Republic of Iraq

Ministry of Higher Education and Scientific Research

Thi-qar University

College Of Medicine

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Left Ventricular Diastolic Dysfunction In Normotensive Type II Diabetic Patients In Thi-Qar At 2019

This study was submitted in partial fulfillment of the requirements for the

M.B.Ch.B

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ACKNOWLEDGEMENTS

Prima facie, we are grateful to God for the good health and wellbeing that were necessary to complete this study.

We would like to show our gratitude to our supervisor for sharing his pearls of wisdom with us during the course of this study.

We thank the members of community medicine department for assistance with methodology and for comments that greatly improved the manuscript.

We take this opportunity to express gratitude to all of the Department faculty members for their help and support .We thank our parents for the unceasing encouragement, support and attention.

❖ Contents

Abstract

Background: The prevalence of diabetes mellitus (DM) is increasing globally. Cardiovascular complications, such as left ventricular dysfunction is a major cause of death in patients with type II DM. Prior to the development of symptomatic heart failure, subclinical left ventricular dysfunction (systolic and diastolic) may exist for some time. Hypertension and age are recognized as important risk factors for left ventricular (LV) diastolic dysfunction. Some studies have shown that diabetes itself may also be an independent risk factor for LV diastolic dysfunction, although this is controversial.

Aim: The aim of this study was to determine the factors associated with LV diastolic dysfunction in patients with type 2 diabetes in the absence of hypertension or ischemic heart disease (IHD).

Methods: Participants in this study consisted of 25 type 2 diabetes patients (M : F = 15 : 10; mean age 51 [26 to 76] years; mean body mass index [BMI] 25.0 kg/m^2) without hypertension, heart disease, or renal disease. Individuals with history of ischemic heart disease were excluded. LV diastolic function was evaluated by echocardiographic studies.

Results: Five patients (20%) showed LV diastolic dysfunction on echocardiographic studies. Patients with LV diastolic dysfunction were older than those without diastolic dysfunction . After adjusting for age and sex, BMI was higher (26.6 vs. 24.6 kg/m^2) and diabetes duration was longer (9.65 vs. 4.71 years) in patients with LV diastolic dysfunction than in those without diastolic dysfunction. There were no differences in sex, smoking, blood pressure or diabetic microvascular complications between the LV diastolic dysfunction group and the normal diastolic function group. After adjusting for age, sex, and BMI, diabetes duration was found to be independently associated with LV diastolic dysfunction.

Conclusion: These results suggest that diabetes duration and obesity may be a risk factors for LV diastolic dysfunction in type 2 diabetic patients without hypertension or IHD.

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.[1]

The prevalence of diabetes mellitus (DM) is increasing globally. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 worldwide.[1]

The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014, it has been rising more rapidly in middle- and low-income countries.[1]

In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths globally, WHO estimates that diabetes was the seventh leading cause of death in 2016 worldwide.[1]

Heart failure is a common comorbidity and fatal complication of diabetes mellitus. The Framingham heart study demonstrated an increased risk of heart failure in patients with diabetes: a two-fold higher incidence in men and a five-fold higher incidence in women with diabetes compared with age-matched non-diabetic subjects.[2]

Many epidemiological studies have confirmed a significantly increased prevalence of cardiac dysfunction in diabetic patients, independent of the influence of relevant covariates.[3-4] Left ventricular (LV) diastolic dysfunction is thought be an early preclinical manifestation of heart failure.[5] The incidence of diastolic dysfunction in diabetic patients has been demonstrated to be 30-75% in recent studies.[6-8]

Diastolic dysfunction is defined as functional abnormalities that exist during LV relaxation and filling. When such abnormalities cause or contribute to the clinical syndrome of heart failure with a normal LV ejection fraction, it is appropriate to describe the condition as diastolic heart failure.[7] Some previous studies demonstrated LV diastolic dysfunction in normotensive patients with diabetes, and the existence of LV diastolic dysfunction in the absence of coronary artery disease and hypertension has been ascribed to diabetic cardiomyopathy. [6-8]

The proposed mechanisms of diabetic cardiomyopathy from animal studies are: i) excessive production of reactive oxygen species [9] , ii) over-activation of poly-(ADP-ribose) polymerase [10], iii) increased activity of protein kinase C[11], iv) dysfunctional calcium handling in cardiomyocytes [12], and v) enhanced activity of the renin-angiotensin-aldosterone system.[13]

Age, hypertension, and ischemic heart disease (IHD) are thought to be important risk factors for diastolic dysfunction in both patients with diabetes and non-diabetics.[14-16]

Although several studies have shown that poor glycemic control and longer duration of

diabetes may be associated with early diastolic dysfunction in type 2 diabetes [17-19], there have been few studies on the factors associated with LV diastolic dysfunction in type 2 diabetes without hypertension or IHD.

