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Relations of Insulin Resistance and Glycemic Abnormalities to Cardiovascular Magnetic Resonance Measures of Cardiac Structure and Function: the Framingham Heart Study

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Abstract

Background—Data regarding the relationships of diabetes, insulin resistance and sub-clinical hyperinsulinemia/hyperglycemia with cardiac structure and function are conflicting. We sought to apply volumetric cardiovascular magnetic resonance (CMR) in a free-living cohort to potentially clarify these associations.

Methods and Results—A total of 1603 Framingham Heart Study Offspring participants (age 64±9 years; 55% women) underwent CMR to determine left ventricular mass (LVM), LVM to end-diastolic volume ratio (LVM/LVEDV), relative wall thickness (RWT), ejection fraction (EF), cardiac output (CO) and left atrial size (LAD). Data regarding insulin resistance (homeostasis model, HOMA-IR) and glycemia categories (normal, impaired insulinemia or glycemia, pre-diabetes and diabetes) were determined. In a subgroup (253 men, 290 women) that underwent oral glucose tolerance testing, we related 2-hr insulin and glucose with CMR measures.

In both men and women, all age-adjusted CMR measures increased across HOMA-IR quartiles, but multivariable-adjusted trends were significant only for LVM/ht$^{2.7}$ and LVM/LVEDV. LVM/LVEDV and RWT were higher in participants with pre-diabetes and diabetes (in both sexes) in age-adjusted models, but these associations remained significant after multivariable-adjustment only in men. LVM/LVEDV was significantly associated with 2-hr insulin in men only, and RWT was significantly associated with 2-hr glucose in women only. In multivariable stepwise selection analyses, the inclusion of BMI led to a loss in statistical significance.

Conclusions—While insulin and glucose indices are associated with abnormalities in cardiac structure, insulin resistance and worsening glycemia are consistently and independently associated with LVM/LVEDV. These data implicate hyperglycemia and insulin resistance in concentric LV remodeling.

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Keywords

Insulin resistance; diabetes; left ventricular mass; left ventricular remodeling; cardiovascular magnetic resonance imaging; glycemia

Introduction

Diabetes is an important risk factor for heart failure.1–3 One potential mechanism for the predisposition to heart failure in people with diabetes is the direct toxic effect of hyperinsulinemia and hyperglycemia on cardiomyocytes and the surrounding interstitium, leading to maladaptive changes in cardiac structure and function that antedate the development of clinical heart failure. 4–6 Several investigators have examined the associations of abnormalities in insulin and glucose metabolism (e.g., insulin resistance, impaired fasting glucose) in individuals without overt diabetes to indices of cardiac structure and function 7–12 and heart failure. 13 Many prior studies have been inconsistent, reporting both a positive association,7,10,11 and a lack of association.8,9,12 These previous studies have largely used transthoracic echocardiographic measures for cardiac structural measurements. Two-dimensional echocardiography is a widely available noninvasive technology. However, echocardiography leads to exclusion of many older subjects and those with higher body mass index (BMI) due to inadequate echocardiograph quality,[10] thereby limiting evaluation of all age groups and the full range of BMI in the population.

Cardiovascular magnetic resonance imaging (CMR) provides a volumetric assessment of cardiac structure and function with successful acquisitions of highly accurate and reproducible datasets,14 including determination of left ventricular (LV) concentricity, in nearly all subjects.15,16 Application of CMR (or other volumetric methods) may therefore facilitate more accurate analysis of the associations of glycemia indices and cardiac measures. We sought to apply CMR methods to further elucidate the potential relationship of increasing insulin resistance, elevated levels of insulin and glucose with cardiac structure and to determine if the presence of pre-diabetes and diabetes is associated with alterations of cardiac structure and function compared to the presence of normal insulin and glucose measures.

Methods

Study Sample and Design

The design and characteristics of the Framingham Heart Study Offspring cohort have been described elsewhere. [17] Briefly, members of the Offspring cohort, (comprising the 5124 children of the original cohort and their spouses) were enrolled in 1971 and have been evaluated approximately every four years (“examination cycles”). Examination cycle 7, attended by 3799 participants during the years 1998 – 2001, constituted the sampling frame for this study. Amongst cycle 7 attendees, 1794 participants with normal sinus rhythm and no contraindications to CMR imaging underwent a CMR study between the years 2002 and 2005 and had contemporaneous fasting glucose and insulin levels available. Participants with an incomplete or poor quality CMR and participants with clinical coronary insufficiency, myocardial infarction, or heart failure, were excluded. The remaining 1603 individuals formed the sample for this study. Participants provided written informed consent for CMR and cycle 7 examinations and testing. The study was approved by the Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center.

