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THE PREVALENCE OF DIABETIC CARDIOMYOPATHY-A POPULATION BASED PROSPECTIVE OBSERVATIONAL STUDY AT TERTIARY CARE HOSPITAL FROM NORTH INDIA

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ABSTRACT

Diabetic cardiomyopathy is relatively common in the community. In the current study, we report that the community population prevalence of diabetic cardiomyopathy is 1.1% and that the morbidity and mortality of patients with the DCM is high, approaching 31% over a decade.[1,2,3,4,5,13] Furthermore, diabetes is independently associated with left ventricular dysfunction. Diabetic cardiomyopathy is relatively common in the community. In the current study, we report that the community population prevalence of diabetic cardiomyopathy is 1.1% and that the morbidity and mortality of patients with the DCM is high, approaching 31% over a decade. Furthermore, diabetes is independently associated with left ventricular dysfunction.[6,7,8,9,10.11.12]

KEYWORD: Cardiac Arrhythmia, Diabetes, Cardiomyopathy.

INTRODUCTION

There is growing recognition of a primary myocardial disease process or "diabetic cardiomyopathy" that predisposes diabetic patients to ventricular dysfunction in the absence of clinically significant coronary, valvular or hypertensive disease Diabetes is associated with an increased risk of cardiovascular complications, including hypertension, coronary artery disease and the development of heart failure (HF)[1,2] Diabetic cardiomyopathy (DCM), defined as either systolic or diastolic left ventricular dysfunction in otherwise healthy diabetic persons, is poorly understood from an epidemiologic and natural history standpoint.

First proposed by Rubler et al. in 1972 based on post-mortem findings, diabetic cardiomyopathy is thought to be secondary to underlying hyperglycemia resulting in a multitude of adverse downstream effects, including impaired myocyte calcium handling, increased oxidative stress, renin-angiotensin-aldosterone activation, microangiopathy and myocardial fibrosis.[12,13,14] Prior studies have attempted to characterize the prevalence of ventricular dysfunction among asymptomatic diabetic patients, but these were non-population-based studies or exhibited a referral bias of patients undergoing cardiovascular testing for clinical indication[15,16] In 2010, From and Chen demonstrated that pre-clinical diastolic dysfunction in diabetic patients was associated with an increased incidence of heart failure and higher mortality[17,18] However, despite adjustment for co-morbidities, a large proportion of patients in the study had pre-existing hypertension and coronary artery disease. Thus, the true population prevalence and natural progression of diabetic cardiomyopathy is unknown.

In this study, we sought to determine a population-based prevalence of diabetic cardiomyopathy. Additionally, we planned to characterize the risk of systolic and/or diastolic left ventricular (LV) dysfunction in diabetic patients and assess the rates of long term survival and development of heart failure in patients with diabetic cardiomyopathy.

METHOD

Sample of residents who were at least 45 years old as of Apr 2008[17,18,19] Participants were enrolled and studied during a 9-year period, ending Apr 2017. Of the 2102 eligible residents invited, 1021(47%) participated. An analysis of the medical records of 250 randomly selected residents who did not participate in the study revealed similar age and sex distribution to that observed in the participants and a similar prevalence of hypertension, coronary artery disease, previous myocardial infarction, diabetes, previous cardiovascular hospitalization, and congestive heart failure[18] Each participant underwent a focused physical examination that included measurement

