Impact of Glucose Intolerance and Insulin Resistance on Cardiac Structure and Function

Sex-Related Differences in the Framingham Heart Study

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Background—Although insulin resistance has been implicated in the pathogenesis of left ventricular (LV) hypertrophy, previous studies have yielded inconsistent results and are limited by referral bias.

Methods and Results—We examined the relations between echocardiographic LV measurements and glucose tolerance status in 2623 Framingham Study subjects (1514 women, mean age 53 years) free of myocardial infarction and heart failure. We also evaluated the relations of insulin resistance (homeostasis model, HOMA-IR) and LV and left atrial (LA) measures within the normal and abnormal glucose tolerance categories (the latter included impaired glucose tolerance, impaired fasting glucose, and newly diagnosed diabetes). LV mass (adjusted for age, height, heart rate, and systolic blood pressure) increased across categories of worsening glucose tolerance; the trend was more striking in women ($P<0.001$) compared with men ($P=0.054$). In subjects with normal (n=2022) and abnormal glucose tolerance (n=327), covariate-adjusted LV mass and LV wall thickness increased across HOMA-IR quartiles in women ($P<0.001$) but not men. In contrast, covariate-adjusted LA size increased with worsening glucose tolerance and across HOMA-IR quartiles in the normal and abnormal glucose tolerance groups in both sexes. Adjustment for body mass index considerably attenuated the relations of LV/LA measures and HOMA-IR, rendering them statistically nonsignificant in the normal glucose tolerance group.

Conclusions—In our large community-based sample, LV mass and wall thickness increased with worsening glucose intolerance, an effect that was more striking in women compared with men. Insulin resistance was associated with increased LV mass in women alone, but this relation was largely accounted for by obesity. **(*Circulation*. 2003;107:448-454.)**

Key Words: insulin ■ echocardiography ■ ventricle, left ■ hypertrophy, ventricular

Increased left ventricular mass (LVM) is a premier risk factor for cardiovascular disease events.[1] Considerable clinical evidence supports a role for insulin resistance in the pathogenesis of left ventricular (LV) hypertrophy. LV hypertrophy has been associated with diabetes mellitus and abnormal glucose tolerance in several epidemiological investigations.[2–5] Furthermore, LV hypertrophy is a feature of several endocrinopathies characterized by insulin resistance.[6,7] Consequently, several investigators[8–13] have evaluated the relations of insulin resistance to LVM.[10] Previous studies have yielded inconsistent results, partly because of small samples, selection bias, varying techniques for assessing insulin resistance, and inconsistent adjustment for key confounders, notably body mass index (BMI) and blood pressure (BP).[10] Additionally, most investigators performed pooled-sex analyses, ignoring the results of other studies[3,11] that have reported sex differences in the impact of diabetes on LV structure.

We hypothesized that LVM would rise with worsening glucose intolerance and with increasing insulin resistance in subjects without diabetes. Furthermore, we theorized that the effects of insulin resistance will likely vary with sex and be influenced by BMI. Accordingly, we examined the sex-specific relations of insulin resistance to echocardiographic indices of LV structure and function in a large community-based sample.

Methods

We evaluated 3799 participants attending the fifth examination (1991–1994) of the Framingham Offspring Study.[14] We excluded

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1176 attendees (31%) for the following reasons: prevalent myocardial infarction or heart failure (n=94), renal insufficiency (n=10), missing covariates (n=128), unavailable (n=62) or inadequate echocardiographic assessment of LV or left atrial (LA) size (n=882). Subjects with previous myocardial infarction, heart failure, or renal failure were excluded because these conditions influence LV measures and insulin resistance.

After exclusions, 2623 subjects (1514 women) remained eligible. Plasma insulin levels were available in 2452 subjects (93.4%). Mean BMI was higher in subjects excluded because of inadequate echocardiographic assessment (29.6 kg/m^2) compared with individuals included in our sample (26.8 kg/m^2).

