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Changes in Diastolic Dysfunction in Diabetes Mellitus Over Time

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Abstract

Several studies have demonstrated evidence for preclinical left ventricular (LV) diastolic dysfunction in patients with diabetes mellitus (DM) independent of coronary disease or hypertension. The objective of our study was to determine if LV diastolic dysfunction determined by tissue Doppler indices worsens with duration of DM and to quantify the severity of dysfunction as a function of DM duration. From 1996 to 2007, all Olmsted County, MN residents with DM free of heart failure who had a subsequent measurement of diastolic function using tissue Doppler echocardiography were identified. We identified a validated group of 486 patients with incident diabetes mellitus with a subsequent tissue Doppler echocardiographic assessment of diastolic function. There was a significant association between the E/e' ratio and the time from diabetes diagnosis to echocardiogram using simple linear regression; for every 1 year after the onset of diabetes, the E/e' increased by 0.23 (95% CI=0.16–0.30; p=0.007) after adjustment for age, gender, body mass index, prior coronary disease, prior hypertension and ejection fraction. A duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction (E/e' > 15) in multivariable logistic regression modeling after adjustment for age, gender, body mass index, prior coronary disease, prior hypertension and ejection fraction (OR=1.91, 95% CI=1.19–3.07; p=0.007). There were 48 deaths in the validated cohort (6 cardiac deaths). In multivariable proportional hazard modeling, the E/e' ratio was predictive of all-cause mortality after adjustment for age, gender, coronary disease, hypertension, ejection fraction, left atrial volume and time from DM to echo (risk ratio= 1.11, 95% CI=1.03–1.20; p=0.005). In conclusion, a duration of DM of ≥ 4 years is correlated with significant LV diastolic dysfunction. LV diastolic dysfunction is predictive of all-cause mortality in patients with DM independent of hypertension and coronary disease.

INTRODUCTION

The objectives of our study were first to determine if left ventricular (LV) diastolic dysfunction worsens with duration of diabetes mellitus (DM) and secondly to quantify the severity of diastolic dysfunction as a function of the duration of DM. We hypothesize that the severity of diastolic dysfunction as assessed by the E/e' ratio worsens with the duration of DM.

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METHODS

After Mayo and Olmsted Medical Center institutional review board approval, all consecutive patients with diabetes in Olmsted County, MN from 1996 to 2007 were identified using an electronic coding system maintained for record identification at Mayo Clinic that closely approximates the International Classification of Disease-9th Revision (ICD-9) code 250 (12,014 patients). We excluded all patients without a tissue Doppler assessment of diastolic function subsequent to the date of diabetes diagnosis (8,772 patients), those with any diagnosis of congestive heart failure (CHF) (1,524 patients), those without information on ejection fraction (84 patients) and those with severe mitral or aortic regurgitation (1 patient). We also excluded patients with a clinic registration date of less than one year prior to the diagnosis of diabetes (1,045 patients) in an attempt to remove patients who may have moved to Olmsted County with a prior history of diabetes which would make identification of incident diabetes difficult. Overall, 588 patients were identified as shown in Figure 1.

To confirm the diagnosis of incident diabetes in this resulting cohort of patients, 63 randomly selected patient records were reviewed. Criteria for diabetes included a physician diagnosis of diabetes mellitus, if unavailable diabetes was defined as a fasting glucose $>126\text{mg/dL}$ on 2 occasions, a random glucose value $>200\text{mg/dL}$ or a glycosylated hemoglobin $>7\%$. To confirm the incident date of diabetes diagnosis, the reviewed records were evaluated to determine if diabetes criteria were met within 90 days of the diagnosis date listed by the electronic coding system. The outcome of this review was examined in aggregate, as well as according to time, age, and sex by using logistic regression. The resulting model was used to construct the validated diabetes mellitus incidence cohort using the criteria above.

