function Across DM Groups, Stratified by High (>7.0%) and Low (≤7.0%) Average HbA_{1c} Over Y20 and Y25



Error bars represent standard error of the mean. Comparisons across hemoglobin A_{1c} (HBA_{1c}) group were made by an analysis of variance with adjustment for year 25 age, sex, race, and body mass index. BSA = body surface area; DM = diabetes mellitus; E/e′ = early peak diastolic mitral inflow velocity/early peak diastolic mitral annular velocity; Ell = longitudinal peak systolic strain; Ell_SRe = longitudinal peak early diastolic strain rate; LV = left ventricular; Y20 = year 20; Y25 = year 25.

any glycemic abnormality for each of the echocardiographic variables. Both early and late DM with poor glucose control (HbA_{1c} >7%: high) were independently associated with the presence of systolic dysfunction (OR: 5.84 [95% CI: 2.08 to 16.39] for early and 4.84 [95% CI: 2.46 to 9.55] for late; $p < 0.005$) and diastolic dysfunction (OR: 3.27 [95% CI: 1.07 to 10.04] for early and 2.21 [95% CI: 1.03 to 4.75] for late; $p < 0.05$) (Table 4, model 1). Late DM with low HbA_{1c} was also associated with the presence of systolic dysfunction (OR: 2.02 [95% CI: 1.02 to 4.00]; $p < 0.001$). The relationship with systolic dysfunction remained significant after adjustment for WHR.

LONGITUDINAL RELATIONSHIPS BETWEEN IR TRAJECTORIES AND LV STRUCTURE AND FUNCTION BETWEEN CARDIA YEAR 0 AND YEAR 25 EXAMINATIONS. The second set of analyses were performed on the cohort without DM and with data that allowed formation of the 3 HOMA-IR trajectories shown in Online Figure 1. Mean HOMA-IR at year 0 was 1.22 ± 0.46 for the low IR, 1.49 ± 0.52 for the moderate IR, and 2.04 ± 0.90 for the high IR trajectory. Mean HOMA-IR at year 25 was 0.99 ± 0.41 for low IR, 2.31 ± 0.97 for moderate IR, and 4.67 ± 2.24 for high IR, respectively (Online Table 2). Relationships of IR trajectories over 25 years to year 25 structural and functional indexes are shown in Table 5. High IR was associated with high relative wall thickness (coefficient: 0.019; $p < 0.0001$), worse Ell in overweight (coefficient: 1.05%; $p < 0.005$), and low e′ in normal weight (coefficient: −1.95 cm/s; $p < 0.005$) and obese (coefficient: −0.49 cm/s; $p < 0.05$) participants but was not associated with LVEF changes. Those with normal BMI and overweight BMI but high IR showed lower Ell_SRe.

TABLE 3 Participants With Glycemic Abnormality Over 25 Years for LV Remodeling and LV Dysfunction at Year 25

	n/N (%)	NGT	IGT/IFG	Late DM	Early DM	p Value for Trend
LV remodeling						
Hypertrophy	412/2,847 (14.5)	175/1,378 (12.7)	147/1,086 (13.5)	67/309 (21.7)	23/74 (31.1)	<0.0001
LV systolic dysfunction						
LVEF <50%	112/2,942 (3.81)	36/1,406 (2.6)	38/1,149 (3.3)	30/314 (9.6)	8/73 (11.0)	<0.0001
Low Ell >−12.0%	278/2,771 (10.0)	84/1,319 (6.4)	118/1,093 (10.8)	55/291 (18.9)	21/68 (30.9)	<0.0001
LV diastolic dysfunction						
E/e′ ratio ≥13	102/3,092 (3.3)	36/1,451 (2.5)	32/1,211 (2.6)	27/351 (7.7)	7/79 (8.9)	<0.0001
Low Ell_Sre <0.51 s^{-1}	262/2,759 (9.5)	99/1,316 (7.5)	102/1,089 (9.4)	47/287 (16.4)	14/67 (20.9)	<0.0001

Values are n/N (%). Hypertrophy: male, LVMI >115 g/m^2; female, LVMI >95 g/m^2. Low Ell (>−12.0): upper 90% of Ell (higher Ell is worse systolic function). Low Ell_SRe (<0.51): lower 90% of Ell_SRe (lower Ell_SRe is worse diastolic function).

Abbreviations as in Table 1.