of blood pressure, height, weight and BMI calculation (kg/m2). Community medical records for each participant were reviewed by trained nurse abstractors to record a history of hypertension or myocardial infarction using established criteria at the time of presentation.[20,21] In addition, historical clinical diagnoses of coronary artery disease, valvular disease, congenital heart disease, and diabetes mellitus were recorded. Each participant's medical records were also reviewed to determine if any diagnosis of heart failure had been made. If so, each medical encounter was reviewed to determine whether the documented clinical information fulfilled Framingham criteria.[25] Participants with either systolic or diastolic dysfunction, but no formal heart failure diagnosis, were considered to have preclinical ventricular dysfunction. Such designation did not imply progression to symptomatic or clinical heart failure All subjects underwent echocardiography, performed using standard methods that have been previously described and validate.[18,19,20] All echocardiograms were performed by 1 of 3 registered diagnostic cardiac sonographers and interpreted by a single echocardiologist .Two dimensional and color Doppler imaging was performed to screen valvular heart disease. Left ventricular ejection fraction measured by visual estimate was used for analysis. As previously described and validated, left ventricular diastolic dysfunction was assessed by pulsed-wave Doppler examination of mitral inflow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus. Diastolic dysfunction was categorized according to the progression of diastolic disease: normal ($0.75<E/A<1.5$ and $E/e'<10$); mild (defined as impaired relaxation without increased filling pressures, $E/A\leq0.75$ and $E/e'<10$); moderate (defined as impaired relaxation associated with moderately elevated filling pressures or pseudonormal filling, $0.75<E/A<1.5$ and $E/e'\geq10$); and severe (defined as advanced reduction in compliance or reversible or fixed restrictive filling, $E/A>1.5$ and $E/e'\geq10$).[18,23.24] Participants were required to have two Doppler criteria consistent with moderate or severe diastolic dysfunction to be so classified. Subjects with one criterion for moderate or severe diastolic dysfunction or those whose parameters were borderline but not definitive for diastolic dysfunction were classified as indeterminate. In this study, left ventricular dysfunction is defined as an ejection fraction of <50% and/or moderate to severe diastolic dysfunction.[28,29.30] Contrary to previous analyses utilizing this Olmsted County cohort, only diabetic patients with both systolic and diastolic ventricular assessments were included in this study.

In keeping with its previously described definitions, diabetic cardiomyopathy was diagnosed in patients with all of the following criteria: 1) the presence of diabetes mellitus[18] documented systolic or at least moderate diastolic dysfunction after the diagnosis of diabetes mellitus, 3) no history of clinical heart failure, 4) no history of coronary disease with or without a previous

angiogram or stress test, 5) no history of hypertension, 6) no history of significant valvular disease and 7) no history of congenital heart disease.

Statistical Analysis

Categorical variables were summarized as percentages and continuous variables as mean ± standard deviation. Comparison between groups was based on a two sample t-test for continuous variables and Pearson's chi-square test for categorical variables. The major endpoints were mortality and development of heart failure. Kaplan-Meier analysis was performed to estimate probabilities of events and the probabilities were compared between groups using the Log rank test. Healthy controls without diabetes, left ventricular dysfunction, hypertension or coronary disease were selected from the Olmsted County population for mortality comparison. Univariable and multivariable associations of clinical and echocardiographic variables with each endpoint were assessed with Cox's proportional hazard modeling. Hypothesized trends in outcomes were tested using the following scoring within Cox's models: 1= subjects with diabetes and no LV dysfunction (D0CM), 2= subjects with diabetic cardiomyopathy (DCM), 3= subjects with diabetes and hypertension or coronary artery disease and any LV dysfunction (D1CM). The presence of LV dysfunction was also assessed using univariable and multivariable logistic regression modeling.

RESULT

Diabetic cardiomyopathy (DCM) was diagnosed in 6 of the total 510 subjects, corresponding to a community population prevalence of 1.1% (95% CI 0.7% to 1.6%). However, among the 33 subjects with diabetes, 16.9% met the diagnostic criteria for diabetic cardiomyopathy. 83% of the subjects with DCM had LV diastolic dysfunction and preserved ejection fraction. The prevalence of LV diastolic dysfunction among diabetic patients in the community was 54.4%, while the prevalence of LV systolic dysfunction was 7.3%. Using multivariable logistic regression analysis, the presence of diabetes was associated with a 1.9 fold increase in risk of any left ventricular dysfunction (HR=1.87; 95% CI (1.32, 2.64), p=0.0004), a 1.7 fold increase in risk of diastolic dysfunction (HR=1.67; 95% CI (1.19, 2.34), p=0.0031), and a 2.2 fold increase in risk of systolic dysfunction (HR=2.23; 95% CI (1.27, 3.91), p=0.0051), after adjustment for age and sex.

Among subjects with diabetic cardiomyopathy, the cumulative probability of death was 18% (95% CI (0.3, 32.7)), the cumulative probability of the development of heart failure was 22% (95% CI (2.9, 37.3)), and of the development of death or heart failure was 31% (95% CI (8.9, 47.3)) at 9 years (**Table 1**).

