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Adverse Association between Diabetic Retinopathy and Cardiac Structure and Function

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Abstract

Background—Recent work has demonstrated a link between retinopathy, a marker of microvascular disease, and the development of heart failure, a finding particularly relevant in individuals with diabetes. Our objective was to assess the relationship between retinopathy and cardiac structure and function in a cohort of individuals with type 2 diabetes.

Methods—Stereoscopic fundus photography of seven standard fields was obtained in 531 Mexican-American adults with type 2 diabetes recruited as sibships from Starr County, Texas. Retinopathy was centrally scored and classified as no retinopathy, early nonproliferative diabetic retinopathy, moderate-to-severe nonproliferative diabetic retinopathy, or proliferative diabetic retinopathy. Echocardiography was used to assess cardiac structure and function. Multilevel mixed models were used to assess associations of clinical and echocardiographic variables with retinopathy while accounting for correlations among siblings.

Results—More severe diabetic retinopathy was associated with the presence of hypertension, previous cardiovascular disease, longer duration of diabetes, elevated glycosylated hemoglobin, and greater albuminuria. With worsening severity of diabetic retinopathy, left ventricular (LV) mass and left atrial dimension increased, and LV ejection fraction and LV fractional shortening decreased, independent of potential confounding variables.

Conclusions—More severe diabetic retinopathy was associated with worse cardiac structure and function by echocardiography independent of potential confounding variables. These data suggest a possible microvascular contribution to the development of diabetes-associated cardiac enlargement and dysfunction. Alternatively, common pathways may be leading to both disorders.

Keywords

diabetes mellitus; echocardiography; retinopathy; left ventricular hypertrophy

Multiple studies have established diabetes mellitus as a strong predictor of cardiovascular events, including development of heart failure.^{1–3} The mechanisms leading to the increased risk of heart failure in individuals with diabetes remain uncertain and are likely multifactorial. Potential pathogenic factors include accelerated atherosclerosis and associated co-morbidities such as hypertension, obesity, and renal dysfunction. In addition, several studies have suggested that diabetes may affect cardiac structure and function independent of traditional risk factors, consistent with the presence of a distinct diabetic cardiomyopathy.^{4–7} Once overt heart failure signs and/or symptoms develop in diabetic patients, the prognosis is poor.^{8–11} Therefore, efforts to understand risk factors contributing to this greater burden of heart failure in diabetic patients are critical in reducing the morbidity and mortality attributed to this disease.

A potential factor contributing to the diabetic cardiomyopathy is the associated microangiopathy of diabetes. Recent data from the Atherosclerosis Risk in Communities (ARIC) study demonstrated a link between retinopathy, a marker of systemic microvascular disease, and the development of heart failure, a finding particularly relevant in individuals with diabetes.^{12, 13} Given the overall burden of diabetes and heart failure, we sought to assess the relations between retinopathy and echocardiographic derived measures of cardiac structure and function in a cohort of individuals with type 2 diabetes in order to identify abnormalities that may contribute to the association between retinopathy and heart failure.

RESEARCH DESIGN AND METHODS

Study Design and Sample

Individuals for this study were recruited in Starr County, Texas, a community located on the Texas-Mexico border in which 97% of residents are Mexican-American,¹⁴ and enrolled in the Family Blood Pressure Program, as previously described.¹⁵ Briefly, subjects were recruited as members of families in which at least 2 siblings had type 2 diabetes mellitus, which was originally defined as onset of diabetes at age ≥ 30 years and either two elevated fasting blood glucose values ≥ 140 mg/dL, use of insulin or hypoglycemic agents for at least 1 year, or current use of insulin or hypoglycemic agents consistent with guidelines from the National Diabetes Data Group in effect at the time of the proband's initial identification. A diagnosis of type 2 diabetes was excluded if age at diagnosis was < 30 years, body mass index (BMI) was < 30 kg/m², and insulin had been used continuously since diagnosis.

At baseline, standardized anthropometric measurements, including BMI and waist/hip ratio, were obtained. Fasting laboratory tests were performed including lipid panel, glycosylated hemoglobin (HbA1c), and glucose levels. Albuminuria was measured by using semi-quantitative Micral test strips (Roche Diagnostics, Indianapolis, Indiana).

