Left Ventricular Hypertrophy in Diabetic Patients and Its Relation to Other Diabetic Complications

Hilal B. shawki** FRCP, FACC, Jawad A. kadhim** MD, FICMS ****, Adil S. Ghafour** FRCP,FACC
*****, Amal Al Marayati** MD, FICMS******, Shakir M. MuhammedMD,** FICMS

Abstract

Background: left ventricular hypertrophy is independent risk factor for cardiovascular morbidity and mortality. The presence of diabetic complications such as autonomic neuropathy and retinopathy may predict cardiac structural changes in diabetic patients.
Objective: To explore the chance of occurrence of left ventricular hypertrophy in diabetic patients and whether it is related to the presence of other diabetic complications.
Methods: ninty seven (97) normotensive diabetic patients (57) type II with mean duration of diabetes of (12±6 y) and forty (40) type I with mean duration of (8±6 y) were studied by echocardiography and compared with 41 patients as control.
Results: The LVMI was significantly higher in type II diabetics compared to control (102±31 vs. 67±16 p< 0.001), although LVMI was higher in type I compared to controls but it was statistically non significant (76.7±18 vs. 76 ±16 P < 0.25). The increased in LVMI was correlated with long duration of diabetes > 15 years in type I but not in type II (p<0.001), retinopathy (34.5% vs. 4.8 p< 0.001), sings and symptoms of autonomic dysfunction (32.7% vs. 10.4% p=0.008) and (38.2% vs. 12.7%p=0.004) respectively. After adjustment for duration of diabetes, age, gender and the type of diabetes, the LVMI was only significantly correlated with long duration of diabetes (>10y).
Conclusion: LV mass index was higher in diabetic patient mainly in type II, more prevalent with long duration of diabetes and if there are other diabetic complications.
Key words: lvh, diabetes, autonomic neuropathy

Al- Kindy Col Med J 2007; Vol.4 (1): p 13-18

Introduction

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency and/or insulin action abnormalities [1,2,3]. Diabetes mellitus is associated with multitude of cardiovascular complications e.g. increased incidence of atherosclerotic coronary artery disease, congestive heart failure, coronary microangiography and arterial hypertension. In addition structural myocardial involvement termed as diabetic cardiomyopathy may be there suggested by clinical, epidemiological and histological studies in large number of diabetics [4, 5, 6].

Prior to the development of symptomatic congestive heart failure, subclinical left ventricular dysfunction (systolic & diastolic) exists for some time [7, 8, 9]. The Framingham heart study [10] found that diabetic men had twice the frequency of congestive heart failure than non-diabetics, while diabetic woman had five fold increased the risk. In diabetic patients left ventricular functional and structural abnormalities have been demonstrated independently from ischemic, Valvular or Hypertensive heart diseases [3, 5, 11]. The possible contributors to diabetic cardiomyopathy are: intramyocardial deposition of collagen, accumulation of advanced glycosylation products (AGEs) [12,13],abnormalities of myocardial calcium handling [14,15], cardiac autonomic neuropathy [16].

Echocardiography has been introduced into epidiological studies [17] with the expectation that it provides diagnostic, pathogenetic and prognostic insights into cardiovascular disease. The aim of this study is to evaluate left ventricular function, other echocardiographic parameters in relation to many variables (age, glycemic control, and obesity, duration of diabetes, micro vascular
Complication, autonomic nervous function, and type of diabetes) that free from clinically evident cardiovascular disease or hypertension.

Methods

The study population consists of already diagnosed diabetic patients attending the out patient clinic of Al-Rasheed teaching hospital & the endocrinology center in Baghdad for the period from April 2001 to July 2002.
Two groups of patient were included, forty (40) IDDM, age range (18-49 y), (31) males and (9) females mean age 28.3±8 years .The second group fifty seven (57) NIDDM, age range (40-69) years, (39) males and (18) females with mean age of 53±6 years.

