Effect of Type 2 Diabetes Mellitus on Left Ventricular Geometry and Systolic Function in Hypertensive Subjects
Hypertension Genetic Epidemiology Network (HyperGEN) Study
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Background—Type 2 diabetes is a cardiovascular risk factor. It remains to be elucidated in a large, population-based sample whether diabetes is associated with changes in left ventricular (LV) structure and systolic function independent of obesity and systolic blood pressure (BP).

Methods and Results—Among 1950 hypertensive participants in the HyperGEN Study without overt coronary heart disease or significant valve disease, 20% (n=386) had diabetes. Diabetics were more likely to be women, black, older, and have higher BMI and waist/hip ratio than were nondiabetics. After adjustment for age and sex, diabetics had higher systolic BP, pulse pressure, and heart rate; lower diastolic BP; and longer duration of hypertension than nondiabetics. LV mass and relative wall thickness were higher in diabetic than nondiabetic subjects independent of covariates. Compared with nondiabetic hypertensives, diabetics had lower stress-corrected midwall shortening, independent of covariates, without difference in LV EF. Insulin levels and insulin resistance were higher in non–insulin-treated diabetics (n=195) than nondiabetic (n=1439) subjects (both P<0.01). Insulin resistance positively but weakly related to LV mass and relative wall thickness.

Conclusions—In a relatively healthy, population-based sample of hypertensive adults, type 2 diabetes was associated with higher LV mass, more concentric LV geometry, and lower myocardial function, independent of age, sex, body size, and arterial BP. (Circulation. 2001;103:102-107.)

Key Words: diabetes mellitus ■ hypertension ■ hypertrophy ■ echocardiography

Although rates of modifiable cardiovascular risk factors such as smoking, high cholesterol levels, and uncontrolled hypertension are decreasing, rates of type 2 diabetes are increasing in the United States.1,2 Diabetes is a cardiovascular risk factor associated with arterial hypertension and accelerated atherosclerosis.3–12

Several studies have suggested that diabetes may be associated with left ventricular (LV) structural and functional abnormalities in addition to, and independent of, atherosclerosis.13,14 In the Framingham cohort, diabetes was associated with higher LV mass in women but not men.15 High blood pressure (BP), obesity, and abnormal lipid profile, which often coexist with diabetes, tend to be associated with preclinical cardiovascular abnormalities16 and may contribute to the association of diabetes with cardiovascular events. Cardiac features of diabetic and nondiabetic hypertensive subjects remain incompletely described in population-based samples. Therefore, we compared clinical and metabolic characteristics, LV geometry, and systolic function between diabetic and nondiabetic hypertensive participants in the Hypertension Genetic Epidemiology Network (HyperGEN) Study.

Methods

Population
The HyperGEN Study is part of the National Heart, Lung, and Blood Institute Family Blood Pressure Program to assess the genetic basis of hypertension in the population. Hypertension was defined by antihypertensive treatment or recorded (BP) measurements ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on ≥2 occasions. To be eligible, hypertensive subjects were required to have onset of hypertension by age 60 years and ≥1 hypertensive sibling who was willing to participate. Individuals with type 1 diabetes were excluded because of high risk of hypertension due to nephropathy. Four of 5 field centers in HyperGEN participated in the ancillary echocardiographic study. Study participants were recruited from existing...
populations previously defined, including the Atherosclerosis Risk in Communities (ARIC) study (Minneapolis and Forsyth County, North Carolina), the Minnesota Heart Study, and the Utah Healthy Family Tree Study. Selected participants from these parent studies previously participated in the NHLBI Family Heart Study,17 from which a large proportion of the hypertensive sibships were sampled for HyperGEN. Many of the Birmingham patients (all black) were selected from the community. The target population was 50% each black and white in Winston-Salem and 100% white in Minnesota and Utah.