Retinopathy Grading

Each participant underwent stereoscopic color fundus photography of seven standard fields of each eye. The photographs were sent to the University of Wisconsin Ocular Epidemiology Reading Center where they were scored using the Early Treatment of Diabetic Retinopathy Study (ETDRS) adaptation of the Airlie House classification system.¹⁶ Scores for the more severely affected eye were used to classify diabetic retinopathy as follows: 10–12: normal or nondiabetic retinopathy; 15–37: early nonproliferative diabetic retinopathy; 43–53: moderate-to-severe nonproliferative diabetic retinopathy; 60–85: proliferative diabetic retinopathy.

Echocardiographic Methods

Two-dimensional, M-mode, and Doppler echocardiograms were performed using a commercially available system (Siemens Acuson Cypress, Mountain View, CA). Participants were studied in the left lateral decubitus position, utilizing standard parasternal and apical acoustic windows to record at least 10 beats. The study was recorded on videotape and was sent for interpretation to the Echocardiography Reading Center at Cornell Medical Center in New York City, NY.

Echocardiographic measurements of left ventricular (LV) internal dimension and interventricular septal and posterior wall thickness were performed according to recommendations of the American Society of Echocardiography.¹⁷ When optimal orientation of the LV M-mode measurements could not be made, LV internal dimensions and wall thickness measurements were made from two-dimensional recordings using the leading edge convention as described by the American Society of Echocardiography.¹⁷ Left atrial size was measured by M-mode or two-dimensional linear diameters in long-axis views. Pulsed Doppler echocardiographic examination was performed by positioning a sample volume at the tip of the mitral leaflets during diastole in the apical four-chamber view. The peak velocities of the transmitral early diastolic (E) and atrial phase (A) waves were measured. The deceleration time was also measured. Isovolumic relaxation time (IVRT) was measured with pulsed or continuous wave Doppler across the base of the anterior mitral valve leaflet to record simultaneous LV inflow and outflow velocities.

End-diastolic LV measurements were used to calculate LV mass using a necropsy-validated formula.¹⁸ LV mass was normalized to body-height^{2.7}.¹⁷ Relative wall thickness, an estimate of LV geometric concentricity, and systolic fractional shortening of the LV internal dimension were calculated by standard methods. End-diastolic and end-systolic LV volumes were calculated by the Teichholz method¹⁹ and used to calculate LV ejection fraction and stroke volume.²⁰ Myocardial performance was assessed by the relation of midwall fiber shortening to midwall circumferential end-systolic stress at the level of the LV minor axis. Using a cylindrical model, circumferential end-systolic stress was estimated at the midwall from LV linear dimensions.²¹ Observed midwall shortening was expressed as a percentage of the value predicted from circumferential end-systolic stress. This value is referred to as stress-corrected midwall shortening.²¹ The ratio of brachial pulse pressure (PP) to stroke volume indexed for body surface area (SVi) was used as an indirect measure of global arterial stiffness (PP/SVi); increased PP/SVi ratio suggests decreased arterial compliance or increased arterial stiffness.²²

Diastolic function was characterized as abnormal if the E/A ratio was less than 0.7 or >1.5. Tissue Doppler indices or pulmonary venous inflow patterns were not recorded.

Statistical Analysis

All analyses were conducted using SAS, version 8.2 (SAS Institute, Cary, North Carolina). Continuous variables are presented as mean $\pm$ standard deviation unless otherwise specified. Baseline characteristics were compared using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Multilevel mixed models were used to assess associations of clinical and echocardiographic variables with retinopathy while accounting for correlations among siblings. Models included age, sex, BMI, systolic and diastolic blood pressure, hypertension status, microalbuminuria status, previous cardiovascular disease, HbA1c, cholesterol, and smoking status. Previous cardiovascular disease was defined as self-reported prior myocardial infarction, stroke, significant carotid artery or coronary artery stenosis, surgical or percutaneous coronary or carotid artery interventions. Two-sided *P* values <0.05 were considered significant. Diabetes duration was not included in the final model due

to the high correlation with retinopathy; models that included diabetes duration did not significantly change the results.

RESULTS

Clinical and retinal gradings were available for 531 participants. Baseline characteristics based on retinopathy classification are described in Table 1. There were 126 (23.7%) individuals without diabetic retinopathy, 231 (43.5%) with early non-proliferative diabetic retinopathy, 107 (20.2%) with moderate-to-severe non-proliferative diabetic retinopathy, and 67 (12.6%) with proliferative diabetic retinopathy. Significant differences in gender, cigarette smoking and serum total cholesterol were seen among the groups. More severe retinopathy was also associated with higher heart rate and systolic blood pressure, previous cardiovascular disease, hypertension, longer duration of diabetes, higher HgBA1C, and greater albuminuria.