Table 1: Cumulative Probability of Death and Heart Failure in Diabetic Cardiomyopathy.

Variable	Diabetic Cardiomyopathy (n=12)	95% Confidence Interval
Death		
• 3 years	0%	(0%, 0%)
• 6 years	4%	(0%, 12.3%)
• 9 years	18%	(0.3%, 32.7%)
Development of HF		
• 3 years	9%	(0%, 19.5%)
• 6 years	17%	(0.4%, 31.5%)
• 9 years	22%	(2.9%, 37.3%)
Death or HF		
• 3 years	9%	(0%, 19.5%)
• 6 years	17%	(0.4%, 31.5%)
• 9 years	31%	(8.9%, 47.3%)

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HF=heart failure

A secondary exploratory analysis of long term outcomes was performed comparing subjects with diabetes and no LV dysfunction (D0CM), subjects with diabetic cardiomyopathy (DCM) and subjects with diabetes and hypertension or coronary artery disease and any LV dysfunction (D1CM).

When comparing baseline characteristics among the three groups, subjects with DCM and D1CM were older than subjects with D0CM. Subjects with D1CM had a higher BMI compared to DCM and D0CM. There was no significant difference in left ventricular ejection fraction among the three groups, and only 17% of subjects with DCM had a left ventricular ejection fraction <50%. Left ventricular mass index was highest in D1CM. There was no significant difference in creatinine measurements among the three groups **(Table 2).**

Table 2: General Characteristics.

Variable	Diabetic with No LV Dysfunction [D0CM] (N=26)	Diabetic Cardiomyopathy [DCM] (N=12)	Diabetic with CAD or HTN and Any LV Dysfunction [D1CM] (N=30)
Age (years)	62.6 ± 9.1	68.5 ± 10.6^{b}	67.6 ± 9.2^{c}
Gender (Male), No. (%)	15 (60%)	8 (74%)	17(54%)
BMI (kg/m2)	29.9 ± 6.1	29.2 ± 4.3	32.3 ± 5.6^{ac}
Hyperlipidemia, No. (%)	9(36%)	2 (18%)	12 (39%)
Smoking, No. (%)	14(54%)	8 (70%)	18 (57%)
LV Ejection Fraction (%)	64.2 ± 5.2	61.7 ± 8.8	62.1 ± 8.9
Reduced LVEF (<=50%), No. (%).	0 (0%)	$2 (17\%)^{b}$	$3(10\%)^{c}$
E/A Ratio	1.0 ± 0.2	0.9 ± 0.4^{b}	0.9 ± 0.3^{c}
E/e' Ratio	7.4 ± 1.3	10.5 ± 2.8^{b}	10.2 ± 2.4^{c}
LV Mass Index (g/m2)	94.6 ± 24.0	105.9 ± 19.9	108.0 ± 29.1^{c}
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.2

Values are mean ± SD or n (%).
[a] $p<0.05$ (DCM vs. D1CM);
[b] $p<0.05$ (DCM vs. DOCM);
[c] $p<0.05$ (D1CM vs. DOCM)

E=passive transmitral left ventricular inflow velocity; A=late transmitral left ventricular inflow during left atrial contraction; e'=tissue Doppler imaging velocity of the medial mitral annulus during passive filling.