The first HyperGEN examination began in 1996 to obtain standardized measurements of BP at rest and its reactivity to several stimuli. Standardized anthropometric measurements included body mass index (BMI), body surface area, and waist/hip ratio. Fasting serum glucose, insulin, and lipid and lipoprotein concentrations were obtained. Diabetes mellitus was diagnosed by American Diabetes Association criteria18 (fasting glucose ≥126 mg/dL or use of hypoglycemic medication). Insulin levels were assessed by immunoassay (Sanofi Access; reference range, 1.9 to 23 μU/mL). Insulin resistance was calculated by use of the previously validated homeostasis model assessment (HOMA).19 Myocardial infarction, coronary bypass, and percutaneous coronary angioplasty were identified by participant reports. Type and number of antihypertensive medications used were recorded at clinical evaluation.

Clinical and echocardiographic information was available for 2161 hypertensive subjects. We excluded subjects without technically satisfactory LV measurements (3.1% of the cohort) or with ≥2+ aortic or mitral disease; dialysis treatment; history of myocardial infarction, coronary bypass, or percutaneous coronary angioplasty; or severe hypokinesis, akinesis, or dyskinesis on echocardiogram.

Echocardiographic Methods
Echocardiograms were performed by use of methods previously described.20–22 A standardized protocol was followed, under which parasternal and apical acoustic windows were used to record ≥10 consecutive beats per each projection. All elements of the protocol were recorded on videotape: additional strip-chart recordings were made in 1 center. Principal sonographers received training, including written material and didactic and hands-on training at the Reading Center in New York City, NY. Additionally, test tapes were sent to each center as part of sonographer training, and feedback on echocardiographic studies was provided to monitor compliance with the protocol. Parasternal long-axis and apical views were used to detect valvular regurgitation by color Doppler.

Echocardiographic Measurements
Correct orientation of planes for imaging and Doppler recordings was verified with standard procedures.23 LV internal and diastolic dimension and interventricular septal and posterior wall thicknesses were measured at end-diastole and end-systole by American Society of Echocardiography recommendations24 on ≤3 cardiac cycles at or just below the tips of mitral leaflets in parasternal long-axis and short-axis views. When optimal orientation of LV M-mode readings could not be obtained, correctly oriented linear 2-dimensional measurements were made at end-diastole and end-systole by American Society of Echocardiography recommendations24 on ≤3 cardiac cycles at or just below the tips of mitral leaflets in parasternal long-axis and short-axis views. When optimal orientation of LV M-mode readings could not be obtained, correctly oriented linear 2-dimensional measurements were made at end-diastole and end-systole by American Society of Echocardiography recommendations24 on ≤3 cardiac cycles at or just below the tips of mitral leaflets in parasternal long-axis and short-axis views.

Differences in LV structure and geometry were adjusted for age, sex, BMI, and systolic BP as their major established covariates,22 with further adjustment for duration of hypertension. Fisher’s Exact Test and odds ratios with 95% confidence intervals were used to test differences for categorical variables in 2×2 tables. Logistic regression analysis was used to derive odds ratio and 95% confidence intervals adjusted for covariates. Multiple regression analyses were performed to assess relation of diabetes to higher LV mass independent of established covariates and duration of hypertension. Two-tailed P<0.05 was considered significant.

Results
General Characteristics of the Study Population
A total of 1950 participants in the HyperGEN Study met selection criteria. Mean age was 54±11 years; BMI was 32.0±7.0 kg/m2; 63% were women; 35% were white, non-Hispanic; and 65% were black. Of the participants, 20% (n=386) had type 2 diabetes, of whom 45% were treated with insulin, 43% with oral hypoglycemics, and 12% with diet only. On average, duration of diabetes was 10 years. Age at
diagnosis of diabetes was 48±12 years, whereas age at diagnosis of hypertension was 39±12 years (P<0.001).