Echocardiographic LV findings by retinopathy classification are shown in Table 2. LV internal diastolic and systolic diameters and interventricular septal and LV posterior wall thickness increased with greater severity of retinopathy. Likewise, LV mass, in absolute terms ($p=0.05$) and after normalization for body-height^{2.7} ($p=0.03$), increased across categories of worsening retinopathy. Left atrial dimension also increased as the category of retinopathy severity increased. The associations of more severe retinopathy with higher LV mass and left atrial dimension persisted after controlling for age, sex, BMI, systolic and diastolic blood pressure, hypertension status, microalbuminuria status, previous cardiovascular disease, HbA1c, cholesterol, and smoking status.

Parameters of LV systolic function also worsened with more severe retinopathy (Table 2). Fractional shortening, LV ejection fraction, midwall shortening and stress-corrected midwall shortening were lower with more severe retinopathy. The differences in LV ejection fraction, LV fractional shortening, and midwall shortening persisted after adjustment for the confounders described. In addition, the ratio of brachial pulse pressure to stroke index (PP/SVi) increased with more severe retinopathy.

Doppler measures of mitral diastolic inflow parameters are shown in Table 3. After adjustment for potential confounders, retinopathy severity was associated with higher late diastolic peak A wave velocity, but there were no differences in the early diastolic peak E wave velocity, the E/A ratio, deceleration time or isovolumic relaxation time. Similarly, when diastolic dysfunction was assessed as a categorical variable, defined as an E/A ratio <0.7 or >1.5 ($n=62$), no statistical association was seen between diastolic dysfunction and retinopathy severity (data not shown).

DISCUSSION

In this cohort of individuals with type 2 diabetes, more severe diabetic retinopathy was associated with worse echocardiographic indices of cardiac structure, including increased LV mass and increased left atrial dimension, independent of potential confounding variables such as hypertension and previous cardiovascular disease. In addition, parameters of LV systolic function also worsened with increasing severity of retinopathy.

Previous studies have linked the presence of retinopathy with increased risk of cardiovascular disease,^{23, 24} including increased risk of heart failure.^{12, 13} In the Atherosclerosis Risk in Communities (ARIC) Study, retinopathy was associated with a more than 2.5-fold higher risk of developing heart failure.¹³ Importantly, among diabetic participants without hypertension or preexisting coronary heart disease in the ARIC study, the population-attributable fraction for heart failure was 30.5%, implicating a microangiopathic process in nearly a third of incident heart failure cases.¹² This relationship between retinopathy and incident heart failure suggests

that a generalized microangiopathy, beyond the microangiopathy affecting the eye, may play a pathogenic role in the cardiac dysfunction leading to a higher frequency of heart failure in diabetic patients or that common underlying pathways exist between the two disorders. Our study extends this observation by demonstrating independent associations of echocardiographic abnormalities of cardiac structure and function with worsening degrees of retinopathy.

In these analyses of individuals with type 2 diabetes, LV mass increased with greater severity of retinopathy, a finding that was independent of hypertension or known cardiovascular disease. This observation is consistent with recent analyses of the Multi-Ethnic Study of Atherosclerosis (MESA) which demonstrated that the presence of retinopathy was associated with increased concentric cardiac remodeling as assessed by cardiac magnetic resonance imaging.²⁵ Although the association between concentric cardiac remodeling and retinopathy was demonstrated in the overall MESA population, the association between retinopathy and concentric remodeling was more pronounced in diabetic individuals²⁵ and did not reach statistical significance in the non-diabetic participants.

The reasons for the increased LV mass associated with diabetic retinopathy are likely multifactorial. The shared characteristic of hypertension and obesity are likely contributing to greater LV mass, but the relationship between severity of retinopathy and LV mass persists even after adjusting for these differences. One potential contributor to the increased LV mass is increased arterial stiffness. Previous studies have demonstrated that retinopathy is associated with increased arterial stiffness²⁶ and that arterial stiffness is increased in individuals with diabetes.²⁷ In turn, increased arterial stiffness may lead to increased hemodynamic load on the heart with subsequent LV hypertrophy and cardiac dysfunction.²⁸ Additionally, higher levels of advanced glycation end products, which are elevated in diabetes, may contribute to cardiac dysfunction through effects on arterial stiffness and direct and indirect effects on cardiac function. The potential pathogenic role of arterial stiffness is supported by our finding that worsening of severity of retinopathy was associated with increased PP/SVi, an indirect surrogate for increased arterial stiffness.²²