Considering the high prevalence and significant morbidity and mortality of heart failure in patients with type 2 diabetes, identification of risk factors for LV diastolic dysfunction and an index of early-stage diabetic cardiomyopathy are necessary to delay or prevent the onset of heart failure. Therefore, we sought to determine the risk factors associated with subclinical LV diastolic dysfunction in type 2 diabetic patients without hypertension or IHD.

METHODS

A cross sectional study was undertaken among type II diabetic patients attending AL-Hussein Teaching Hospital and diabetes center, between January 2019 and April 2019.

The study subjects consisted of 25 type 2 diabetic patients without hypertension or IHD (M : F = 15 : 10) mean age 51 [26-76] years; mean body mass index [BMI] 25.0 kg/m^2).

Inclusion criteria were: normal arterial blood pressure (< 130/85 mm Hg) without antihypertensive medication, no symptoms or signs of heart disease, no history of coronary heart disease or valvular heart disease, no evidence of severe medical illness including liver cirrhosis, end stage renal disease, or cancer. Patients were excluded from participation in the study if either of the following criteria applied diabetes diagnosed before the age of 26 or history of type 1 diabetes or diabetic ketoacidosis.

Echocardiographic study

The examination was performed while the patient was in a period of quiet respiration. Echocardiograms were analyzed by more than one examiner. Left ventricular systolic function was determined by estimation of left ventricular ejection fraction (LVEF), The normal range of LVEF was 65 %.

The following criteria were used for the diagnosis of LV diastolic dysfunction [20]: impaired relaxation pattern was defined as E/A ratio < 1.0, pseudonormal pattern as E/A ratio from 1.0 - 2.0 with E' < A' and E/E' ratio > 10; and restrictive pattern as E/A ratio > 2.0 and DT < 150 ms.

RESULTS

The median duration of diabetes for the study subjects was 5 years (range, 0 to 26).

Five patients (20%) showed diastolic dysfunction on echocardiographic study. The characteristics of the patients with and without prevalent diastolic dysfunction are compared in Table (1). Patients with LV diastolic dysfunction were older than patients without LV diastolic dysfunction (60.0 vs. 51.5 years). There was no difference in the sex ratio between the two

groups. After adjusting for age and sex, BMI was found to be higher (26.6 vs. 24.6 kg/m$^{2)}$and diabetes duration was found to be longer (9.65 vs. 4.71 year) in patients with LV diastolic dysfunction than in those without LV diastolic dysfunction.

There were no differences in smoking, blood pressure or diabetic microvascular complications between the LV diastolic dysfunction group and the normal LV diastolic function group.

Table 1. Age, sex and age and sex-adjusted characteristics according to the presence of diastolic dysfunction in type 2 diabetic patients without hypertension

	Normal left ventricular diastolic function (*n* = 20)	left ventricular diastolic dysfunction (*n* = 5)	***P* value**
Age, yr	**51.2**	60.0	**<0.01**
Men/Total	**12/20**	3/5	**0.52**
BMI, kg/m^2	**24.6**	26.6	**0.01**
Current smoking, %	**25**	20	**0.74**
Duration of diabetes, yrs.	**4.71**	9.65	**<0.01**
Diabetic retinopathy, %	**10**	20	**0.15**
Diabetic neuropathy, %	**8**	**20**	**0.13**

Echocardiographic parameters

No subject had LV systolic dysfunction and no differences in LVEF were found between the LV diastolic dysfunction group and the normal LV diastolic function group .The E/ A ratio was lower in patients with LV diastolic dysfunction (0.70 vs. 1.07). There were no significant differrences in other parameters between the LV diastolic dysfunction group and the normal LV diastolic function group (Table 2)

Table 2. Echocardiographic parameters

	Normal left ventricular diastolic function	**Left ventricular diastolic dysfunction**	***P* value**
	(*n* = 20)	(*n* = 5)	
E/A ratio	**1.07**	0.70	**<0.001**
E/E' ratio	**8.5**	9.5	**0.25**
LVEF, %	**67.5**	**65.5**	**0.18**

Data are expressed as mean

E/A, the ratio of early and late left ventricular diastolic filling. E/E', the ratio of E and E' where E'the early diastolic velocity,LVEF, left ventricular ejection fraction.