Clinical and Metabolic Features of Diabetic and Nondiabetic Hypertensive Subjects

Subjects with diabetes were older; had higher BMI, waist/hip ratio, systolic BP, pulse pressure, and heart rate; had lower diastolic BP; and were slightly more likely to be female than subjects without diabetes Table 1. The proportion of subjects who had smoked >100 cigarettes was similar between the groups, as was age at diagnosis of hypertension. Duration of hypertension was longer among diabetics (19±12 versus 14±11 years; P<0.001). Diabetic patients more frequently were on antihypertensive treatment than nondiabetics (94% versus 89%; P<0.01) and more frequently received ACE inhibitors (48% versus 27%; P<0.01), whereas no between-group differences were seen in β-blocker (16% versus 20%), calcium channel blocker (45% versus 37%), or diuretic (50% versus 47%) use (all P=NS). Diabetics were more frequently on ≥2 medications than nondiabetics (47% versus 34%; P<0.01), which yielded, on average, a higher number of antihypertensive medications in diabetics than nondiabetics (1.6 [range, 0 to 6] versus 1.3 [range, 0 to 5]; P<0.001).

Laboratory Data

After adjustments were made for age and sex, diabetic patients had higher fasting plasma glucose, triglyceride, and creatinine levels (Table 2). Total cholesterol did not differ between groups, but HDL cholesterol was lower and total cholesterol/HDL cholesterol and triglyceride/HDL cholesterol ratios were higher in diabetics. Insulin (11.2 versus 9.7 μU/mL) and HOMA (4.5 versus 2.5) levels were higher in non–insulin-treated diabetics (n=195) than nondiabetic (n=1439) subjects (both P<0.01).

LV Mass and Geometry

Subjects with diabetes had higher LV wall thicknesses, mass, and RWT than those without diabetes independent of age, systolic BP, BMI, and sex, with no between-group difference in LV internal diameter (Table 3). After additional consideration of duration of hypertension as covariate, between-group differences in LV mass (178 versus 172 g) and RWT (0.36 versus 0.35) were confirmed (both P<0.05). LV mass (178 versus 172 g) and RWT (0.36 versus 0.35, both P<0.01) remained higher in diabetics after further adjustment for variables that indicated major antihypertensive medication classes. Likelihood of LV hypertrophy was higher in diabetic than nondiabetic subjects (38% versus 26%, P=0.03; systolic BP and BMI adjusted-odds ratio, 1.32; 95% CI, 1.02 to 1.70), but the difference did not reach statistical significance when duration of hypertension was included in the previous model (OR, 1.19; 95% CI, 0.9 to 1.6). Subjects with LV hypertrophy versus those without had longer duration of hypertension (18±12 versus 14±11 years; P<0.01) and tended toward longer duration of diabetes (11±10 versus 9±9 years; P=0.055). A multiple linear regression model showed sig-

### Table 1. Clinical Features of Subjects With or Without Diabetes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diabetic (n=386)</th>
<th>Nondiabetic (n=1564)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±10</td>
<td>53±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>66</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.8±7.1</td>
<td>31.5±7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±9</td>
<td>167±9</td>
<td>NS</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.95±0.07</td>
<td>0.92±0.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137±24</td>
<td>132±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>72±11</td>
<td>75±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>65±18</td>
<td>57±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±13</td>
<td>69±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (&gt;100 cigarettes), %</td>
<td>50</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Treated for hypertension, %</td>
<td>94</td>
<td>89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diagnosis of hypertension, y</td>
<td>38±12</td>
<td>39±12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values in tables are mean±SD or percentage.

### Table 2. Fasting Laboratory Data in Diabetic and Nondiabetic Hypertensive Subjects

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>166±37</td>
<td>98±35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>199±39</td>
<td>202±39</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49±15</td>
<td>52±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>157±92</td>
<td>134±91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol</td>
<td>4.4±1.4</td>
<td>4.2±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride/HDL cholesterol</td>
<td>3.92±2.98</td>
<td>2.97±2.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.07±0.43</td>
<td>0.99±0.28</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Mean±SD and P values are adjusted for age and sex.