Assessment of Glucose and Insulin Levels and Insulin Resistance

Baseline samples for glucose and insulin were drawn after an overnight fast. In a stratified sub-sample, we also obtained measurements 2 hours after a 75 g glucose load administered to fasting participants (2-hr insulin and 2-hr glucose).

Glucose measurements were performed with a hexokinase reagent kit (Roche Diagnostics, Indianapolis, IN). Insulin measurements were done by radioimmunoassay (Trinity Biotech, St.Louis, MO). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as:[18]

$$\text{HOMA}-\text{IR}=\frac{\text{fasting glucose (mmol/L)} \times \text{fasting insulin (microU/ml)}}{22.5}$$

Both elevated fasting glucose and fasting insulin predict incident diabetes.[19,20] Fasting insulin is highly correlated with HOMA-IR[21] and a threshold of 75th percentile has been previously described as identifying those with insulin resistance and increased risk for cardiovascular disease.[22–24] Therefore, we utilized a fasting plasma glucose threshold of 100mg/dl and a fasting plasma insulin threshold of 75th percentile to classify participants into a spectrum of worsening glycemic milieu as follows: 1) Diabetes (n = 122), including those with a fasting plasma glucose ≥ 126 mg/dl or receiving insulin or other hypoglycemic therapy 2) Pre-diabetes (n = 176), for those without diabetes but with both fasting glucose > 100mg/dl and fasting insulin > 75th percentile of distribution 3) Impaired insulinemia/ glycemia (n = 442) included those participants with either fasting insulin > 75th percentile of distribution or fasting glucose > 100mg/dl (but not both) and 4) Normal (n = 863), including those with both fasting glucose ≤ 100mg/dl and fasting insulin ≤ 75th percentile of distribution.

Definition of Covariates

Data for covariates were obtained from the contemporaneous examination cycle. Blood pressure was calculated using the average of two auscultated measurements performed while seated. Hypertension was defined as a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg or receiving antihypertensive therapy. “Cardioactive drugs” were defined as agents with consistent evidence for favorable effects on LV remodeling, and they include angiotensin converting enzyme inhibitors, angiotensin receptor blockers or aldosterone antagonists.[25,26] Smoking status was defined as regular smoking in the year preceding the examination.

CMR Methods and Definition of Cardiac Measures

Cine CMR images were acquired with subjects in the supine position on a 1.5 Tesla CMR scanner (Gyroscan ACS/NT, Phillips Medical Systems, Best, the Netherlands) using a 5-element cardiac array receiver coil. Eight to 12 contiguous 10-mm thick LV short axis images were acquired using an ECG-gated steady state free precession sequence, with a 30–40 ms temporal resolution and 1.92 × 1.56 mm^2 in-plane spatial resolution, during a series of end-tidal breath holds.

Epicardial (end-diastolic) and endocardial (end-diastolic and end-systolic) borders were manually traced by a blinded expert observer (CJS) using an EasyScil workstation (Phillips Medical Systems). LV end diastolic and end systolic volumes (EDV and ESV) were calculated integrating over multiple slices using the summation of discs method. LV mass (LVM) was calculated by multiplying diastolic LV myocardial volume with density of myocardium (1.05g/ml), and indexed to height$^{2.7}$. We divided LVM by LVEDV to obtain

the LVM/LVEDV ratio (also known as concentricity). LV ejection fraction (EF) was calculated as (EDV-ESV)/EDV. Cardiac output was calculated as (EDV-ESV)*heart rate. LV end diastolic dimension (LVEDD) and infero-lateral wall thickness (ILWT) were measured in end-diastole from a short axis frame immediately basal to the tip of papillary muscle tips. Relative wall thickness (RWT) was calculated as 2*ILWT/LVEDD. The intra-observer correlations for duplicate readings for LV EDV and ESV were 0.95 and 0.92, respectively.

Statistical Analysis

We compared men and women with regard to categorical clinical variables using the chi-square test. For continuous clinical variables and for CMR measures we compared the sexes using the t-test. In our pre-specified primary analysis, we related sex-specific quartiles of HOMA-IR and glycemia categories to CMR measures. We used sex-specific analysis of covariance (ANCOVA) to assess trends in adjusted means of CMR measures across glycemia categories and HOMA-IR quartiles in a two-step fashion: step one adjusted for age alone and step two adjusted jointly for age, systolic blood pressure, BMI, smoking status and use of cardioactive drugs.