Assessment of Glucose Tolerance

Known diabetes was defined as fasting plasma glucose ≥126 mg/dL at any two previous examinations or self-reported use of hypoglycemic drugs. A standard 75-g oral glucose tolerance test was administered to subjects not known to have diabetes, with measurements of fasting and 2-hour post-challenge blood glucose and plasma insulin levels. Subjects were categorized on the basis of the results of the oral glucose tolerance test as having normal glucose tolerance, impaired glucose tolerance, impaired fasting glucose, or newly diagnosed diabetes, in accordance with the recent World Health Organization guidelines.[15]

Assessment of Insulin Resistance

Insulin levels (fasting and 2 hours after glucose challenge) were measured in plasma as total immunoreactive insulin and were standardized to serum levels for reporting purposes. Insulin resistance was assessed from fasting insulin and glucose levels and the previously validated homeostasis model assessment (HOMA-IR),[16] thus: HOMA-IR=fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5.[17]

Echocardiographic Methods

Two experienced sonographers performed routine transthoracic echocardiography on all participants with a single Hewlett Packard (model 77020 AC) ultrasound machine and a standardized protocol. M-mode LV end-diastolic diameter (LVEDD), interventricular septum (IVST) and posterior LV wall (PWT) thicknesses at end diastole, and LA size at end systole were measured with hand-held calipers by use of a leading edge technique according to the guidelines of the American Society of Echocardiography.[18] End-diastolic LV wall thickness (LVWT) was calculated as the sum of IVST and PWT, whereas relative wall thickness (RWT) was computed as (IVST+PWT)/LVEDD. LVM was calculated as $0.8[1.04(\text{LVEDD}+\text{LVWT})^3-(\text{LVEDD})^3]+0.6$. Fractional shortening was used as an indicator of LV systolic function. Excellent interreader and intrareader correlations of echocardiographic measurements were observed, and the mean values of measurements were consistent across the years of the examination cycle.

Statistical Analyses

Initial analyses examined the relations of glucose tolerance status to cardiac measurements. The four categories of glucose tolerance were (1) normal, (2) combined impaired glucose tolerance and impaired fasting glucose, (3) newly detected diabetes mellitus, and (4) known diabetes. The following echocardiographic variables were examined separately: LVM, LVEDD, LVWT, RWT, fractional shortening, and LA size. Sex-specific analyses of covariance (ANCOVA) were used to evaluate trends in mean values of covariate-adjusted LV measures across these groups in two steps: Initially, cardiac measurements were adjusted for age, height, heart rate, and systolic BP (model 1); next, models incorporated all above covariates and BMI (weight in kilograms divided by the square of height in meters; model 2). We chose this analytical strategy because relations of insulin resistance to LV measures may be confounded by obesity.[19] Analyses of LA size adjusted also for mitral regurgitation and atrial fibrillation (model 3).

Subsequent analyses assessed relations of HOMA-IR and echocardiographic measures with the use of sex-specific ANCOVA in subjects with normal glucose tolerance and those with abnormal glucose tolerance (defined as impaired glucose tolerance/impaired fasting glucose/newly detected diabetes). Subjects with known diabetes were not included in the abnormal glucose tolerance group because of potential confounding by diabetes treatment and complications. Analyses were sex specific because of statistically significant sex–HOMA-IR interactions for several LV measures in the two glucose tolerance strata. Separate analyses were performed for normal glucose tolerance and abnormal glucose tolerance groups. Results are presented as trends in mean values of covariate-adjusted cardiac measures across HOMA-IR quartiles. Analyses were adjusted for covariates as above (models 1 to 3). A probability value <0.05 was considered statistically significant.

Results

Systolic BP, BMI, and HOMA-IR increased with worsening glucose intolerance (Table 1). HOMA-IR was strongly associated with BMI (r=0.41 [women] to 0.45 [men] in the normal glucose tolerance group; r=0.48 [women] to 0.55 [men] in the abnormal glucose tolerance group, $P<0.0001$). In subjects with normal glucose tolerance, BMI increased across quartiles of HOMA-IR from 23.3 (Q1) to 28.2 kg/m^2 (Q4) in women and from 25.6 (Q1) to 29.6 kg/m^2 (Q4) in men. A similar pattern emerged in the abnormal glucose tolerance group; BMI increased from 25.7 to 32.5 kg/m^2 (women) and from 26.9 to 31.7 kg/m^2 in men from Q1 to Q4 of HOMA-IR.