Mortality information was collected in June 2007. Co-morbid diseases were ascertained using ICD-9 codes. Ejection fraction was evaluated by a modification of the method of Quinones et al.¹ Doppler echocardiography was performed to determine the early mitral velocity (E) and tissue Doppler evaluation was performed of the medial mitral annulus velocity (e') as previously described.²

Patient characteristics are summarized as mean and standard deviation or number and percentage, as appropriate. Multivariable linear regression was used to determine the association between the duration of diabetes mellitus and the E/ e' ratio. The Cox proportional hazard model with death as the outcome was used to determine the predictive value of the E/ e' ; the time from the echocardiogram to death or latest follow-up was used in this analysis. Using a receiver operator characteristics (ROC) curve, we determined the optimal cut-point for duration of diabetes in predicting LV diastolic dysfunction. C-statistics were used to assess how clearly duration of diabetes was associated with LV diastolic dysfunction. Finally, multivariable logistic regression modeling was used to assess the association between duration of DM and LV diastolic dysfunction. Left ventricular mass index was not used in the analysis because this value is calculated using the body mass index variable and is associated with this value.

All analyses were replicated in 1000 random samples to ensure that results were robust. Analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC)

RESULTS

Overall, 588 patients were identified. Of the 63 charts sampled, 62 (98%) met criteria for the diagnosis of diabetes; of these, 51 (82%) met criteria for the diagnosis of diabetes mellitus within 90 days of the diagnosis date listed by the electronic coding system. Based on this validation rate for the sample group adjusted for age, sex and date of incident diabetes, a cohort

of 486 patients with a validated incident diagnosis of diabetes mellitus in Olmsted County, MN was assembled.

The baseline characteristics are shown in Table 1. The indications for the echocardiograms included paroxysmal atrial fibrillation in 22 (4%), arrhythmia in 22 (4%), coronary disease in 63 (13%), chest pain in 34 (7%), dyspnea in 43 (9%), edema in 8 (2%), hypertension in 16 (3%), assessment of left ventricular function in 64 (13%), murmur in 96 (19%), syncope in 14 (3%), assessment of valvular disease or suspected valvular disease in 24 (5%) and non-specified in 90 (18%).

Among the validated cohort, there was a significant association between the E/e' ratio and the time from diabetes diagnosis to echocardiogram using simple linear regression; for every 1 year after the onset of diabetes, the E/e' increased by 0.23 (95% CI=0.16–0.30; $p=0.007$) after adjustment for age, gender, body mass index, prior coronary disease, prior hypertension and ejection fraction. Furthermore, the left atrial volume increased by 1.3 cm³ for every 1 year increase in the duration of diabetes after adjustment for age, gender, body mass index and E/e' ratio ($p=0.003$). Using the E/A ratio to define diastolic dysfunction (defined as an E/A ratio <0.75 or >1.5); increasing duration of diabetes was associated with an odds ratio of diastolic dysfunction of 0.96; this association was not significant ($p=0.2$).

A total of 104 patients (21%) had E/e' ratio ≥ 15 , using this value as the definition for LV diastolic dysfunction, we used receiver operating characteristic analysis to assess how clearly the duration of DM was associated with LV diastolic dysfunction. Using the ROC curve, we determined that the optimal cut-point for duration of diabetes was ≥ 4 years in predicting LV diastolic dysfunction (area under the curve=0.58). Indeed, a duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction in multivariable logistic regression modeling after adjustment for age, gender, body mass index, prior coronary disease, prior hypertension and ejection fraction, (OR=1.91, 95% CI=1.19–3.07; $p=0.007$) (Table 2).

There were 48 deaths in the validated cohort (6 cardiac deaths). In multivariable proportional hazard modeling, the E/e' ratio was predictive of all-cause mortality after adjustment for age, gender, coronary disease, hypertension, ejection fraction, left atrial volume and time from DM to echo (risk ratio= 1.11, 95% CI=1.03–1.20; $p=0.005$). We found that an E/e' ≥ 15 was a significant predictor of all cause mortality in multivariable proportional hazard modeling after adjustments for age, gender, coronary disease, hypertension, ejection fraction, left atrial volume and time from DM to echo (RR=3.74, 95% CI=1.77–7.87; $p<0.001$) (Figure 2).

Results from replication of this analysis in 1000 random samples were similar and confirmed the results from the validation sample.

DISCUSSION

The major findings of our study include: 1) demonstrating that there is an association between duration of DM and LV diastolic dysfunction, 2) demonstrating that a duration of DM ≥ 4 years has the strongest association with LV diastolic dysfunction and 3) showing that in DM, an increasing E/e' ratio is associated with all-cause mortality which, to our knowledge, is the first study to measure the prognostic power of the E/e' ratio in a population of diabetic patients without clinical heart failure.