In secondary analyses, we related quartiles of 2-hr glucose and 2-hr insulin with CMR measures in the subgroup of participants who underwent oral glucose tolerance testing. Finally, we performed multivariable stepwise selection analysis relating HOMA-IR and glycemia categories to CMR measures to elucidate the significant covariates contributing to the associations.

Results are presented as trends in adjusted mean values for CMR measures with a test for linear trend. We individually tested for linear trend between the quartiles of HOMA-IR and glycemic categories with the CMR measures by entering the quartile or category (coded 0, 1, 2, and 3) as a continuous variable in the ANCOVA model. The test for linear trend comprised of the 1 degree of freedom t-test for the quartile. A significant linear trend test implies the trajectory of the CMR measure increases or decreases with increasing HOMA-IR quartile or glycemic category. Conversely, a non-significant trend test implies there is no decreasing or increasing trajectory across quartiles/categories. All analyses were performed with SAS version 8.1 (SAS institute, Cary, NC). A two-sided p-value of 0.05 was used to ascertain statistical significance.

Results

Clinical and biochemical characteristics and summary statistics of CMR measures by sex are shown in Table 1. Mean age for the entire group was 64±9 years. Men had a higher BMI and greater prevalence of hypertension compared with women. Nine percent of men and six percent of women had diabetes. Oral glucose tolerance data were available in one-third of participants (253 men, 290 women).

Relations of HOMA-IR to CMR Measures

For both men and women, all age-adjusted CMR measures increased significantly across quartiles of HOMA-IR (all $p<0.005$; Table 2). In multivariable analyses, we observed a significant increasing linear trend in mean LVM/LVEDV ($p<0.005$). We noted a significant decreasing trend in mean LVM/$ht^{2.7}$ ($p<0.05$), across quartiles of HOMA-IR in both men and women consistent with a prior report from Framingham. The significant decreasing trend in association with LVM/$ht^{2.7}$ is seen in the multivariable model that includes BMI in the model, whereas a significant increasing trend is noted in the age-adjusted model (Table 2) and in models that included all of the covariates except BMI (data not shown). In men

(but not in women), we also observed a modest yet statistically significant increasing linear trend in mean EF across HOMA-IR quartiles, after multivariable adjustment (p=0.009; Table 2). However, the trends we observed for age-adjusted means of LAD, RWT and CO were not statistically significant upon multivariable adjustment, in both men and women.

Relations of Glycemia Categories to CMR Measures

Summary data for the groups with pre-diabetes, diabetes and high FPG/high FPI, and normal are presented in Table 3. In age-adjusted analyses we observed that CMR measures were lowest in the normal group, intermediate in the impaired insulinemia/glycemia group and highest in the pre-diabetes and diabetes groups. These trends were statistically significant ($p<0.005$) in age-adjusted analyses for all CMR measures in both sexes except for EF. Participants with pre-diabetes had similar elevations in CMR measures compared to those with diabetes. Upon multivariable adjustment, these associations were not statistically significant in women. However, in men, both LVM/LVEDV and RWT continued to demonstrate a modest but significant increasing trend even after multivariable adjustment. The associations of LAD, LVM/ht$^{2.7}$, EF and CO were not statistically significant after multivariable adjustment.

Relations of 2-hr Insulin to CMR Measures

When relations of 2-hr insulin to CMR measures were evaluated in women, we found a pattern similar to that observed with the glycemia categories; whereas adjusted means of CMR measures increased across quartiles of 2-hr insulin, the relations were not statistically significant after multivariable adjustment (Supplementary Table 2). In men, covariate-adjusted mean LVM/LVEDV increased significantly across increasing quartiles of 2-hr insulin, in multivariable adjusted analyses. Associations of LAD, LVM/ht$^{2.7}$, RWT, EF and CO with 2-hr insulin were not statistically significant in multivariable analyses in men.

Relations of 2-hr Glucose to CMR Measures

In men, we observed an increasing trend of LVM/LVEDV, RWT and CO across quartiles of 2-hr glucose, in age-adjusted but not in multivariable adjusted models (Supplementary Table 3). LAD, LVM/ht$^{2.7}$ and EF were not associated with 2-hr glucose in men. In women, we observed that only RWT was significantly associated with 2-hr glucose in multivariable adjusted models (Supplementary Table 3).

Stepwise Selection Analyses

We performed stepwise selection including one covariate at a time in the multivariable models. We observed that in those multivariable analyses relating HOMA-IR and glycemia categories to CMR measures that were non-significant, glycemia measures lost statistical significance observed in the age-adjusted analyses upon inclusion of BMI.