Any patient with clinical evidence of concomitant illness (IHD, CVD, valvular heart disease, hypertension) was excluded. All patients were either known to be diabetic on oral hypoglycemic agents or insulin or were newly diagnosed as diabetic according to following criteria: Fasting blood sugar > or = 126 mg /dl on more than two occasions or random blood sugar > or =200 mg /dl on more than two occasions (3). The study populations were matched with (41) healthy non-diabetic, normotensive subjects, (30) males and (11) females, age range 18-73 years, mean age of 36±12.

All patients were subjected to clinical examination including cardiovascular system, body height and weight to calculate body mass index (BMI > or = 25 kg/m2 were considered as index of overweight). Blood pressure measurement were performed with standard sphygmomanometer after ten minutes of rest in recumbent and standing position, any systolic drop of 20 mm Hg or diastolic drop of 10 mm Hg was considered as postural hypotension [(18)], standard ECG was obtained for all patients, any patient with ECG changes was not included. Echocardiography performed by one experienced operator by the machine (ultra mark 6),M mode recordings guided by two dimensional views were obtained.

Left ventricular mass (LVM) in grams was calculated according to Devereux modified American Society of Echocardiography cubic formula [(19)]: LV mass= 0.8 [1.04 (LVEDD + PWT + VST)^3 – LVEDD^3] + 0.6 and was indexed to body surface area, LVMI = LVM (gm) / BSA (m^2). LVH was considered to be present when LVMI exceeded 116 gm / m^2 and 104 gm / m^2 in women [(20)].

Ophthalmologic examination was performed by experienced ophthalmologist to detect diabetic retinopathy, neuropathy was considered to be present when there was absent ankle reflexes and /or typical gloves and stocks sensory loss. Peripheral vascular disease was considered to be present when there was diminished or absent peripheral pulses. All patients were asked for symptoms of autonomic dysfunction (nocturnal diarhorroea, impotence, urine retention). Aglycosylated hemoglobin (HbAIc) measurement was obtained for all patients within one month from echocardiographic exam. (>7% was considered as index of uncontrolled DM.

Results

The mean duration of diabetes in type I subjects was 8.2 ± 6 years (ranged from 2 months – 23 years), and in type II subjects was 12.8 ± 6.5 (one month – 30 years), *table (1)*.

The mean BMI was (25.7 ± 4) in type II diabetics, which is significantly higher than in type I diabetics (22.8 ± 3) (P<0.001) *table (1)*. Over weight was reported in 29/57 (50.8%) of type II diabetics and in 8/40 (20%) of type I diabetics. The prevalence of abdominal obesity was significantly higher in type II 35/57 (61.4%) than in type I diabetics 5/40 (12.5%) (P< 0.001).

Both groups of diabetics were poorly controlled as reflected by the mean HbAIC, which was (11.5 ± 2) and (10.4 ± 2) in type I and type II diabetics respectively.

Symptoms of autonomic dysfunction (postural dizziness, nocturnal diarrhea, impotence) were more prevalent in type II DM than type I (36/57 63.2% vs. 13/40 32.5%), postural hypotension was more common in type II DM (27/57 47.4% vs. 7/40 17.5%) while retinopathy was almost equal in both types of DM (44/57 77.1% vs. 11/40 78%) **(*Table-1)*.**

Table (1) also presents a comparison of mean M mode echocardiographic values between diabetic groups, and between each of them and healthy controls. The mean LVMI was significantly higher in type II diabetics (102.9 ±31) compared to both type I (76.7 ±18), and healthy controls (67 ±16) (P<0.001), although type I had higher mean LVMI than controls, this difference was not significant statistically (P = 0.25). F.S was significantly lower in type II diabetics (29%) compared to both type I (34.2%) and controls (36.5%) (P<0.001), but there was no significant difference of F.S between type I and controls (P = 0.78).