B-type natriuretic peptide (BNP) levels were highest in subjects with D1CM. There was no statistically significant difference in BNP levels in subjects with DCM compared to subjects with D0CM (Figure 1).
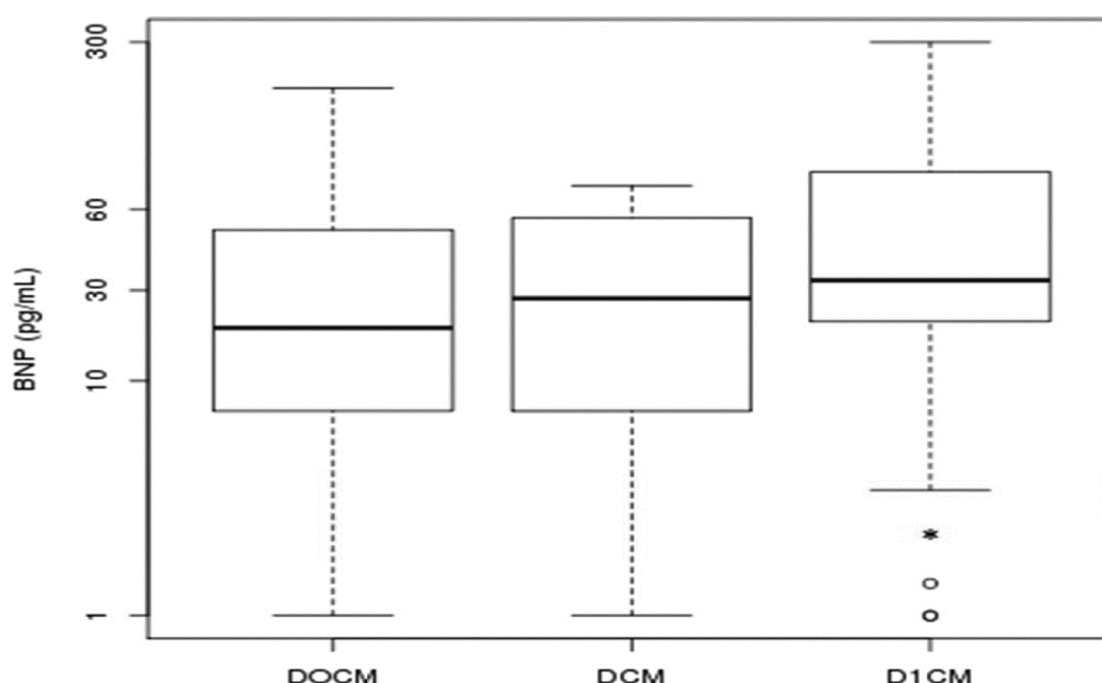
Figure 1: Comparison of B-type Natriuretic Peptide Levels.

The top of box is the 25% percentile, the middle bar in the box is the median and the bottom of box is the 75% percentile. The end lines outside the box are the statistical range. The open circles are the statistical outliers. The asterisk represents a statistically significant difference (*p*<0.05) when comparing D1CM to DOCMUsing Kaplan-Meier analysis of survival among the three groups compared to healthy controls, there was a statistically significant increased risk of mortality in subjects with DCM compared to healthy controls and a trend toward increased risk after adjustment for age and sex (HR 1.25; 95% CI (0.42, 3.68), *p*=0.1377, adjusted for age/sex). There was a statistically significant increased risk of mortality in subjects with D1CM compared to healthy controls, before and after adjustment for age and sex (HR 2.09; 95% CI (1.05, 4.14), *p*=0.0012, adjusted for age/sex). There was no statistically significant difference in survival when comparing subjects with D0CM and healthy controls (HR 1.12; 95% CI (0.39, 3.18), *p*=0.9636, adjusted for age/sex) (Figure 2).
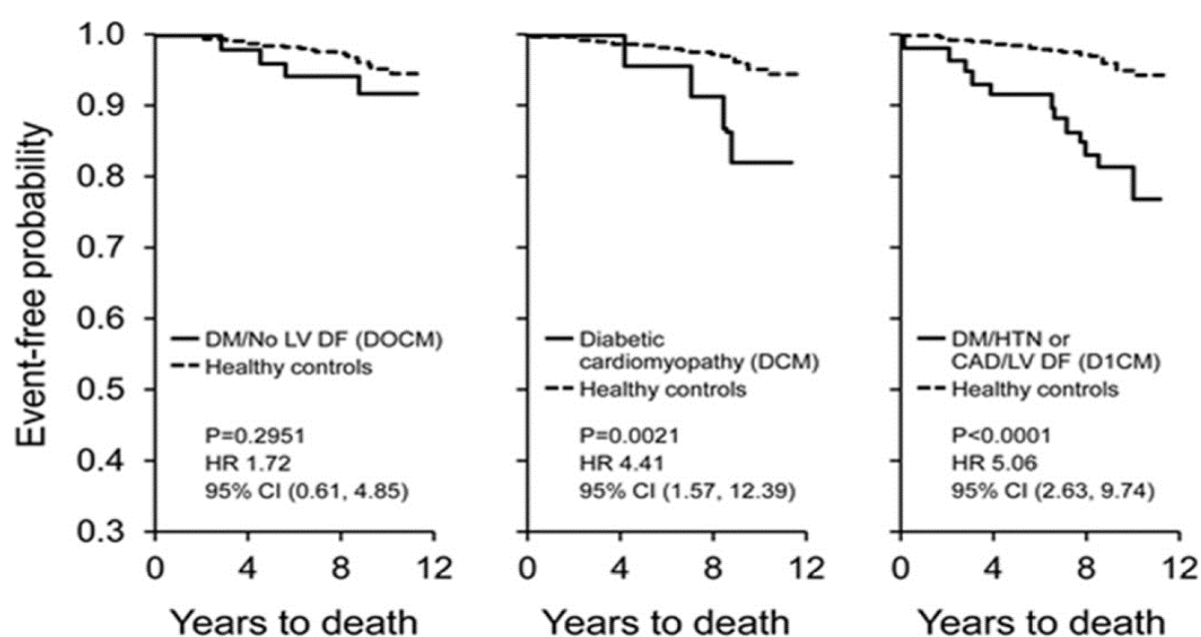