DISCUSSION

In this 25-year study of a biracial cohort, DM (particularly long-standing DM) had an impact on adverse LV remodeling and impaired LV function. Furthermore, poorly controlled DM was related to subclinical LV dysfunction (17). Moreover, we found that the effects of high IR might constitute an important lifetime risk for development of adverse LV remodeling and LV dysfunction among young adults. Given the current obesity epidemic and consequent increased prevalence of glycemic abnormalities and high IR, these findings have important public health implications.

We interpret our data to indicate that long-standing glycemic abnormality has a cumulative adverse effect on LV remodeling. We have previously shown that a long duration of DM affects LV remodeling (18). This previous study also indicated that IR and central obesity are associated with concentric LV remodeling independent of cardiovascular risk factors (6,19). In the Framingham Study, higher LV mass and wall thickness were associated with worsening levels of glucose intolerance and higher levels of IR (20). Our findings also indicate that both high IR and obesity contribute to concentric remodeling (6).

High IR was related to worse LV diastolic function but was not related to global indexes of LV systolic function such as LVEF or cardiac output (5,19). The duration of DM was associated with worse longitudinal strain in asymptomatic DM patients with normal LVEF in a small case-control study (21). Our study is consistent with these findings and suggests that a long duration of cumulative exposure to glycemic abnormality with poor glucose control in young adulthood could lead to worse LV function in middle age (17).

Long-term cumulative exposure to hyperglycemia could have a direct effect on the cardiac myocyte and myocardial contractility (22). As for LV diastolic dysfunction, CVD risk factors and long-term cumulative exposure to hyperglycemia could have an effect on reactive interstitial fibrosis and extracellular collagen deposition, leading to cardiac stiffness (23). Those with later-onset DM had a higher prevalence of central obesity, smoking, and hypertension; higher IR and C-reactive protein; and lower physical activity than did those with early-onset DM. These risk factors could stimulate reactive interstitial fibrosis and thus

TABLE 4 Participants With Glycemic Abnormality Over 25 Years for LV Systolic and Diastolic Dysfunction at Year 25

			Late DM		Early DM	
	N	IGT/IFG	Low*	High*	Low*	High*
Model 1						
LV systolic dysfunction (LVEF <50%)	112	0.95 (0.59–1.53)	2.02† (1.02–4.00)	4.84‡ (2.46–9.55)	1.68 (0.38–7.37)	5.84‡ (2.08–16.39)
LV diastolic dysfunction (E/e′ ≥13)	102	1.00 (0.60–1.67)	1.29 (0.65–2.60)	2.21† (1.03–4.75)	1.46 (0.32–6.70)	3.27† (1.07–10.04)
Model 2						
LV systolic dysfunction (LVEF <50%)	112	0.93 (0.57–1.50)	1.91 (0.95–3.83)	4.42‡ (2.16–9.06)	1.63 (0.37–7.18)	5.44§ (1.91–15.52)
LV diastolic dysfunction (E/e′ ≥13)	102	0.97 (0.58–1.62)	1.22 (0.60–2.48)	2.01 (0.90–4.47)	1.39 (0.30–6.45)	2.99 (0.96–9.37)

Values are odds ratio (95% confidence interval). *High = high average HbA_{1c} (HbA_{1c} >7.0%); Low = low average HbA_{1c} (HbA_{1c} ≤7.0%). †$p < 0.05$. ‡$p < 0.001$. §$p < 0.005$ vs. NGT (n = 1,391 for LV systolic dysfunction and n = 1,435 for LV diastolic dysfunction) as the reference among 4 glycemic abnormality groups. Model 1: adjusted for age, sex, race, physical activity, educational level, alcohol intake, systolic blood pressure, antihypertension medications, smoking status, and heart rate. Model 2: adjusted for model 1 plus waist-hip ratio.

Abbreviations as in Table 1.

TABLE 5 Relationships of IR Trajectories Over 25 Years to Year 25 Structural and Functional Indexes With Test of BMI × IR Trajectory Interaction

	BMI × IR Group Interaction, p Value	Moderate IR	High IR
LVMI, g/m^2	0.39	−0.93 (0.96)	−1.01 (1.32)
RWT	0.29	0.008 (0.004)*	0.019 (0.005)†
LVEF, %	0.63	0.20 (0.34)	−0.24 (0.47)
Ell, %	0.08		
Normal BMI		−0.040 (0.182)	1.264 (0.779)
Overweight		0.275 (0.168)	1.048 (0.253)†
Obese		0.292 (0.267)	0.448 (0.274)
e′, cm/s	0.09		
Normal BMI		−0.17 (0.16)	−1.95 (0.62)‡
Overweight		−0.40 (0.15)*	−0.37 (0.23)
Obese		−0.45 (0.24)§	−0.49 (0.25)*
Ell_SRe, s^{-1}	0.04		
Normal BMI		0.035 (0.020)§	−0.143 (0.083)§
Overweight		0.009 (0.018)	−0.060 (0.027)*
Obese		−0.021 (0.029)	−0.022 (0.029)