Echocardiographic Measures Across Glucose Tolerance Categories

In both sexes, covariate-adjusted mean values for LVM increased across groups of worsening glucose tolerance in models without adjustment for BMI. On adjustment for BMI, this trend persisted in women but became statistically nonsignificant in men. In women, LVEDD and LVWT increased across the groups in models without BMI, but this relationship was attenuated on adjustment for BMI. A similar pattern emerged for LVWT in men. Models incorporating waist circumference instead of BMI yielded nearly identical results to those in Table 2 (data not shown). Fractional shortening was not related to glucose tolerance status in either sex (results not shown).

LA size increased across categories of worsening glucose tolerance in both sexes and was statistically significant in models with and without adjustment for BMI. Additional adjustment for atrial fibrillation and mitral regurgitation attenuated the relations in men (but not in women), rendering them nonsignificant.

Echocardiographic Measures Across Quartiles of HOMA-IR

In women with normal glucose tolerance, covariate-adjusted LVM, LVWT, and LA size increased across quartiles of HOMA-IR in model 1 (Table 3). Additional adjustment for BMI (model 2) rendered these relations nonsignificant. In men with normal glucose tolerance, only LA size increased across quartiles of HOMA-IR in model 1. Inclusion of BMI in the model resulted in a pattern of decreasing LVEDD and LVWT across quartiles of HOMA-IR.

TABLE 1. Clinical and Biochemical Characteristics

	Normal Glucose Tolerance		Impaired Fasting Glucose/ Impaired Glucose Tolerance		New Diabetes		Known Diabetes	
Variables	Women (n=1219)	Men (n=875)	Women (n=204)	Men (n=139)	Women (n=38)	Men (n=28)	Women (n=53)	Men (n=67)
Age, y	52±9	52±10	58±9	56±9	57±10	55±9	59±8	58±8
BMI, kg/m^2	25.5±4.5	27.3±3.4	28.4±5.3	28.7±3.8	30.2±6.4	29.8±4.4	28.8±5.7	28.5±4.3
Height, m	1.62±0.06	1.76±0.06	1.61±0.06	1.75±0.06	1.60±0.07	1.75±0.07	1.61±0.06	1.74±0.06
Waist circumference, in	33±5	38±4	36±5	40±4	39±7	41±4	38±7	39±4
Systolic BP, mm Hg	119±18	125±15	133±20	134±17	140±24	141±16	141±20	135±20
Diastolic BP, mm Hg	72±10	76±10	75±10	79±10	78±10	87±11	75±10	78±11
Hypertension Rx, %	10.0	12.0	24.0	30.2	34.2	17.9	45.3	34.3
Heart rate, bpm	65±9	61±9	69±10	66±13	70±11	68±13	74±13	66±14
Total cholesterol, mg/dL	204±38	201±35	214±36	206±35	222±43	204±31	210±38	199±38
HDL cholesterol, mg/dL	58±15	45±11	55±15	41±11	46±11	36±10	46±14	40±12
Atrial fibrillation, %	0.7	1.6	0	3.6	0	7.1	0	6.0
Mitral regurgitation, %*	1.2	1.4	1.0	1.5	2.8	0	1.9	4.7
Fasting glucose, mg/dL	91±8	95±7	102±11	106±10	129±35	153±54	166±78	158±70
Fasting insulin, U	7±6	8±6	10±8	14±10	18±13	19±13	26±54	18±21
HOMA-IR, U	1.55±1.39	1.94±1.50	2.55±2.11	3.61±2.66	6.27±5.55	6.88±4.83	13.26±34.9	7.22±9.44

Values are mean±SD. For women, insulin levels were available in 1170 with normal glucose tolerance, 198 with abnormal glucose tolerance, 34 with new diabetes, and in 20 with known diabetes. For men, insulin levels were available in 852 with normal glucose tolerance, 129 with abnormal glucose tolerance, 25 with new diabetes, and in 24 with known diabetes.

P for trend across groups (within sex comparisons) <0.001 for all variables other than height.

*Mitral regurgitation refers to moderate or greater degree of regurgitation on Doppler color flow imaging.

In women with abnormal glucose tolerance, covariate-adjusted LVM, LVWT, and LA size increased across quartiles of HOMA-IR in models without BMI (model 1; Table 4). Adjustment for BMI attenuated these relations, although statistical significance was maintained in the case of LVWT and RWT. Among men with abnormal glucose tolerance, only LA size was related positively to HOMA-IR quartiles (in model 1 only).