Discussion

Principal Findings

In this middle-aged to elderly community-based cohort, we demonstrate that higher levels of HOMA-IR are associated with increasing LVM/ht$^{2.7}$ and LVM/LVEDV in both sexes. Upon multivariable adjustment (especially BMI), the trend in LVM/ht$^{2.7}$ is reversed suggesting that the association between insulin resistance and LVM/ht$^{2.7}$ is modified by covariates (mainly BMI). The direction and significance of association between HOMA-IR and LVM/LVEDV was unchanged by multivariable-adjustment, suggesting a graded increase in concentricity with increasing insulin resistance. We also observed a graded increase in LVM/LVEDV and RWT across glycemia categories in men but not in women. Associations

of 2-hr insulin and glucose with CMR measures in women were similar to those seen with glycemia categories; however, in men, increasing concentricity continued to be a significant correlate of 2-hr insulin.

An intriguing finding of our investigation is the consistent association between glycemic abnormalities and ventricular concentricity (LVM/LVEDV), only in men. Adjustment for BMI caused a loss of statistical significance for this relationship only in the ANCOVA evaluating 2-hr glucose. This suggests that both rising HOMA-IR and movement into a worse glycemia category may influence ventricular remodeling, independent of other correlates of concentricity such as blood pressure and BMI. Our study thus extends the findings of prior investigations that reported increased prevalence of concentric remodeling in those with diabetes, insulin resistance and glucose intolerance.[12]

Comparison to Previous CMR Literature

Two prior investigations using a different segmented k-space gradient echo CMR imaging sequence evaluated participants from the Multi-ethnic Study of Atherosclerosis (MESA) and reported on the associations of glycemia indices to CMR measures of absolute LVM and LVEDV. Bertoni et al observed that in multivariable-adjusted analyses, participants with diabetes and impaired fasting glucose did not have a significantly higher LVM, but had significantly lower LVEDV.[27] In a subsequent MESA report, Heckbert et al reported that participants with diabetes had a higher LVM and lower LVEDV, while participants with impaired fasting glucose had a lower LVEDV compared to those with normal glucose tolerance.28 Although neither study reported LVM/LVEDV, their findings that are consistent with an association of increased concentricity with diabetes and glycemic abnormalities. In our study, we directly assessed LVM/LVEDV in a comprehensive set of analyses evaluating its relationship to insulin resistance, glycemia categories, and 2-hr insulin and glucose. When we evaluated the individual components of LVM/LVEDV, we observed a decreasing trend in LVEDV across quartiles of HOMA-IR (Supplementary Table 4) and categories of glycemia (Supplementary Table 5), consistent with those reported from MESA by Bertoni et al and Heckbert et al. Thus, our findings confirm and extend those from previous CMR literature, and add to the literature assessing relations of glycemia to cardiac measures using echocardiography, with which estimates of evaluated three-dimensional volumetric change are limited by greater variability.

Contrasts with Prior Echocardiography Literature

As noted previously, investigations relating glycemic abnormalities to transthoracic echocardiographic measures of cardiac structure and function reported conflicting results. In a previous Framingham Heart Study report, Rutter et el[10] noted increasing LVM with worsening glycemia status (but not with insulin resistance) that was more striking in women. The effect was largely attenuated by adjustment for BMI. In contrast, Devereux et al evaluated 1542 hypertensive participants without diabetes and did not observe any associations between insulin and LVM. [29] In studies evaluating insulin resistance measured via hyperinsulinemic-euglycemic clamp,.Olsen and colleagues noted no associations with LV hypertrophy or other structural measures,30 while Paolisso and co-workers found a weak association with LV wall thickness. One limitation of studies using transthoracic echocardiography is the increased likelihood of exclusion of older and more obese subjects10, thereby limiting the ability to clearly evaluate the associations of glycemia indices and LV structural measures.

Mechanisms Underlying the Associations

Experimental evidence and observations in humans implicate hyperglycemia, hyperinsulinemia and impaired responses to a glucose load in ventricular remodeling.

Experimentally induced hyperinsulinemia in rats leads to increased body mass, relative myocardial mass and blood pressure, and lower cardiac output31 and also causes characteristic changes in angiotensin receptor expression leading to modulation of ventricular remodeling responses to blood pressure.32 Panagia et al[33] reported that db/db mice (an animal model of type 2 diabetes) had lower cardiac output and impaired post-ischemic recovery compared to controls. Similarly, serial CMR measurements in db/db mice demonstrate a progressive increase in LVM and RWT followed by a later increase in LV end-diastolic dimension and decrease in contractile function.[34] Potential molecular mechanisms underlying the effects of insulin and glucose on the myocardium in humans are extensively reviewed elsewhere.35–37

Limitations

Our study has several limitations. We used a cross-sectional design in a middle-aged to elderly Caucasian population that limits our ability to draw causal inferences or generalize to other age or ethnic groups. We had a single measurement of insulin and glucose; longitudinal measures may be more reflective of the effects on the heart. Finally, only a third of our cohort had oral glucose tolerance test results available, limiting our ability to fully evaluate the relations of 2-hr insulin and glucose to CMR measures.