Figure 2: Analysis of Survival.
The unadjusted P value is for comparison to the healthy controls.

The probability of developing heart failure using Kaplan-Meier analysis was highest in subjects with D1CM, followed by subjects with DCM and lastly, D0CM (HR 1.60; 95% CI (1.03, 2.48), *p*=0.0364 for trend, adjusted for age/sex) (Figure 3). Similarly, the probability for the development of death or heart failure, based on Kaplan-Meier analysis, was highest in subjects with D1CM, followed by subjects with DCM, then D0CM; there remained a strong trend after adjustment for age and sex (HR 1.41; 95% CI (0.97, 2.07), *p*=0.0724 for trend, adjusted for age/sex) **(Figure 4)**.
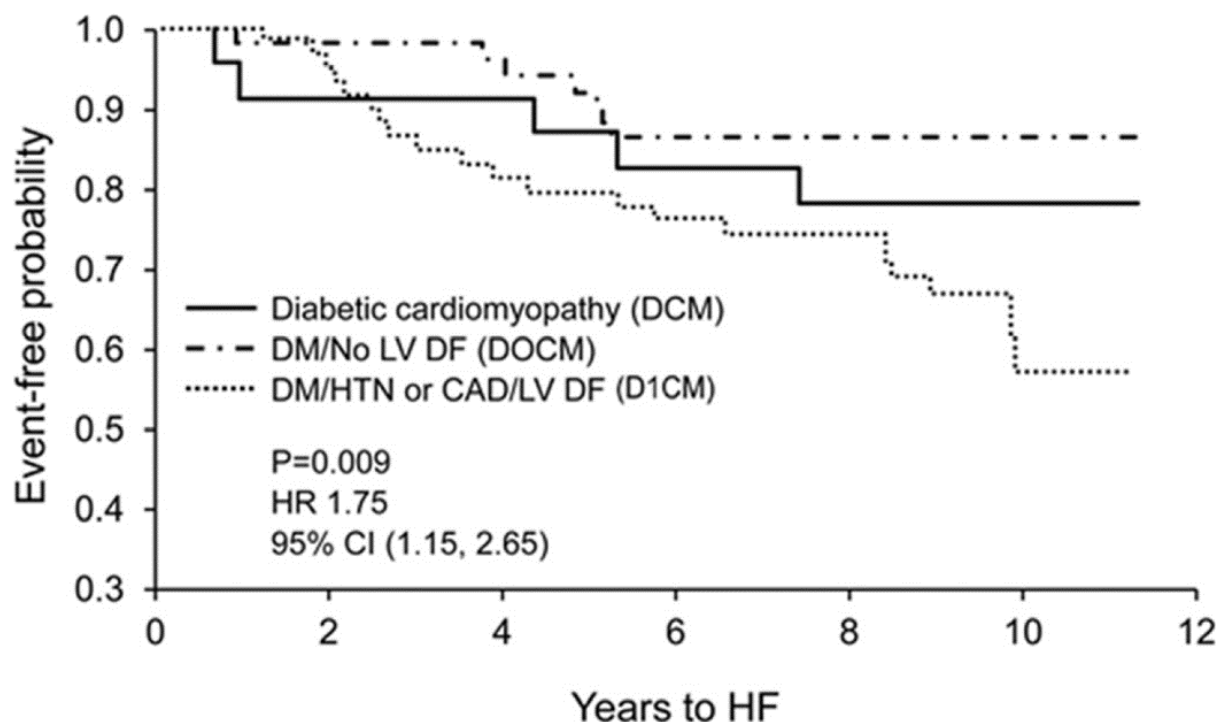