Fractional shortening was not related to HOMA-IR in either sex or in either the normal or abnormal glucose tolerance groups (results not shown). Relationships between covariate-adjusted cardiac measures and fasting plasma insulin were very similar to data presented for HOMA-IR in normal and abnormal glucose tolerance strata (data not shown). Models incorporating waist circumference yielded nearly identical results to those with BMI shown in Tables 3 and 4 (data not shown).

Statistical Power

Because LVM was related to glucose intolerance and HOMA-IR in women alone, we assessed statistical power to detect such an association in men. We had 90% power to detect a trend for a 4-g increment in LVM across categories of glucose intolerance in men (an effect size similar to that noted in women) at $\alpha=0.05$. Similarly, we had 90% power to detect the following increments in LV measures across HOMA-IR quartiles in men (at $\alpha=0.05$): normal glucose tolerance group, 3.3 g for LVM, 0.02 cm for LVWT, and 0.006 for RWT; abnormal glucose tolerance group, 7.2 g for LVM, 0.06 cm for LVWT, and 0.02 for RWT.

Discussion

It is widely acknowledged that diabetes mellitus is a premier risk factor for heart failure[20] and this association is partly mediated by its effect on LV structure.[2,5] Consequently, investigators have examined the relations of lesser degrees of glucose intolerance and insulin resistance to LV structure.[8–13] Prior studies are limited by small samples, sex-pooled analyses, and inadequate adjustment for key confounders (BP and BMI) in multivariable analyses.[10] The present investigation extends previous research by examining the sex-specific relations of glucose intolerance (with contemporary World Health Organization definitions) and insulin resistance (assessed by HOMA-IR) to echocardiographic measurements in a large community-based sample. We performed separate analyses for groups with normal and abnormal glucose intolerance and examined multivariable models with and without adjustment for BMI.

Principal Findings

We observed that the severity of hyperglycemia is more strongly related to LVM in women than in men. These sex-related differences were attenuated but persisted in multivariable models adjusting for BMI. In comparison, LA size increased with worsening glucose tolerance in both sexes. Fractional shortening was not influenced by glucose intolerance in either sex, consistent with some earlier reports.[4]

In analyses performed within the normal and abnormal glucose tolerance groups, increasing insulin resistance was related to increasing LVM and LVWT in women but not in men in multivariable models without BMI as a covariate.

TABLE 2. Covariate-Adjusted LV Measures by Glucose Tolerance Category

Echo Variables/ Model*	Normal Glucose Tolerance	Impaired Fasting Glucose or Impaired Glucose Tolerance	New Diabetes	Known Diabetes	*P* for Trend
Women					
LVM, g					
1	142	149	155	154	<0.001
2	143	145	148	151	0.01
LVEDD, cm					
1	4.57	4.63	4.70	4.69	0.001
2	4.58	4.59	4.63	4.66	0.07
LVWT, cm					
1	1.81	1.84	1.87	1.86	0.01
2	1.82	1.83	1.84	1.85	0.19
RWT					
1	0.400	0.401	0.403	0.399	0.92
2	0.400	0.400	0.403	0.399	0.95
LA, cm					
1	3.50	3.63	3.78	3.71	<0.001
2	3.52	3.56	3.66	3.65	0.003
3	3.52	3.57	3.65	3.66	0.002
Men					
LVM, g					
1	184	190	189	191	0.054
2	185	188	185	189	0.26
LVEDD, cm					
1	4.97	4.98	5.02	4.96	0.96
2	4.98	4.96	5.00	4.95	0.59
LVWT, cm					
1	1.99	2.04	2.00	2.04	0.02
2	1.99	2.02	1.98	2.03	0.09
RWT					
1	0.402	0.412	0.404	0.414	0.07
2	0.402	0.411	0.402	0.413	0.11
LA, cm					
1	3.98	4.06	4.15	4.11	0.002
2	3.99	4.02	4.08	4.08	0.05
3	3.99	4.02	4.07	4.07	0.11

Data are adjusted mean values.