Values are β coefficient (SE). *p < 0.10, †p < 0.05, ‡p < 0.005, §p < 0.001 (including p < 0.0001) vs. low IR (n = 915) as the reference among 3 IR trajectory groups. Model: adjusted for age, sex, race, physical activity, educational level, alcohol intake, systolic blood pressure, antihypertension medications, smoking status, heart rate, and BMI category (normal: BMI <25.0 kg/m^2; overweight: 25 ≤BMI kg/m^2 <30; obese: 30 ≤BMI kg/m^2).

Abbreviations as in Table 1.

influence diastolic function (23,24). In this regard, because early diastolic strain rate is correlated with LV relaxation and filling pressures (25), a reduction of its magnitude indicates slower lengthening during LV filling or reduced myocardial relaxation. In our study, longer duration of DM was independently associated with worse LV remodeling, which is likely linked to a worse Ell_SRe among participants in the glycemic abnormality groups.

Previous reports indicate that higher IR is associated with impaired myocardial systolic and diastolic function even though LVEF is preserved (6). Our findings suggest that changes in LV systolic function occurred in those with obesity and high IR levels or IGT/IFG before the development of overt DM (**Table 5**). There are numerous potential pathophysiological mechanisms relating IR and glucose intolerance to LV dysfunction. Hyperglycemia and hyperinsulinemia can cause myocardial remodeling associated with cardiomyocyte hypertrophy, perivascular fibrosis, and increased collagen deposition (23,24,26). In addition, atrophy due to high ceramide levels causing cardiomyocyte apoptosis could lead to LV dysfunction (26,27).

Our findings demonstrate that the presence of DM, particularly long-standing DM, is associated with subclinical LV dysfunction. Other studies suggest that these findings might be associated with future development of HF (9,28). Those with DM and diastolic dysfunction are at a higher risk for developing HF than those with DM but without diastolic dysfunction (26,28). Previous randomized trials enrolling patients with a mean duration of DM of 10 years suggested that strict glucose control did not produce better outcomes in long-standing DM (29). On the other hand, the UK Prospective DM Study enrolled patients with new-onset DM and suggested a beneficial effect on CVD outcomes, including HF, during the 10 years of post-trial follow-up (30). Longer duration of DM has been shown to be associated with progressive systolic dysfunction (21). IR at 50 years of age has been independently associated with worse LV systolic and diastolic function over 20 years of follow-up (31,32). Our study suggests that the progression to overt ventricular dysfunction associated with DM/IR begins with subclinical dysfunction in early adulthood.

STUDY LIMITATIONS. The study did not include euglycemic insulin clamp glucose disposal rate, which more accurately characterizes IR (27). We did not assess the relation of diabetic complications to altered LV structure and function. We used a single vendor, Artida cardiac ultrasound scanner (Toshiba Medical Systems), to measure cardiac structure and function. Because of the variability of strain values among vendors, strain values are not necessarily applicable to patients examined with other systems (33). The average frame rate of 46 frames/s might have limited the accuracy of peak Ell_SRe assessment. However, the clinical literature reports that acquisition frame rates ranging from 40 to 80 Hz have been widely used to measure motion and deformation at normal heart rates (16). In this regard, the echocardiography image acquisition and reading processes in the CARDIA study have been highly reproducible, including robust results for STE analyses (13).

CONCLUSIONS

Cumulative exposure to DM and higher IR from early adulthood to middle age are risk factors for adverse LV remodeling and subclinical LV dysfunction later in life. LV remodeling and worse myocardial deformation are important determinants of lifetime risk for developing future cardiovascular morbidity and mortality, including clinical HF with both depressed and preserved LVEF (4,8).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Longer duration of cumulative exposure to DM and poor glucose control from early adulthood to middle age could predict clinical heart failure. Our findings indicate that long-standing DM in early adulthood contributes to adverse LV remodeling and impaired LV function by middle age. Furthermore, poorly controlled DM was related to subclinical LV dysfunction. These findings suggest that uncontrolled DM and insulin resistance could increase the lifetime risk of incident heart failure in the general population.