Figure 3: Analysis of Development **of Heart Failure.**
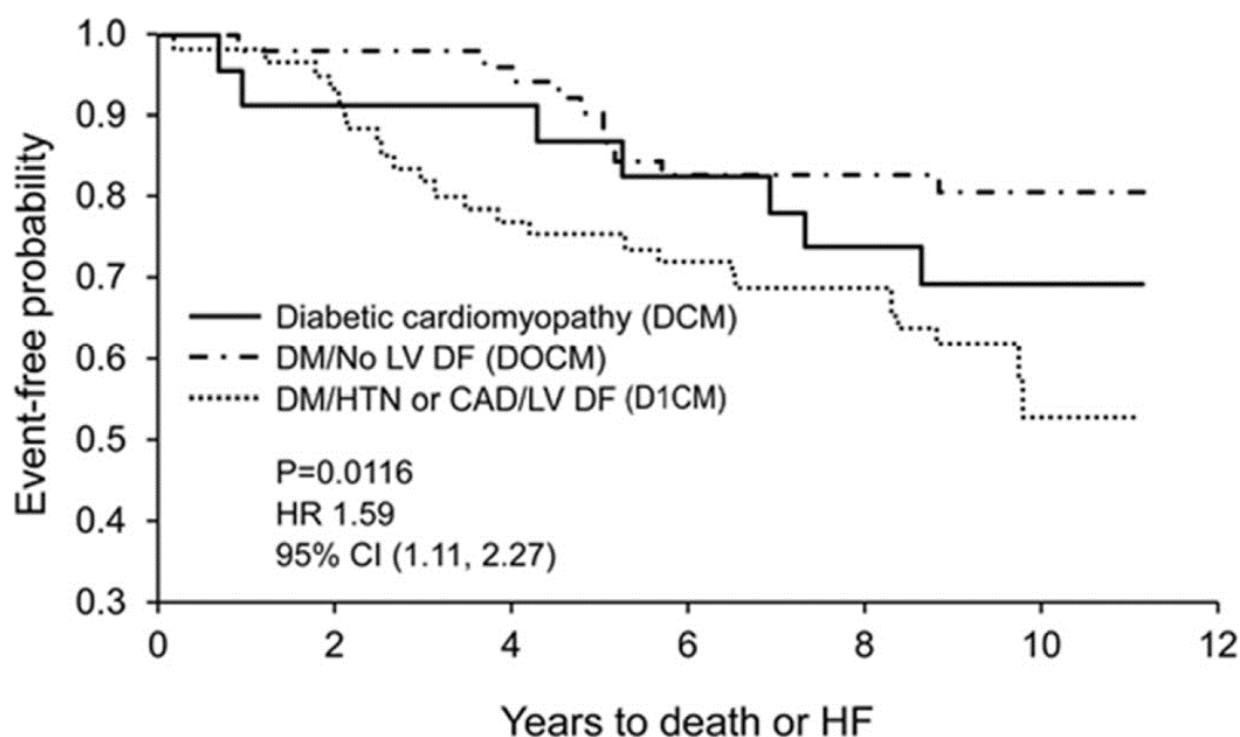The unadjusted P value is for trend.

Figure 4: Kaplan-Meier Analysis of Survival and Development of Heart Failure.
The unadjusted P value is for trend.