Previous studies have demonstrated associations between retinopathy and abnormal LV diastolic function as assessed by pulsed wave Doppler assessment of the mitral inflow E/A ratio.²⁹ In this study, the increased late diastolic peak transmitral A wave velocity likely reflects a greater contribution of atrial systole to LV diastolic filling. We found no difference in the E/A ratio of the mitral inflow when examined as either a continuous or a categorical variable. The lack of association between retinopathy and mitral E/A categories may be due to the inability to distinguish normal mitral inflow from a “pseudonormal” pattern of filling.³⁰ The association of retinopathy and diastolic dysfunction is supported by the finding of higher left atrial diameter with worsening retinopathy. Left atrial enlargement, as a consequence of elevated LV diastolic pressure due to abnormalities of diastole and LV compliance, has been shown to be a marker of diastolic dysfunction severity.³¹ Similar to the findings with LV mass, the independent association of left atrial enlargement with more severe retinopathy implicates a microvascular process in the diastolic dysfunction often seen in patients with diabetes.

Limitations

This study represents a cross-sectional analysis and adverse clinical outcomes such as heart failure are not available. Nonetheless, the echocardiographic abnormalities identified in this study have been shown to be associated with subsequent adverse cardiovascular outcomes.^{22, 32–34} Further studies will need to be performed to assess the clinical outcomes seen in these patients. In addition, these findings demonstrate associations between retinopathy and cardiac structure and function among Mexican-American individuals, an ethnic group which has a disproportionate burden of diabetes. It is expected that this relationship will hold for other

ethnic groups, but further studies will be required to confirm the applicability of these findings to different ethnic groups. Similarly, studies will need to be performed to confirm these findings in individuals with type 2 diabetes who are not ascertained through family membership. Finally, although multivariable statistical models were used to adjust for heterogeneity between retinopathy groups, residual unmeasured confounding may remain.

Conclusions

This study demonstrates an association between more severe diabetic retinopathy and worse echocardiographic indices of cardiac structure, including increased LV mass and increased left atrial dimension, independent of potential confounding variables. This association between diabetic retinopathy and abnormalities of cardiac structure and function in this study and the previously demonstrated association between adverse clinical cardiovascular events and retinopathy^{12, 13, 23, 24} highlight need for future studies identifying mechanisms by which microvascular disease as manifested by retinopathy may be contributing to adverse outcomes and potential therapeutic targets to prevent these cardiovascular abnormalities. At a minimum, however, our results suggest that retinopathy in an individual with type 2 diabetes should trigger consideration of further cardiac assessment.

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References

1. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001;161:996–1002. [PubMed: 11295963]
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035–2038. [PubMed: 430798]
3. Nichols GA, Gullion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–1884. [PubMed: 15277411]
4. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 2000;101:2271–2276. [PubMed: 10811594]
5. Galderisi M, Anderson KM, Wilson PW, et al. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 1991;68:85–89. [PubMed: 2058564]
6. Palmieri V, Bella JN, Arnett DK, et al. 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. 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;107:448–454. [PubMed: 12551870]
8. Bertoni AG, Hundley WG, Massing MW, et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699–703. [PubMed: 14988288]
9. De Groote P, Lamblin N, Mouquet F, et al. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004;25:656–662. [PubMed: 15084370]
10. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006;27:65–75. [PubMed: 16219658]
11. From AM, Leibson CL, Bursi F, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. *Am J Med* 2006;119:591–599. [PubMed: 16828631]