Conclusions

In a free-living adult population without clinical coronary disease, we observed a fairly consistent association of abnormalities in insulin and glucose levels and insulin resistance with LVM/LVEDV and we found that LVM/LVEDV was consistently associated with hyperglycemia and insulin resistance in multivariable analyses. However, the associations of diabetes, insulin resistance and subclinical glycemia abnormalities with LVM/$ht^{2.7}$ and other structural and functional abnormalities were primarily mediated by elevated BMI. These data suggest an important role for hyperglycemia and insulin resistance in concentric LV remodeling.

Prior studies evaluating the associations of diabetes, insulin resistance and sub-clinical hyperinsulinemia/hyperglycemia with abnormal cardiac structure and function reported conflicting results. Cardiovascular magnetic resonance (CMR) provides accurate, volumetric measurements and may help clarify these relations. Since cardiac remodeling precedes and predicts cardiovascular disease, such biological insights may help in risk stratification or elucidation of therapeutic targets. We used sex-specific multivariable-adjusted analysis of covariance models to evaluate the associations of insulin resistance (assessed by the homeostasis model assessment [HOMA-IR]) and of glycemia categories of fasting plasma glucose and insulin with CMR measures of cardiac structure and function (left atrial dimension, left ventricular [LV] mass, LV mass to end-diastolic volume ratio [LVM/LVEDV], relative wall thickness, cardiac output and ejection fraction) in a large cohort of free-living individuals without prevalent cardiovascular disease. In age-adjusted models in both men and women, we observed that HOMA-IR was significantly and positively related to all the cardiac indices; glycemia categories were similarly associated with all cardiac measures except ejection fraction. In multivariable models, LVM/LVEDV was the major correlate of both HOMA-IR and glycemia categories, whereas associations of other cardiac measures and glucose/insulin metabolism were mediated by body mass index. Our observations provide additional evidence for an important role for insulin resistance and glycemic alterations in influencing LV remodeling in individuals free of overt cardiovascular disease, and we

also confirm the important role of body mass index in mediating associations of metabolic abnormalities with cardiac remodeling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

List of Abbreviations

BMI	body mass index
CMR	cardiovascular magnetic resonance imaging
CO	cardiac output
EF	ejection fraction
FPG	fasting plasma glucose
FPI	fasting plasma insulin
HOMA-IR	homeostasis model assessment - insulin resistance
LAD	left atrial dimension
LV	left ventricle/ventricular
LVM	left ventricular mass
LVEDV	left ventricular end-diastolic volume
RWT	relative wall thickness

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References

1. Aronow WS, Ahn C. Incidence of heart failure in 2,737 older persons with and without diabetes mellitus. Chest 1999;115:867–868. [PubMed: 10084505]
2. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154–e235. [PubMed: 16160202]
3. Kenchaiah S, Narula J, Vasan RS. Risk factors for heart failure. Med Clin North Am 2004;88:1145–1172. [PubMed: 15331311]
4. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 2000;101:2271–2276. [PubMed: 10811594]
5. Lee M, Gardin JM, Lynch JC, Smith VE, Tracy RP, Savage PJ, Szklo M, Ward BJ. Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: The Cardiovascular Health Study. Am Heart J 1997;133:36–43. [PubMed: 9006288]

6. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. Circulation 2001;103:102–107. [PubMed: 11136693]
7. Anan F, Yonemochi H, Masaki T, Takahashi N, Fukunaga N, Teshima Y, Iwao T, Kaneda K, Eshima N, Saikawa T, Yoshimatsu H. High-density lipoprotein cholesterol and insulin resistance are independent and additive markers of left ventricular hypertrophy in essential hypertension. Hypertens Res 2007;30:125–131. [PubMed: 17460382]
8. Ebinc H, Ebinc FA, Ozkurt ZN, Dogru T, Yilmaz M. Relationship of left ventricular mass to insulin sensitivity and body mass index in healthy individuals. Acta Cardiol 2006;61:398–405. [PubMed: 16970048]
9. Galvan AQ, Galetta F, Natali A, Muscelli E, Sironi AM, Cini G, Camastra S, Ferrannini E. Insulin resistance and hyperinsulinemia: No independent relation to left ventricular mass in humans. Circulation 2000;102:2233–2238. [PubMed: 11056098]
10. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. Circulation 2003;107:448–454. [PubMed: 12551870]
11. Shigematsu Y, Norimatsu S, Ohtsuka T, Okayama H, Higaki J. Sex-related differences in the relations of insulin resistance and obesity to left ventricular hypertrophy in Japanese hypertensive patients. Hypertens Res 2006;29:499–504. [PubMed: 17044662]
12. Sundstrom J, Lind L, Nystrom N, Zethelius B, Andren B, Hales CN, Lithell HO. Left ventricular concentric remodeling rather than left ventricular hypertrophy is related to the insulin resistance syndrome in elderly men. Circulation 2000;101:2595–2600. [PubMed: 10840010]
13. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Ryden L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. Diabetes Care 2005;28:612–616. [PubMed: 15735197]
14. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. Am J Hypertens 1995;8:221–228. [PubMed: 7794570]
15. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR Am J Roentgenol 2006;186:S357–S365. [PubMed: 16714609]
16. Salton CJ, Chuang ML, O'Donnell CJ, Kupka MJ, Larson MG, Kissinger KV, Edelman RR, Levy D, Manning WJ. Gender differences and normal left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. J Am Coll Cardiol 2002;39:1055–1060. [PubMed: 11897450]
17. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol 1979;110:281–290. [PubMed: 474565]
18. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. 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. [PubMed: 10857969]
19. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP. Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. Diabetes 2004;53:160–165. [PubMed: 14693710]
20. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 2007;167:1068–1074. [PubMed: 17533210]
21. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. Diabetes 2005;54:333–339. [PubMed: 15677489]

22. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care 2003;26:3320–3325. [PubMed: 14633821]
23. Meigs JB, Rutter MK, Sullivan LM, Fox CS, D'Agostino RB Sr. Wilson PW. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. Diabetes Care 2007;30:1219–1225. [PubMed: 17259468]
24. Rutter MK, Wilson PW, Sullivan LM, Fox CS, D'Agostino RB Sr, Meigs JB. Use of alternative thresholds defining insulin resistance to predict incident type 2 diabetes mellitus and cardiovascular disease. Circulation 2008;117:1003–1009. [PubMed: 18250267]
25. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003;115:41–46. [PubMed: 12867233]
26. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, Kleiman J, Krause S, Burns D, Williams GH. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation 2003;108:1831–1838. [PubMed: 14517164]
27. Bertoni AG, Goff DC Jr, D'Agostino RB Jr, Liu K, Hundley WG, Lima JA, Polak JF, Saad MF, Szklo M, Tracy RP, Siscovick DS. Diabetic cardiomyopathy and subclinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2006;29:588–594. [PubMed: 16505511]
28. Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. 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;48:2285–2292. [PubMed: 17161261]
29. Devereux RB, de Simone G, Palmieri V, Oberman A, Hopkins P, Kitzman DW, Rao DC, Arnett DK. Relation of insulin to left ventricular geometry and function in African American and white hypertensive adults: the HyperGEN study. Am J Hypertens 2002;15:1029–1035. [PubMed: 12460697]
30. Olsen MH, Hjerkinn E, Wachtell K, Hoieggen A, Bella JN, Nesbitt SD, Fossum E, Kjeldsen SE, Julius S, Ibsen H. Are left ventricular mass, geometry and function related to vascular changes and/or insulin resistance in long-standing hypertension? ICARUS: a LIFE substudy. J Hum Hypertens 2003;17:305–311. [PubMed: 12756402]
31. Holmang A, Yoshida N, Jennische E, Waldenstrom A, Bjorntorp P. The effects of hyperinsulinaemia on myocardial mass, blood pressure regulation and central haemodynamics in rats. Eur J Clin Invest 1996;26:973–978. [PubMed: 8957202]
32. Samuelsson AM, Bollano E, Mobini R, Larsson BM, Omerovic E, Fu M, Waagstein F, Holmang A. Hyperinsulinemia: effect on cardiac mass/function, angiotensin II receptor expression, and insulin signaling pathways. Am J Physiol Heart Circ Physiol 2006;291:H787–H796. [PubMed: 16565309]
33. Panagia M, Schneider JE, Brown B, Cole MA, Clarke K. Abnormal function and glucose metabolism in the type-2 diabetic db/db mouse heart. Can J Physiol Pharmacol 2007;85:289–294. [PubMed: 17612636]
34. Yue P, Arai T, Terashima M, Sheikh AY, Cao F, Charo D, Hoyt G, Robbins RC, Ashley EA, Wu J, Yang PC, Tsao PS. Magnetic resonance imaging of progressive cardiomyopathic changes in the db/db mouse. Am J Physiol Heart Circ Physiol 2007;292:H2106–H2118. [PubMed: 17122193]
35. Taegtmeyer H, McNulty P, Young ME. Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation 2002;105:1727–1733. [PubMed: 11940554]
36. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. J Am Coll Cardiol 2008;51:93–102. [PubMed: 18191731]
37. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: Part II: potential mechanisms. Circulation 2002;105:1861–1870. [PubMed: 11956132]