TRANSLATIONAL OUTLOOK: This study demonstrates the relationship between duration of glycemic abnormality and alterations of LV structure and function. Additional studies are needed to investigate whether adequate glycemic control prevents LV remodeling and dysfunction among diabetic or pre-diabetic individuals by middle age. Furthermore, additional studies are needed to define the relationship between duration of glycemic abnormality during early adulthood and cardiovascular events. The data could be helpful in the management of the young adult patient with DM in clinical practice.

REFERENCES

1. Huffman MD, Berry JD, Ning H, et al. Lifetime risk for heart failure among white and black Americans: Cardiovascular Lifetime Risk Pooling Project. J Am Coll Cardiol 2013;61:1510–7.

2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2013 update: a report from the American Heart Association [published correction appears in Circulation 2013;127:e841]. Circulation 2013;127:e6–245.

3. Kishi S, Armstrong AC, Gidding SS, et al. Relation of left ventricular mass at age 23 to 35 years to global left ventricular systolic function 20 years later (from the Coronary Artery Risk Development in Young Adults Study). Am J Cardiol 2014;113:377–83.

4. Bluemke DA, Kronmal RA, Lima JA, 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;52:2148–55.

5. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle. the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol Img 2010;3:266–74.

6. Kishi S, Armstrong AC, Gidding SS, et al. Association of obesity in early adulthood and middle age with incipient left ventricular dysfunction and structural remodeling: the CARDIA Study (Coronary Artery Risk Development in Young Adults). J Am Coll Cardiol HF 2014;2:500–8.

7. Heckbert SR, Post W, Pearson GDN, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging. the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;48:2285–92.

8. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Img 2009;2:356–64.

9. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34.

10. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41:1105–16.

11. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–7.

12. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57–63.

13. Armstrong AC, Ricketts EP, Cox C, et al. Quality control and reproducibility in M-mode, two-dimensional, and speckle tracking echocardiography acquisition and analysis: the CARDIA Study, Year 25 examination experience. Echocardiography 2014;32:1233–40.

14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

15. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.

16. Voigt J-U, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183–93.

17. Gerstein HC, Miller ME, Ismail-Beigi F, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014;384:1936–41.

18. Gidding SS, Liu K, Colangelo LA, et al. Longitudinal determinants of left ventricular mass and geometry: the CARDIA Study. Circ Cardiovasc Imaging 2013;6:769–75.

19. Shah RV, Abbasi SA, Heydari B, et al. Insulin resistance, subclinical left ventricular remodeling, and the obesity paradox: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013;61:1698–706.

20. Rutter MK, Parise H, Benjamin EJ, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. Circulation 2003;107:448–54.

21. Nakai H, Takeuchi M, Nishikage T, Lang RM, Otsuji Y. Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle tracking echocardiography: correlation with diabetic duration. Eur J Echocardiogr 2009;10:926–32.

22. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213–23.

23. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891–903.

24. Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol 2010;56:89–97.

25. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. Circulation 2007;115:1376–83.

26. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes. Relevance to Incidence of Heart Failure. J Am Coll Cardiol 2010;55:283–93.

27. Ingelsson E, Sundström J, Ärnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–41.

28. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction. a population-based study [published correction appears in J Am Coll Cardiol 2010;56:1612]. J Am Coll Cardiol 2010;55:300–5.

29. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes trials. a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol 2009;53:298–304.

30. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.

31. Ärnlöv J, Lind L, Sundström J, Andrén B, Vessby B, Lithell H. Insulin resistance, dietary fat intake and blood pressure predict left ventricular diastolic function 20 years later. Nutr Metab Cardiovasc Dis 2005;15:242–9.

32. Ärnlöv J, Lind L, Zethelius B, et al. Several factors associated with the insulin resistance syndrome are predictors of left ventricular systolic dysfunction in a male population after 20 years of follow-up. Am Heart J 2001;142:720–4.

33. Thomas JD, Badano LP. EACVI-ASE-industry initiative to standardize deformation imaging: a brief update from the co-chairs. Eur Heart J Cardiovasc Imaging 2013;14:1039–40.

KEY WORDS diabetes mellitus, echocardiography, insulin resistance, left ventricular function, obesity, speckle-tracking echocardiography

APPENDIX For supplemental tables and a figure, please see the online version of this article.