12. Wong TY, Rosamond W, Chang PP, et al. Retinopathy and risk of congestive heart failure. *JAMA* 2005;293:63–69. [PubMed: 15632337]
13. Cheung N, Wang JJ, Rogers SL, et al. Diabetic retinopathy and risk of heart failure. *J Am Coll Cardiol* 2008;51:1573–1578. [PubMed: 18420100]
14. Brown SA, Becker HA, Garcia AA, et al. Measuring health beliefs in Spanish-speaking Mexican Americans with type 2 diabetes: adapting an existing instrument. *Res Nurs Health* 2002;25:145–158. [PubMed: 11933008]
15. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). *Hypertension* 2002;39:3–9. [PubMed: 11799070]
16. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98(5 Suppl):786–806. [PubMed: 2062513]
17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463. [PubMed: 16376782]
18. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458. [PubMed: 2936235]
19. Teichholz LE, Kreulen T, Herman MV, et al. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976;37:7–11. [PubMed: 1244736]
20. Devereux RB, Roman MJ, Paranicas M, et al. Relations of Doppler stroke volume and its components to left ventricular stroke volume in normotensive and hypertensive American Indians: the Strong Heart Study. *Am J Hypertens* 1997;10:619–628. [PubMed: 9194507]
21. Devereux RB, de Simone G, Pickering TG, et al. Relation of left ventricular midwall function to cardiovascular risk factors and arterial structure and function. *Hypertension* 1998;31:929–936. [PubMed: 9535417]
22. de Simone G, Roman MJ, Koren MJ, et al. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. *Hypertension* 1999;33:800–805. [PubMed: 10082490]
23. Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 2007;30:1742–1746. [PubMed: 17389333]
24. Juutilainen A, Lehto S, Ronnema T, et al. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. *Diabetes Care* 2007;30:292–299. [PubMed: 17259497]
25. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol* 2007;50:48–55. [PubMed: 17601545]
26. Ogawa O, Hayashi C, Nakaniwa T, et al. Arterial stiffness is associated with diabetic retinopathy in type 2 diabetes. *Diabetes Res Clin Pract* 2005;68:162–166. [PubMed: 15860245]
27. Cruickshank K, Riste L, Anderson SG, et al. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085–2090. [PubMed: 12379578]
28. Kawaguchi M, Hay I, Fetics B, et al. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714–720. [PubMed: 12578874]
29. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. *J Am Soc Echocardiogr* 2001;14(9):885–891. [PubMed: 11547274]
30. Quinones MA. Assessment of diastolic function. *Prog Cardiovasc Dis* 2005;47:340–355. [PubMed: 16003649]
31. Pritchett AM, Mahoney DW, Jacobsen SJ, et al. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol* 2005;45:87–92. [PubMed: 15629380]

32. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993;88:1444–1455. [PubMed: 8403291]
33. Kizer JR, Bella JN, Palmieri V, et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). *Am Heart J* 2006;151:412–418. [PubMed: 16442908]
34. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561–1566. [PubMed: 2139921]

Table 1

Baseline characteristics of the cohort by diabetic retinopathy status

	No Retinopathy (n=126)	Early Nonproliferative Retinopathy (n=231)	Moderate-Severe Nonproliferative Retinopathy (n=107)	Proliferative Retinopathy (n=67)	p- value [*]
Age, years	61.5 (10.6)	59.9 (10.1)	60.6 (10.0)	61.4 (8.4)	0.46
Female, %	69.0	63.6	46.7	67.2	<0.01
BMI, kg/m ²	33.3 (6.5)	32.3 (6.7)	31.6 (5.8)	32.6 (6.5)	0.22
Waist/Hip ratio	0.99 (0.07)	1.00 (0.06)	1.00 (0.07)	1.01 (0.06)	0.67
Heart Rate, bpm	68.6 (10.1)	69.8 (9.5)	72.7 (9.7)	72.3 (11.6)	<0.01
Systolic Blood Pressure, mm Hg	129 (17.0)	134 (17.6)	137 (22.7)	143 (24.0)	<0.01
Diastolic Blood Pressure, mm Hg	71 (8.5)	71 (9.8)	73 (10.9)	71 (10.4)	0.301
Cardiovascular Disease, %	26.8	29.0	29.9	50.6	<0.01
Hypertensive, %	27.8	34.2	43.0	53.7	<0.01
Current Smoking, %	15.9	11.3	18.7	4.5	0.03
Diabetes Duration, yrs	8.7 (7.0)	13.2 (8.4)	15.6 (8.6)	17.3 (7.7)	<0.01
Glucose, mg/dL	168 (61.1)	190 (66.6)	189 (68.4)	181 (75.9)	0.03
HbA1C, %	9.5 (2.8)	10.5 (2.9)	11.4 (3.6)	10.4 (2.4)	<0.01
Cholesterol, mg/dL	182 (43.7)	192 (45.8)	210 (66.5)	195 (50.3)	<0.01
Triglycerides, mg/dL	181 (106)	233 (231)	277 (342)	205 (104)	0.08
HDL Cholesterol, mg/dL	46.3 (13.2)	45.2 (11.7)	44.7 (14.3)	46.8 (12.3)	0.63
LDL Cholesterol, mg/dL	98.9 (32.5)	105 (35.5)	114 (37.1)	104 (37.5)	0.03
Albuminuria, mg/L, %	61.1	61.9	34.6	29.9	<0.01
None	21.4	17.3	19.6	16.4	
20	16.7	15.6	29.9	26.9	
50	0.8	5.2	15.9	26.9	
100					

Data expressed as mean (standard deviation), or percentage.