Table 1

Clinical and CMR Characteristics of Study Participants

Variables	All (N=1603)	Men		Women		p-value†
	Mean (SD) or %	Mean (SD) or %	Sample Size*	Mean (SD) or %	Sample Size*	
Age, years	64 (9)	64 (9)	725	65(9)	878	0.96
Body mass index, kg/m^2	27.8 (5.0)	28.4 (4.2)	724	27.2 (5.5)	878	<0.0001
Systolic blood pressure, mmHg	125 (17)	126 (16)	724	123 (18)	878	0.0002
Hypertension (%)	51	58	725	45	878	<0.0001
Hypertension treatment (%)	32	36	725	29	878	0.003
Cardio-active drugs (%)	14	16	724	12	877	0.02
Diabetes (%)	8	9	725	6	878	0.02
Current Smoking (%)	10	10	724	10	878	0.79
Fasting plasma glucose, mg/dl	101 (23)	105 (25)	725	98 (20)	878	<0.0001
Fasting plasma insulin, μU/ml	14 (8)	16 (10)	718	13 (7)	866	<0.0001
Homeostasis model assessment – insulin resistance	4.1 (3.5)	4.7 (4.1)	718	3.6 (2.8)	866	<0.0001
Characteristics of Cardiac Measures						
LAD, cm	3.0 (0.5)	3.2 (0.5)	691	2.9 (0.5)	850	<0.0001
LVM/ht$^{2.7}$, g/m$^{2.7}$	25.62 (5.51)	28.15 (5.54)	720	23.54 (4.53)	876	<0.0001
RWT	0.27 (0.05)	0.28 (0.05)	721	0.26 (0.05)	876	<0.0001
LVM/LVEDV, gm/ml	0.84 (0.16)	0.90 (0.17)	720	0.80 (0.13)	876	<0.0001
LVEF (%)	67 (7)	66 (7)	720	69 (6)	876	<0.0001
CO, L/min	5.3 (1.2)	5.9 (1.2)	720	4.8 (1.0)	876	<0.0001

SD = standard deviation; CO = cardiac output; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVM = left ventricular mass; RWT = relative wall thickness

*Sample size for individual parameters.

†Cells present chi-square p-values for categorical clinical variables and t-test p-values for comparisons of continuous clinical variables and CMR measures, for differences between men and women.

Table 2

Adjusted CMR measures across HOMA-IR quartiles

Men						
	Models	**Quartile 1 0.41–2.43† (n = 176)**	**Quartile 2 2.44–3.55† (n = 174)**	**Quartile 3 3.56–5.64† (n = 168)**	**Quartile 4 5.66–57.31† (n = 132)**	**p-value***
LAD, mm	Age-adjusted	30	32	32	33	<0.0001
	MV-adjusted	31	32	32	31	0.42
LVM/ht$^{2.7}$, g/m$^{2.7}$	Age-adjusted	27.1	27.5	27.9	29.7	<0.0001
	MV-adjusted	28.8	28.0	27.3	27.6	0.01
LVM/LVEDV gm/ml	Age-adjusted	0.85	0.89	0.89	0.97	<0.0001
	MV-adjusted	0.87	0.89	0.88	0.94	0.003
RWT	Age-adjusted	0.27	0.29	0.28	0.30	0.0004
	MV-adjusted	0.28	0.29	0.28	0.29	0.20
CO, L/min	Age-adjusted	5.7	5.8	6.0	6.1	0.003
	MV-adjusted	6.0	5.9	5.9	5.6	0.17
LVEF (%)	Age-adjusted	64	66	66	67	0.0003
	MV-adjusted	65	66	66	67	0.009
Women						
	Models	**Quartile 1 0.23–2.03† (n = 216)**	**Quartile 2 2.04–2.84† (n = 213)**	**Quartile 3 2.85–4.25† (n = 208)**	**Quartile 4 4.26–43.01† (n = 175)**	**p-value***
LAD, mm	Age-adjusted	27	28	28	30	<0.0001
	MV-adjusted	29	28	28	28	0.17
LVM/ht$^{2.7}$, g/m$^{2.7}$	Age-adjusted	22.6	22.7	23.4	25.6	<0.0001
	MV-adjusted	24.1	23.3	23.2	23.2	0.03
LVM/LVEDV gm/ml	Age-adjusted	0.77	0.79	0.80	0.83	<0.0001
	MV-adjusted	0.78	0.79	0.80	0.81	0.01
RWT	Age-adjusted	0.25	0.26	0.26	0.27	0.0009
	MV-adjusted	0.25	0.26	0.26	0.26	0.16
CO, L/min	Age-adjusted	4.6	4.6	4.9	5.2	<0.0001