Diabetes duration as an independent determinant for diastolic dysfunction

Logistic regression analysis for diastolic dysfunction with age, sex, BMI, and diabetes duration as covariates showed that diabetes duration and BMI were independent determinants (Table 3). When participants were classified into four groups based on the duration of diabetes (≤ 1, >1 and ≤ 5, > 5 and ≤ 10, > 10 years), the frequency of LV diastolic dysfunction increased with increasing duration of diabetes after adjusting for age, sex, and BMI(Fig. 1).

Table 3. Logistic regression analysis of diastolic dysfunction in type 2 diabetic patients without hypertension with age, sex, BMI, and diabetes duration as covariates

	Exp (B) (95% CI)	*P* value
Age	1.04 (0.96 to 1.12)	0.385
Female	0.57 (0.09 to 3.75)	0.558
BMI	2.03 (1.21 to 3.41)	0.008
DM duration	1.39 (1.12 to 1.72)	0.003

BMI, body mass index; Exp (B), exponentiation of the B coefficient; DM, diabetes mellitus; CI, confidence interval.

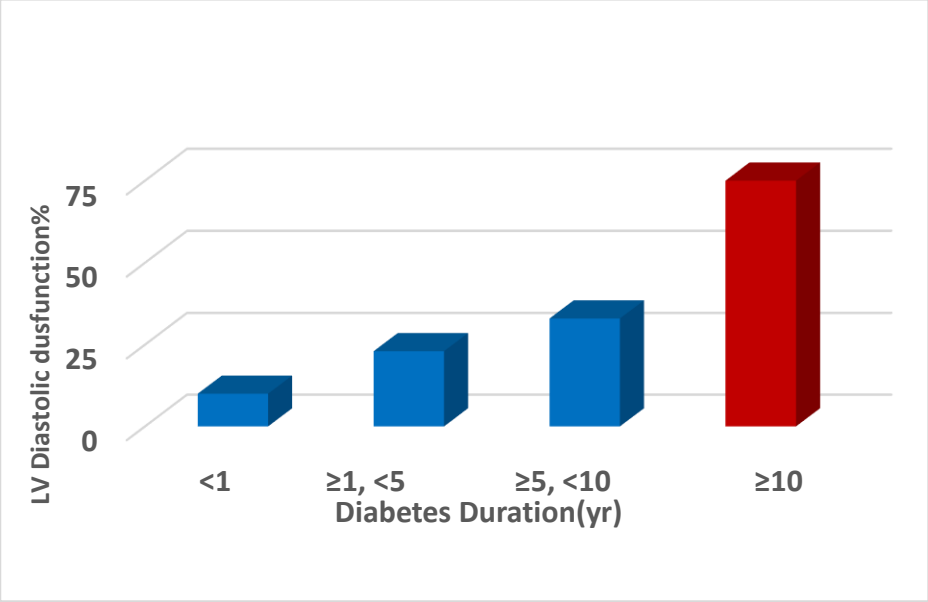

Fig. 1. Frequency of LV diastolic dysfunction according to diabetes duration in type 2 diabetic patients without hypertension.

DISCUSSION

In the present study, we found that duration of diabetes was associated with the presence of LV diastolic dysfunction in type 2 diabetic patients without hypertension or IHD. After adjusting for age, sex, and BMI, the frequency of LV diastolic dysfunction correlated positively with the duration of diabetes. Aging and duration of diabetes were related to LV diastolic dysfunction in normotensive type 2 diabetic patients in a previous study [14], which was also demonstrated in this study.