* p-values obtained using ANOVA for continuous variables and chi-square tests for categorical variables

Table 2

Echocardiographic Features of individuals with type 2 diabetes stratified by severity of diabetic retinopathy.

	No Retinopathy (n=121)	Early Nonproliferative Retinopathy (n=229)	Moderate-to- Severe Nonproliferative Retinopathy (n=106)	Proliferative Retinopathy (n=64)	p-value [*]
LV Diastolic Dimension, cm	5.2 (0.4)	5.2 (0.5)	5.3 (0.5)	5.4 (0.6)	0.05
LV Systolic Dimension, cm	3.6 (0.5)	3.5 (0.5)	3.7 (0.6)	3.9 (0.8)	0.01
Posterior Wall Thickness, cm	0.76 (0.09)	0.78 (0.09)	0.80 (0.12)	0.81 (0.09)	0.18
Interventricular Septal Thickness, cm	0.84 (0.11)	0.86 (0.10)	0.88 (0.12)	0.89 (0.11)	0.22
LV Mass, g	147 (37)	150 (37)	160 (43)	172 (45)	0.05
LV Mass/Height ^{2.7} , g/m ^{2.7}	41.9 (10.8)	41.2 (9.8)	42.3 (12.4)	48.5 (12.4)	0.03
Relative Wall Thickness	0.29 (0.04)	0.30 (0.04)	0.31 (0.05)	0.30 (0.04)	0.20
Left atrial dimension, cm	3.51 (0.47)	3.49 (0.49)	3.58 (0.53)	3.78 (0.57)	0.02
LV Fractional Shortening, %	31.29 (4.11)	32.17 (4.51)	30.95 (6.27)	29.38 (6.79)	0.01
LV Ejection Fraction, %	58.5 (6.2)	59.8 (6.8)	57.7 (9.9)	55.20 (11.1)	0.009
Midwall Shortening, %	17.6 (1.9)	17.8 (2.0)	17.0 (2.7)	16.4 (3.2)	0.004
Stress-Corrected Midwall Shortening, %	110 (11)	111 (11)	108 (13)	109 (15)	0.07
Pulse Pressure/Stroke Volume Index, mm Hg/mL per m ²	1.44 (0.36)	1.55 (0.46)	1.62 (0.49)	1.73 (0.46)	<0.001 [†]

Data expressed as mean (standard deviation)

^{*} p-values are adjusted for age, sex, BMI, systolic and diastolic blood pressure, hypertension status, microalbuminuria status, previous cardiovascular disease, HbA1c, cholesterol, and smoking status. Previous cardiovascular disease is defined as self-reported prior myocardial infarction, stroke, significant carotid artery or coronary artery stenosis, surgical or percutaneous coronary or carotid artery interventions.

[†] model for PP/SVi does not include systolic and diastolic blood pressure.

LV=left ventricular; PP/SVi= brachial pulse pressure/stroke volume index

Table 3

Doppler indices of mitral inflow in individuals with type 2 diabetes stratified by severity of retinopathy.

	No Retinopathy (n=121)	Early Nonproliferative Retinopathy (n=229)	Moderate-to- Severe Nonproliferative Retinopathy (n=106)	Proliferative Diabetic Retinopathy (n=64)	p-value
Peak E velocity, cm/s	73.6 (14.8)	78.1 (16.8)	78.2 (17.1)	81.8 (18.4)	0.11
Peak A velocity, cm/s	74.1 (13.6)	78.2 (17.3)	81.0 (19.2)	85.2 (19.2)	<0.001
E/A ratio	1.02 (0.26)	1.04 (0.32)	1.01 (0.36)	1.00 (0.35)	0.42
Deceleration time, msec	198 (36.7)	202 (39.9)	202 (46.1)	200 (60.3)	0.80
Isovolumic relaxation time, msec	79.9 (11.1)	81.1 (12.6)	81.8 (13.4)	81.4 (15.6)	0.66

Data expressed as mean (standard deviation)

* p-values are adjusted for Models included age, sex, BMI, systolic and diastolic blood pressure, hypertension status, microalbuminuria status, previous cardiovascular disease, HbA1c, cholesterol, and smoking status. Previous cardiovascular disease is defined as self-reported prior myocardial infarction, stroke, significant carotid artery or coronary artery stenosis, surgical or percutaneous coronary or carotid artery interventions.