### Table 3. LV Geometry in Diabetic and Nondiabetic Hypertensive Subjects

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass, g</td>
<td>178±38</td>
<td>173±37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV internal diameter, cm</td>
<td>5.1±0.4</td>
<td>5.1±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Interventricular septum, cm</td>
<td>0.9±0.12</td>
<td>0.9±0.12</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.89±0.11</td>
<td>0.89±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.36±0.05</td>
<td>0.35±0.05</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Mean±SD and P values are adjusted for age, sex, systolic BP, and BMI.
significant association of diabetes with higher LV mass (r=2.2, slope=5.9; P=0.02) independent of established covariates and duration of hypertension (R=0.56; P<0.001). Bivariate relations of HOMA to LV mass (r=0.08; P<0.01) and RWT (r=0.19; P<0.001) were relatively weak and became weaker after adjustment for covariates (r=0.003, P=NS to LV mass; r=0.06, P=0.02 to RWT). Among subjects not treated with insulin, a regression model that included HOMA instead of BMI showed association of diabetes with LV mass (r=3.6, slope 3.9; P<0.001) independent of covariates (R=0.46; P<0.001).

Myocardial Function and LV Chamber Systolic Performance
Diabetics had similar EF (either from LV linear dimension or from wall motion score) but lower MWS than did nondiabetic independent of age, sex, and BMI (Table 4). cESS, a measure of afterload, was higher in diabetics. Stress-corrected MWS was lower in diabetic subjects independent of covariates and variables that indicated major antihypertensive medication classes (104% versus 106%; P<0.05).

LV Structure and Function in Diabetic Subjects Divided According to Antidiabetic Treatment
Insulin-treated subjects (n=175) did not differ from those not receiving insulin (n=211) in age (both mean of 57 years) or proportion of women (69% versus 64%). Blacks more commonly received insulin (83% versus 67%; P<0.0005). Systolic BP was higher in insulin-treated diabetics (141±25 versus 133±22 mm Hg; P<0.01) as was fasting glucose (180±80 versus 155±61 mg/dL; P<0.01). Diastolic BP (both 72±11 mm Hg) and BMI (34.5±7.5 versus 33.1±6.7 kg/m²) did not differ. LV mass (184±42 versus 181±42 g; P>0.1) and EF (62.4% versus 62.9%; P>0.5) were similar in insulin-treated and non-insulin-treated diabetics. RWT was higher (0.37±0.05 versus 0.36±0.05; P<0.05) and stress-corrected MWS was lower in diabetics who received insulin (102±10% versus 105±10%, P<0.01) independent of covariates.

Discussion
In a large, population-based cohort of substantially clinically healthy diabetic and nondiabetic hypertensives, we found associations of type 2 diabetes with higher LV mass and concentric LV geometry. Effects of obesity and high BP did not completely account for higher LV mass and LV RWT in diabetics. Consideration of duration of hypertension or insulin resistance (HOMA) in addition to other covariates did not eliminated the association of diabetes with higher LV mass and RWT. Diabetic hypertensives had significantly lower stress-corrected MWS (myocardial systolic function) despite similar endocardial EFs versus nondiabetic hypertensives independent of age, sex, BMI, and afterload. Cardiovascular abnormalities found to be independently associated with diabetes in the present study are known to predict higher rates of cardiovascular events in both asymptomatic and symptomatic subjects.16

Clinical and Laboratory Data
Diabetes is associated with hypertension.3–12 However, in the present population, hypertension was unlikely to be consequence of type 2 diabetes, because mean age at diagnosis of hypertension was younger by 8 years than age at diagnosis of diabetes. Although diabetics were more likely to be on antihypertensive treatment, more frequently with ≥2 medications, systolic BP and pulse pressure were greater in diabetic patients, a likely manifestation of greater arterial stiffness.42 Increase in systolic stress, by increased arterial stiffness, is a stimulus for LV wall thickening,43 thereby potentially contributing to higher LV wall thickness, whereas lower diastolic BP in diabetics probably negatively affects coronary perfusion.44 Diabetics had a worse lipid profile than nondiabetic subjects, which contributes to atherosclerosis and coronary heart disease.