The E/e' ratio has been well correlated with LV filling pressure.³ Our formal evaluation of the duration of DM and the association with LV diastolic dysfunction as determined by the E/e' ratio, confirms and extends previous studies which demonstrated that DM has independent adverse effects on diastolic function and that the duration of DM may be associated with worsening LV diastolic dysfunction.^{4–10} Our results show that there is a direct correlation

between the duration of DM and LV diastolic dysfunction and that significant LV diastolic dysfunction occurs 4 years after the onset of DM independent of coronary disease or hypertension. Perhaps a focused screening of diabetic patients with disease duration longer than four years could improve the sensitivity of previously proposed methods for cardiomyopathy screening among diabetics.^{11–13}

Given the association between duration of DM and LV diastolic dysfunction after adjustment for coronary disease and hypertension, we speculate that the etiology of LV diastolic dysfunction must in part be due to DM itself or to consequences of DM. Indeed, this is consistent with data from the Strong Heart Study which suggested that DM has independent adverse cardiac effects that may contribute to cardiovascular events in diabetic individuals.⁵ Certainly, the association between duration of DM and degree of LV diastolic dysfunction not only suggests that microvascular disease may play a part in the development of decreased left ventricular compliance as described previously,^{14,15} but also alludes to the role of autonomic deregulation and cardiac fibrosis in the etiology of LV diastolic dysfunction, both well known consequences of DM.

Our study has several limitations. First, the study was performed retrospectively and is subject to the inherent biases of the retrospective study design. The Olmsted population is predominantly white¹⁶ and therefore, may not be representative of other patient populations. Lastly, subjects were not recruited randomly from the community, but were clinically referred by their physicians for echocardiography which may decrease the generalizability of the results.

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16. Bureau USC. Census Data for Olmsted County. MN United States Census. 2000

Figure 1.
Patient Selection

Figure 2.
Mortality Stratified by Diastolic Dysfunction

Table 1

Baseline Characteristics

Characteristics	All Patients (N=588)	Validation Sample (N=486)
Age (years)	59 (13)	58 (13)
Male	283 (48%)	260 (54%)
* Body Mass Index (kg/m ²)	32 (8)	32 (7)
Coronary Disease	139 (24%)	113 (23%)
Hypertension	475 (81%)	387 (80%)
Ejection Fraction (%)	62 (8)	62(8)
Mitral E/e' Ratio	12 (5)	12 (4)
** Left Atrial Volume (cm ³)	63 (27)	63 (27)
[†] Deceleration Time (seconds)	216 (49)	213 (48)
[‡] Left Ventricular Mass Index (g/m ²)	94 (22)	94 (22)

For each variable the mean (SD) or the total number (%) are displayed

* Body mass index was available in 581 of all patients and 481 of the validation sample

** Left atrial volume was available in 561 of all patients and 464 of the validation sample

[†] Deceleration time was available in 546 of all patients and 452 of the validation sample

[‡] Left ventricular mass index was available in 502 of all 415 of patients and the validation sample

Table 2

The Associations with Diastolic Dysfunction

Characteristics	Univariate Model		Multivariate Modeling	
	OR (95% CI)	P-value	OR (95% CI)	P-value
DM Duration $\geq$ 4 years	1.62 (1.05, 2.50)	0.03	1.91 (1.19, 3.07)	0.007
Age	1.06 (1.04, 1.08)	<0.001	1.07 (1.05, 1.09)	<0.001
Female Gender	1.53 (0.99, 2.37)	0.06	1.43 (0.89, 2.31)	0.14
Body Mass Index	1.00 (0.98, 1.04)	0.64	1.04 (1.00, 1.08)	0.03
Coronary Disease	1.75 (1.08, 2.82)	0.57	1.59 (0.94, 2.67)	0.63
Hypertension	1.53 (0.87, 2.83)	0.14	0.81 (0.42, 1.58)	0.52
Ejection Fraction *	1.10 (0.84, 1.48)	0.48	1.02 (0.76, 1.40)	0.87

* OR reported per 10 unit change in parameter