PWTD, IVSTD, LVEDD and LAD all were significantly higher in type II diabetics compared with healthy controls (P<0.001), while in type I diabetics only the PWTD was significantly higher than controls (P = 0.01).

The prevalence of LVH was significantly higher in type II 19/57 (33.3%) compared to type I 2/40 (5%) (P<0.001). The rate of abnormal F.S was significantly higher in type II 35/57 (61/4%) compared with type I diabetes 11/40 (27.5%) (P<0.001).

To study the relation between the duration of diabetic state and LVMI, patients were divided into four groups according to the duration of diabetes: <5 years, 5-9 years, 10-14 years and >

or =15 years. The LVMI was only significantly higher in patients with type I diabetes of 15 years duration and more in comparison to the duration of less than 5 years, while there was no significant correlation between LVMI and duration of diabetes in type II diabetics.

The rate of LVH was significantly higher among diabetic subjects who had symptoms (32.7% VS 10.4%) (P = 0.008) and signs (38.2% VS 12.7%) (P = 0.004) of autonomic dysfunction or retinopathy (34.5% VS 4.8%) (P<0.001) compared with patients with no such complications, LVH also was significantly higher in patients who had diabetes for (10) years or more (29.2% in 10-14 years; 36.4% in >= 15 years duration) (P = 0.009) compared with those with duration of < 10 ears (5.6%, 4.5%). There was no any significant correlation between abnormal F.S and any of the measured variables.

A multiple regression model was used to assess the net & independent effect of being type I or II DM on having higher LV mass index (compared to healthy control), after adjusting for the possible confounding effect of age, gender and body mass index. Both types showed significant association with LV mass index, bening type II DM was associated with a mean increase in LV mass index of 30.8 gm/m2 compared to healthy control, which is higher than type I DM of 12 gm/m2. Age has positive correlation with BMI, coming 3rd after the two types of DM, yet its effect on LV mass index was statistically not significant, (***Table -2)*.**

Signs of vascular affection such as diminished peripheral pulses, retinopathy, peripheral neuropathy and signs & symptoms of autonomic dysfunction were tested for the presence & magnitude of prediction of increased LV mass index .A multiple regression model was used with these variables as independent predictors & LV mass as the dependant variable .The model showed that that the presences of retinopathy predicted a mean increase in LV mass index of 18.4 gm/m2, while sings & symptoms of autonomic dysfunction was associated with mean increase of 11.2 gm/m2, **(*Table -3)***.

After adjusting for age, type and duration of DM in addition to the mentioned sings & symptoms of autonomic dysfunction in an other multiple regression model, retinopathy & signs & symptoms of autonomic dysfunction lost their predictive power for the increase of LV mass index and only the duration of DM exceeding 15 y was statistically significant associated with increase in LV mass index of 18.9 gm/m2. Coming second is type II DM of 13gm/m2 (yet statistically not significant)**(*Table -4)*.**

Discussion

The mean resting heart rates in type I and type II diabetics were significantly higher than controls (P<0.001). The Framingham Heart Study concluded that diabetics had higher resting heart rates than non-diabetics, which may represent early evidence of autonomic dysfunction [18].

In the present study the prevalence of autonomic neuropathy signs and symptoms, macro vascular, and micro vascular complications were significantly higher in type II diabetics compared with type I, and this could be explained by the longer duration of diabetes in type II diabetics (12.8 ± 6.5 VS 8.2 ±6), in addition to the preclinical course of type II DM that may reach to a decade, and that about 50% of type II diabetics presented with complications.

LVMI was significantly higher in type II diabetics compared with controls, which were comparable to the result of other studies [21,22].

On the other hand the rate of LVH (LVMI >116 mg/m2 in male and >104 in female) was also significantly higher in type II compared with type I diabetics (P= 0.001), a similar result was found by Robillon JF) [23].