Several studies have suggested that hyperglycemia alters the metabolism of cardiac myocytes and could be the primary insult in the pathogenesis of diabetic cardiomyopathy.[21,22] Even in type 2 diabetic patients without cardiac involvement, uncontrolled hyperglycemia is known to provoke diastolic LV dysfunction.[16-17] Nichols et al. [23] demonstrated that a reduction in HbA1C coupled with a lower baseline HbA1C was predictive of a decreased incidence of heart failure in a multivariate model, emphasizing the importance of glycemic control for prevention of heart failure, In this study it was not possible to determine HbA1C level in most of patients due to logistic problems.

Some data have suggested that diabetic cardiomyopathy could be one of the microvascular complications of diabetes related to endothelial dysfunction. [21] Considering that duration of diabetes is the strongest predictor for diabetic microvascular complications, the strong association of duration of diabetes with LV diastolic dysfunction observed in this study is plausible, whereas diabetes duration was a significant determinant, suggesting that cumulative exposure to hyperglycemia may be important for the development of LV diastolic dysfunction.

Several studies have reported that obesity is associated with heart failure and ventricular dysfunction.[24], Another study found that reduced LV diastolic function was apparent in 24% of severely obese subjects, and that the risk was linearly associated with BMI.[24] From the results of this study, we suggest that obesity may be associated with LV diastolic dysfunction independent of other clinical parameters related to diastolic dysfunction in type 2 diabetic patients without hypertension or IHD.

In this study, the prevalence of LV diastolic dysfunction was lower than in other studies.[6-8] which could be because of the relatively short duration of diabetes, and our selection criteria excluding patients with hypertension or IHD. We did not find a significant association of diabetic microvascular complications such as retinopathy, nephropathy, and neuropathy with LV diastolic dysfunction, although frequencies of each microvascular complication tended to increase with the presence of LV diastolic dysfunction. This non-significant association may be explained by the earlier development of LV diastolic dysfunction compared with other microvascular complications [25], relatively well-controlled hyperglycemia, short duration of diabetes, and

selection criteria excluding patients with hypertension or IHD.

The first limitation of our study is that it was cross-sectional and unable to suggest a causal relationship.

The second limitation of this study: it was not possible to tell whether the increased incidence of LVDD is due to the duration of DM or due to aging itself. To answer this question, we need a controlled study (rather than cross sectional study design) to detrmine the exact role of diabetes as a precursor for LVDD. Other limitations were the uncertainty of ischemic heart disease and diabetes duration. Our exclusion of IHD based on history and presence of symptoms might have not ruled out IHD completely. Besides, the onset of type 2 diabetes is not always clear, and previous medical records related to initial diagnosis were not available, another prospective study for individuals with newly detected type 2 diabetes is needed to confirm the results of our study.

Despite the limitations of the study, our data showed that duration of diabetes and obesity could be a marker for LV diastolic dysfunction independent of other diastolic dysfunction-related variables in type 2 diabetic patients without hypertension or IHD.