DISCUSSION

This study is one of the few to determine a population-based prevalence of diabetic cardiomyopathy as defined by left ventricular dysfunction in diabetic patients in the absence of coronary, valvular or hypertensive disease. Using data from prospectively enrolled cohort from study population, we determined the community population prevalence of diabetic cardiomyopathy to be 1.1%. In addition, the prevalence of DCM in diabetic patients is 16.9% and the prevalence of diastolic dysfunction in diabetic patients is 54%. We estimated that the presence of diabetes was associated with an increased risk of systolic, diastolic and any left ventricular dysfunction, even after adjustment for age and gender. Lastly, we demonstrated that diabetic cardiomyopathy is associated with a relatively high cumulative probability of the development of heart failure and death.The results of this study add to the growing evidence in support of a primary myocardial disease process predisposing diabetic patients to pre-clinical ventricular dysfunction, heart failure, and increased mortality. Several epidemiologic studies have confirmed that people with diabetes are more likely to develop heart failure compared with people without diabetes: a) The Framingham Heart Study investigators demonstrated that diabetes was an independent risk factor for heart failure[25]; b) The Cardiovascular Health Study reported a 2-fold increase in risk of development of heart failure associated with diabetes[26]; c) The Strong Heart Study also reported that diabetes is an independent risk factor for heart failure[7]. In a population-based cohort of 602 subjects, the authors showed a 1.5-fold higher risk of heart failure in patients with diabetes after adjustment for multiple cofactors. Importantly, the survival of patients with diabetes and heart failure was also reduced relative to those without diabetes[27].Despite several epidemiological studies demonstrating an increased risk of development of heart failure in diabetic patients, the prevalence and natural history of diabetic cardiomyopathy remains poorly defined. Recent studies have attempted to non-invasively detect and define the cardiovascular changes of diabetic cardiomyopathy with aggressive adjustment for multiple co-morbid diseases in biased selections of patients. The Strong Heart Study examined the left ventricular systolic and diastolic function of diabetic patients as compared to non-diabetic patients, but did not isolate groups of patients with or without confounding hypertension or coronary disease at enrollment as in our cohort. We previously reported that pre-clinical diastolic dysfunction in diabetic patients was associated with an increased incidence of heart failure and higher mortality[27] However, despite adjustment for co-morbidities, a large proportion of patients in the study had pre-existing hypertension and coronary artery disease. In the current study, we report that the community population prevalence of diabetic cardiomyopathy is 1.1% and that the morbidity and mortality of patients with the DCM is high, approaching 31% over a decade.Prior data suggests that LV diastolic dysfunction may precede LV systolic dysfunction in diabetic patients, which may explain why 83% of the patients with DCM in our cohort have diastolic dysfunction while only 17% have systolic dysfunction [28]. Previous studies of small or biased groups of patients have estimated the prevalence of diastolic dysfunction in diabetic patients to vary from 28% to 75%[29.30.31.32]. In the current study, we report that the prevalence of diastolic dysfunction among community population-based diabetic patients is 54%.

Recognizing that the number of patients with diabetic cardiomyopathy was modest, we still set out to perform an exploratory analysis of long term outcomes, comparing subjects with diabetic cardiomyopathy (DCM) to subjects with diabetes and LV dysfunction and co-morbidities (D1CM) and to subjects with diabetes and no LV dysfunction (D0CM). Through these analyses, we discovered that the cumulative probability of the development of heart failure and death is highest in diabetic patients with LV dysfunction and co-morbidities, followed by subjects with diabetic cardiomyopathy, then diabetic patients with no LV dysfunction. However, these secondary analyses of long term outcomes need to be confirmed by larger, prospective cohort study

CONCLUSION

Diabetic cardiomyopathy is relatively common in the community. In the current study, we report that the community population prevalence of diabetic cardiomyopathy is 1.1% and that the morbidity and mortality of patients with the DCM is high, approaching 31% over a decade. Furthermore, diabetes is independently associated with left ventricular dysfunction.

Abbreviations

HF	heart failure
DCM	diabetic cardiomyopathy
LV	left ventricular
E	passive transmitral left ventricular inflow velocity
A	late transmitral left ventricular inflow during left atrial contraction
e'	tissue Doppler imaging velocity of the medial mitral annulus during passive filling
D0CM	subjects with diabetes and no left ventricular dysfunction
D1CM	subjects with diabetes and hypertension or coronary artery disease and any left ventricular dysfunction
	HR-hazard ratio

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