Men						
	Models	**Quartile 1 0.41–2.43† (n = 176)**	**Quartile 2 2.44–3.55† (n = 174)**	**Quartile 3 3.56–5.64† (n = 168)**	**Quartile 4 5.66–57.31† (n = 132)**	**p-value***
	MV-adjusted	4.9	4.7	4.9	4.8	0.42
LVEF (%)	Age-adjusted	68	69	69	69	0.03
	MV-adjusted	68	69	69	69	0.33

Cells present mean values of LV measures;

*p-value for linear trend;

†range of HOMA-IR for the respective quartile.

MV-adjusted = multivariable-adjusted; MV model adjusted for age, BMI, systolic blood pressure, cardioactive drug therapy and smoking status.

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Table 3

Adjusted CMR measures by glycemia categories

Men						
	Models	**Normal (n = 330)**	**High FPG/FPI (n = 235)**	**Pre-Diabetes (n = 92)**	**Diabetes (n = 68)**	**p-value***
LAD, mm	Age-adjusted	31	32	33	34	<0.0001
	MV-adjusted	32	32	31	32	0.94
LVM/ht$^{2.7}$, g/m$^{2.7}$	Age-adjusted	27.2	28.2	30.2	29.9	<0.0001
	MV-adjusted	28.3	27.7	28.4	28.5	0.90
LVM/LVEDV gm/ml	Age-adjusted	0.87	0.90	0.99	0.92	<0.0001
	MV-adjusted	0.88	0.89	0.97	0.90	0.01
RWT	Age-adjusted	0.28	0.29	0.30	0.29	<0.0001
	MV-adjusted	0.28	0.29	0.30	0.29	0.01
CO, L/min	Age-adjusted	5.8	5.9	6.1	6.2	0.0003
	MV-adjusted	5.9	5.9	5.8	6.0	0.98
LVEF (%)	Age-adjusted	65	66	67	65	0.48
	MV-adjusted	66	66	67	64	0.88
Women						
	Models	**Normal (n = 533)**	**High FPG/FPI (n = 207)**	**Pre-Diabetes (n = 84)**	**Diabetes (n = 54)**	**p-value***
LAD, mm	Age-adjusted	28	29	31	31	<0.0001
	MV-adjusted	28	29	28	29	0.37
LVM/ht$^{2.7}$, g/m$^{2.7}$	Age-adjusted	22.7	24.0	26.6	25.0	<0.0001
	MV-adjusted	23.7	23.2	23.8	22.7	0.14
LVM/LVEDV gm/ml	Age-adjusted	0.79	0.80	0.85	0.84	<0.0001
	MV-adjusted	0.80	0.80	0.82	0.81	0.19
RWT	Age-adjusted	0.25	0.26	0.27	0.27	0.003
	MV-adjusted	0.26	0.26	0.26	0.26	0.57
CO, L/min	Age-adjusted	4.7	5.0	5.3	5.3	<0.0001
	MV-adjusted	4.8	4.8	4.9	4.9	0.58

Men						
	Models	**Normal (n = 330)**	**High FPG/FPI (n = 235)**	**Pre-Diabetes (n = 92)**	**Diabetes (n = 68)**	**p-value***
LVEF (%)	Age-adjusted	69	69	70	68	0.36
	MV-adjusted	69	69	69	68	0.53

"Normal" group includes participants with both fasting plasma glucose ≤ 100mg/dl and fasting plasma insulin ≤ 75th percentile of distribution; "High FPI/FPG" group includes those with either fasting plasma insulin > 75th percentile of distribution or fasting plasma glucose > 100mg/dl (but not both); and "pre-diabetes" includes those without diabetes but with both fasting plasma glucose > 100mg/dl and fasting plasma insulin > 75th percentile of distribution. Cells present mean values of LV measures;

* p-value for linear trend.

MV-adjusted = multivariable-adjusted; MV model adjusted for age, BMI, systolic blood pressure, cardioactive drug therapy and smoking status.