REFERENCES

1) https://www.who.int/news-room/fact-sheets/detail/diabetes
2) Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA 1979;241:2035-8
3) Candido R, Srivastava P, Cooper ME, Burrell LM. Diabetes mellitus: a cardiovascular disease. Curr Opin Investig Drugs 2003;4:1088-93.
4) Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434-44.
5) Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, Ostergren J, McKelvie RS; Investigators of the CHARM Echo- cardiographic Substudy-CHARMES. Diastolic dysfunction in heart failure with preserved systolic function: need for objec- tive evidence: results from the CHARM Echocardiographic Substudy-CHARMES. J Am Coll Cardiol 2007;49:687-94.
6) Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Dia- stolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiograph- ic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001;24:5-10.
7) Assessment of Left Ventricular Diastolic Function and Recognition of Diastolic Heart Failure, William H. Gaasch and William C. Little ,Originally published7 Aug 2007
8) Boyer JK, Thanigaraj S, Schechtman KB, Pérez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normo- tensive patients with diabetes mellitus. Am J Cardiol 2004;93: 870-5.
9) Wold LE, Ceylan-Isik AF, Fang CX, Yang X, Li SY, Sreejayan N, Privratsky JR, Ren J. Metallothionein alleviates cardiac dysfunc- tion in streptozotocin-induced diabetes: role of Ca2+ cycling proteins, NADPH oxidase, poly(ADP-Ribose) polymerase and myosin heavy chain isozyme. Free Radic Biol Med 2006;40: 1419-29.
10) Minchenko AG, Stevens MJ, White L, Abatan OI, Komjáti K, Pacher P, Szabó C, Obrosova IG. Diabetes-induced overexpres- sion of endothelin-1 and endothelin receptors in the rat renal cortex is mediated via poly(ADP-ribose) polymerase activation. FASEB J 2003;17:1514-6.
11) Way KJ, Isshiki K, Suzuma K, Yokota T, Zvagelsky D, Schoen FJ, Sandusky GE, Pechous PA, Vlahos CJ, Wakasaki H, King GL. Expression of connective tissue growth factor is increased in injured myocardium associated with protein kinase C beta2 activation and diabetes. Diabetes 2002;51:2709-18.
12) Vetter R, Rehfeld U, Reissfelder C, Weiss W, Wagner KD, Gün- ther J, Hammes A, Tschöpe C, Dillmann W, Paul M. Transgen- ic overexpression of the sarcoplasmic reticulum Ca2+ATPase improves reticular Ca2+ handling in normal and diabetic rat hearts. FASEB J 2002;16:1657-9.
13) Privratsky JR, Wold LE, Sowers JR, Quinn MT, Ren J. AT1 block- ade prevents glucose-induced cardiac dysfunction in ventricu- lar myocytes: role of the AT1 receptor and NADPH oxidase. Hypertension 2003;42:206-12.
14) Masugata H, Senda S, Goda F, Yoshihara Y, Yoshikawa K, Fujita N, Daikuhara H, Okuyama H, Taoka T, Kohno M. Left ventric- ular diastolic dysfunction in normotensive diabetic patients in various age strata. Diabetes Res Clin Pract 2008;79:91-6.

15) Danielsen R. Factors contributing to left ventricular diastolic dysfunction in long-term type I diabetic subjects. Acta Med Scand 1988;224:249-56.
16) Nicolino A, Longobardi G, Furgi G, Rossi M, Zoccolillo N, Fer- rara N, Rengo F. Left ventricular diastolic filling in diabetes mel- litus with and without hypertension. Am J Hypertens 1995;8: 382
17) von Bibra H, Hansen A, Dounis V, Bystedt T, Malmberg K, Rydén L. Augmented metabolic control improves myocardial diastolic function and perfusion in patients with non-insulin dependent diabetes. Heart 2004;90:1483-4.
18) Grandi AM, Piantanida E, Franzetti I, Bernasconi M, Maresca A, Marnini P, Guasti L, Venco A. Effect of glycemic control on left ventricular diastolic function in type 1 diabetes mellitus. Am J Cardiol 2006;97:71-6.
19) Celentano A, Vaccaro O, Tammaro P, Galderisi M, Crivaro M, Oliviero M, Imperatore G, Palmieri V, Iovino V, Riccardi G. Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 1995;76:1173-6.
20) Konduracka E, Gackowski A, Rostoff P, Galicka-Latala D, Frasik W, Piwowarska W. Diabetes-specific cardiomyopathy in type 1 diabetes mellitus: no evidence for its occurrence in the era of intensive insulin therapy. Eur Heart J 2007;28:2465-71.
21) Du X, Matsumura T, Edelstein D, Rossetti L, Zsengellér Z, Szabó C, Brownlee M. Inhibition of GAPDH activity by poly (ADP- ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest 2003;112: 1049-57.
22) Farhangkhoee H, Khan ZA, Mukherjee S, Cukiernik M, Barbin YP, Karmazyn M, Chakrabarti S. Heme oxygenase in diabetes-induced oxidative stress in the heart. J Mol Cell Cardiol 2003; 35:1439-48.
23) Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk fac- tors. Diabetes Care 2001;24:1614-9.
24) Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial charac- teristics associated with obesity. Circulation 2004;110:3081-7.
25) Gough SC, Smyllie J, Barker M, Berkin KE, Rice PJ, Grant PJ. Diastolic dysfunction is not related to changes in glycaemic con- trol over 6 months in type 2 (non-insulin-dependent) diabetes mellitus. A cross-sectional study. Acta Diabetol 1995;32:110.