*Model 1=age, height, heart rate, systolic BP. Model 2=Model 1+BMI. Model 3=Model 2+atrial fibrillation+MR (for LA). MR refers to moderate or greater degree of mitral regurgitation on Doppler color flow imaging.

Additional adjustment for BMI rendered nonsignificant the association of insulin resistance with LV measures in women with normal glucose tolerance. Similar adjustment for BMI attenuated relations of insulin resistance and LVM in women with abnormal glucose tolerance, but statistical significance was maintained for LVWT and RWT. These data suggest that the association of insulin resistance with LVM is related largely to the association of the former with obesity, as suggested by some other investigators.[10] The distribution of HOMA-IR values had a wider spread in individuals with abnormal glucose tolerance (Table 4) and this may have contributed to an increased ability to detect associations in this group.

Sex Differences in Relations of Glucose Intolerance, Insulin Resistance, and LV Structure

At least two prior investigations that performed sex-specific analyses reported an association of diabetes with increased LVM in women but not in men.[3,11] In another recent investigation, LVWT was increased in women with impaired glucose tolerance but not in men with the condition.[4] The present investigation confirms these observations. Although

TABLE 3. Covariate-Adjusted Cardiac Measures Across Quartiles of HOMA-IR in Subjects With Normal Glucose Tolerance

	Quartiles of HOMA-IR				
Echo Variables/Model*	Q1	Q2	Q3	Q4	*P* for Trend
Women (n=1170)					
HOMA-IR range, U	0.16–0.70	0.71–1.23	1.24–1.97	1.98–14.38	
LVM, g					
1	136	141	140	145	<0.001
2	141	143	140	140	0.56
LVEDD, cm					
1	4.55	4.58	4.56	4.59	0.28
2	4.59	4.59	4.56	4.54	0.05
LVWT, cm					
1	1.77	1.80	1.80	1.83	<0.001
2	1.79	1.81	1.80	1.81	0.39
RWT					
1	0.393	0.397	0.399	0.401	0.07
2	0.393	0.397	0.399	0.401	0.15
LA, cm					
1	3.39	3.48	3.48	3.58	<0.001
2	3.47	3.50	3.48	3.48	0.91
3	3.47	3.50	3.47	3.48	0.97
Men (n=852)					
HOMA-IR range, U	0.18–0.94	0.95–1.57	1.58–2.60	2.61–12.09	
LVM, g					
1	184	182	180	187	0.54
2	188	184	180	182	0.03
LVEDD, cm					
1	5.01	4.97	4.95	4.98	0.29
2	5.04	4.98	4.94	4.94	0.003
LVWT, cm					
1	1.97	1.97	1.97	2.01	0.15
2	1.99	1.98	1.96	1.98	0.64
RWT					
1	0.396	0.399	0.400	0.406	0.08
2	0.397	0.400	0.400	0.405	0.24
LA, cm					
1	3.90	3.94	3.97	4.06	<0.001
2	3.98	3.98	3.96	3.95	0.42
3	3.98	3.97	3.98	3.95	0.56

Data are adjusted mean values.
*See Table 2 for description of models.

speculative, the presence of estrogen receptors in cardiomyocytes and greater activation of the serine/threonine protein kinase Akt (an inhibitor of myocyte apoptosis) in women[21] support the notion of sex-specific differences in LV remodeling.

Glucose Intolerance, Insulin Resistance, and LA Size

Few prior investigations have examined the relations of insulin resistance and diabetes mellitus to LA size.[22] We noted an association of LA size with glucose intolerance in women in all models. In men, a similar relation was noted but became nonsignificant on adjustment for atrial fibrillation and valvular regurgitation.