As expected from previous studies,45 insulin resistance was positively associated with LV mass and was higher in non-insulin-treated diabetics than in nondiabetic hypertensives in the present study.

LV Geometry
Diabetic hypertensives had higher LV mass and concentric geometry independent of sex, age, obesity, BP, and duration of hypertension or insulin resistance (HOMA) in alternative models as a result of statistical collinearity of the latter variable with BMI. Those findings were confirmed after further consideration of major antihypertensive medication classes used. Notably, diabetics were more frequently black, which may be an important additional finding. However, race was not used as a covariate in multivariate models because of collinearity with other independent variables in the present population. In fact, an exploratory multiple linear regression analysis in which race was included in addition to standard covariates and diabetes resulted in a slightly lower multiple R (0.55) and low tolerance (0.79) for race.

Negative prognostic relevance of LV hypertrophy has been identified in clinical and population-based samples.16,29–32

### TABLE 4. LV Systolic Function in Diabetic and Nondiabetic Hypertensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF, %</td>
<td>62±7</td>
<td>63±7</td>
<td>NS</td>
</tr>
<tr>
<td>EF from wall motion score, %</td>
<td>62.9±2.5</td>
<td>62.9±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential end-systolic stress, kdyne/cm²</td>
<td>163±36</td>
<td>159±36</td>
<td>NS</td>
</tr>
<tr>
<td>Midwall fractional shortening, %</td>
<td>17.0±1.9</td>
<td>17.4±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stress-corrected midwall fractional shortening, %</td>
<td>104±11</td>
<td>106±11</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Mean±SD and P values are adjusted for age and sex.
Diabetics with LV hypertrophy had longer duration of diabetes and hypertension than those with normal LV mass. Likelihood of LV hypertrophy was 1.32-fold (95% CI, 1.02 to 1.70) higher in diabetic than nondiabetic hypertensives independent of most common clinically assessed conditions, such as sex, BP, and obesity. When duration of hypertension was further considered, relation of diabetes to LV hypertrophy became statistically insignificant, although a trend toward higher prevalence of LV hypertrophy in diabetic hypertensives was confirmed. Subjects with LV hypertrophy had longer duration of hypertension and a clear trend toward long duration of diabetes. These findings suggest that diabetes magnifies over time the alterations of the cardiovascular system induced by increased afterload of systemic hypertension and that the pathophysiological substrate for higher morbidity and mortality in diabetic subjects is multifactorial.

**LV Systolic Function**

Diabetic subjects, predominantly healthy due to exclusion of individuals with ischemic or valvular heart disease or renal failure, had lower myocardial systolic function than nondiabetic subjects independent of covariates. The concern that diabetes-associated atherosclerosis might affect noninvasive estimation of myocardial function in diabetics by reducing systolic BP augmentation between the central aorta (the BP to which the LV is exposed) and the cuff BP used to calculate end-systolic stress (which overestimates central BP in young individuals) is diminished by our finding in a separate population of 418 hypertensive adults that the difference between brachial and central systolic BP calculated by applanation tonometry was similar between diabetics and nondiabetics (12±7 versus 13±9; P=NS [M.J. Roman, R.B.D., personal communication, 2000]). Low stress-corrected MWS is an independent predictor of cardiovascular events in asymptomatic hypertensive patients with preserved EF, but its prognostic relevance in diabetic hypertensive individuals requires further study.

**Clinical Implications**

The present report identifies diabetes-associated increase in LV mass and RWT and decrease in LV midwall function, which may contribute in part to high rates of overt coronary heart disease and heart failure to which diabetic individuals are predisposed. Although abnormalities of LV geometry and myocardial function were mildly greater in diabetic than nondiabetic hypertensive patients, our results suggest that those differences may amplify over time. Our identification of a cluster of abnormalities of LV geometry and function with factors associated with diabetes supports multifactorial approach for preventing high rates of cardiovascular morbidity and mortality in type 2 diabetics.2,47,48

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**References**


29. Koren MJ, Devereux RB, Casale PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991;114:345–352.


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