We observed increasing LA size with greater insulin resistance, an effect likely mediated by increasing BMI across HOMA-IR quartiles.[23] It is intriguing that in the present study, although relations of LVM and insulin resistance varied between the two sexes, LA size was related to insulin resistance in both men and women. A possible explanation is

TABLE 4. Covariate Adjusted Cardiac Measures Across Quartiles of HOMA-IR in Subjects With Abnormal Glucose Tolerance

	Quartiles of HOMA-IR				
Echo Variables/Model*	Q1	Q2	Q3	Q4	*P* for Trend
Women (n=232)					
HOMA-IR range, U	0.20–1.13	1.15–2.25	2.27–3.69	3.81–25.66	
LVM, g					
1	142	152	156	164	<0.001
2	148	156	153	157	0.21
LVEDD, cm					
1	4.56	4.62	4.63	4.69	0.08
2	4.64	4.68	4.60	4.59	0.38
LVWT, cm					
1	1.81	1.88	1.91	1.97	0.001
2	1.83	1.89	1.91	1.95	0.02
RWT					
1	0.402	0.409	0.415	0.425	0.06
2	0.398	0.406	0.417	0.430	0.01
LA, cm					
1	3.63	3.59	3.75	3.94	<0.001
2	3.76	3.68	3.69	3.78	0.91
3	3.75	3.68	3.71	3.77	0.85
Men (n=154)					
HOMA-IR range, U	0.24–2.04	2.06–3.04	3.09–5.54	5.61–17.49	
LVM, g					
1	189	193	195	196	0.32
2	193	196	193	189	0.57
LVEDD, cm					
1	4.97	4.96	4.97	4.96	0.94
2	4.98	4.96	4.97	4.94	0.75
LVWT, cm					
1	2.03	2.07	2.08	2.09	0.30
2	2.07	2.09	2.07	2.04	0.72
RWT					
1	0.412	0.422	0.424	0.424	0.44
2	0.418	0.427	0.422	0.416	0.92
LA, cm					
1	3.97	4.10	4.11	4.33	0.002
2	4.04	4.15	4.08	4.24	0.15
3	4.06	4.13	4.10	4.22	0.24

Data are adjusted mean values.
*See Table 2 for description of models.

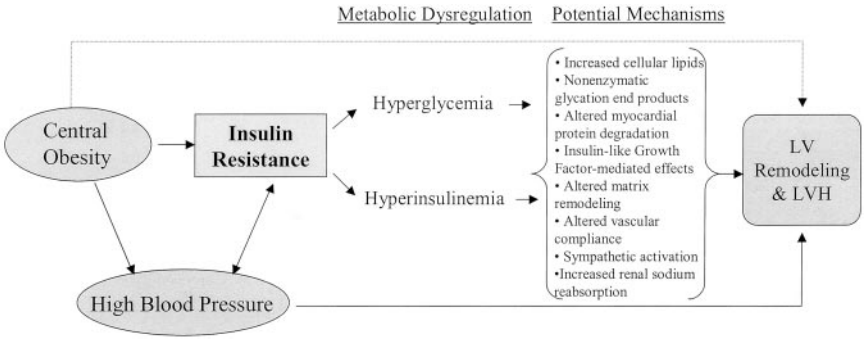
that LA size may be influenced by clinical factors independent of their impact on LVM.[24] Additionally, an increase in LA size may be an early marker of LV diastolic impairment even when LVM is normal.[25]

Insulin Resistance and Cardiac Changes: Potential Mechanisms

Insulin resistance can influence cardiac structure through several mechanisms that are reviewed elsewhere[26] and summarized in the Figure.

Limitations

Our cross-sectional investigation does not permit any causal inferences. Furthermore, M-mode measurements of LVM may be prone to error when the LV is distorted. We avoided this problem in part by excluding subjects with myocardial infarction and heart failure. Any measurement errors would be random and would bias us toward the null hypothesis of no association of insulin resistance and LV measurements. Because subjects excluded as a result of inadequate echocardiography had higher BMIs, we may have underestimated the



Potential mechanisms by which insulin resistance and its precursors/correlates are associated with LV hypertrophy (LVH) (see reference 26 for review).

impact of obesity and/or insulin resistance on cardiac structure. An additional limitation is that we did not assess LV diastolic function (using LV filling indices and tissue Doppler imaging). Lastly, our study sample was white, limiting the generalizability of our findings to other ethnicities.

Clinical Implications

In our investigation, glucose intolerance was more strongly related to increased LVM and wall thickness in women than in men. Insulin resistance was associated with these LV measures in women but not in men, and these relations were largely accounted for by obesity. The greater impact of hyperglycemia on LV structure in women may help to explain the increased relative risk for heart failure in women with diabetes compared with men.[20] Overall, our findings assume contemporary significance given the rising burden of obesity and glucose intolerance in the United States.

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