In this study we found that PWTD, IVSD, LVEDD & LAD were significantly higher and the F.S was significantly lower in type II diabetics compared with controls, while only PWTD in type I diabetics was significantly higher than controls. This result was comparable to the results of other studies (Robillon JF) [23].

On the other hand, the rate of abnormally low F.S (<30%) was significantly higher in type II compared with type I diabetics (P=0.001). This result was comparable to the result of Mustonen JN et al [24] in which abnormally low EF (<50%) by radionuclide angiography was reported in 31%of type II diabetics compared with 7% in type I.

In the present study we found a significant correlation between increased LVMI and a duration of diabetes of more than 15 years in type I, while no significant correlation was found between type II and duration of diabetes, although the mean LVMI was significantly higher in type II than type I diabetics. This can be explained by the long preclinical course in type II diabetes that may reach up to a decade [18] and this will underestimate the actual duration of type II diabetes.

On the other hand, we found a significant correlation between the rate of LVH in diabetic patients as a whole (type I + type II) with the presence of autonomic signs and symptoms, retinopathy and long duration of diabetes (more than 10 years), a finding that is supported by other studies (Cardiovascular Health Study; Vanninen E) [23].

On a Multivariate analysis model which studied the net effect of each variable on LVMI independently, both type II and type I had independent significant correlation with LVMI with a mean increase in LVMI of 30.8 gm/m2 in type II and 12 gm/m2 in type I, noteworthy, type I had no statistically significant effect on LVMI compared to healthy controls in univariant analysis but after adjustment for age its effect became more obvious and statistically significant, and this might be due to the significantly higher mean age for the controls group (36.8) than the mean age for type I diabetics (28.3) (P<0.001),(age positively correlated with LVMI).

No significant independent correlations were found between age, sex and BMI with LVMI. This means that the effect of diabetes on LVMI was far more and minimizes the effect of age, sex and BMI in non-diabetic subjects. (Age, sex and BMI are positively correlated with LVMI in non-diabetic subjects) [25,21].

Among the diabetic complications, we found that the presence of retinopathy, and symptoms of autonomic dysfunction were good independent predictors of increased LVMI, but after adjustment for duration of diabetes, age and the type of diabetes their predictive power were lost and only duration of diabetes exceeding 15 years was associated with a statistically significant increase in LVMI (18 gm/m2). Coming second in importance (although not significant statistically) was having type II diabetes (13 gm/m2). This can be explained by the fact that these micro vascular complications are already related to duration of diabetes, and by the longer duration of disease in type II diabetics compared to type I in addition to the long preclinical course of disease that often precedes the diagnosis of type II diabetes.

The remaining unexplained variation in LVMI is attributed to other factors, which were not included in our study, like hyperinsulinaemia and genetic constitution.

Finally it is worthy to mention that the estimation of LVM by echocardiography offers prognostic information beyond that provided by evaluation of the traditional cardiovascular risk factors. An increase in LVM predicts higher incidence of clinical events including death attributable to coronary heart disease (increase morbidity and mortality) [27].

Conclusions

Increased LVMI occurs in normotensive diabetics (both type I and type II), more frequent in type II. The presence of retinopathy and autonomic neuropathy may be predictors of structural changes in diabetic hearts. The duration of diabetes is the most significant independent risk factors for increased LVMI in diabetic subjects.

(Table- 1)
Demographic Characteristics of the Study Group

	Healthy control	***Type I DM***	***Type II DM***	***P value***
Gender	**F:** 11 (26.8 %) **M:** 30 (73.2 %) **T:** 41	**F:** 9 (22.5 %) **M**: 31 (77.5 %) **T:** 40	**F:** 18 (31.6 %) **M:** 39 (68.4 %) **T**: 57	
Mean age	36.8 yr	28.3 yr	53.3 yr	0.001
Mean BMI		22.8	25.7	0.001
Duration of DM (mean)		8.2 yr	12.8 yr	0.001
Diabetic complications				
Symptoms of aut. dysfunction		13 (32.5 %)	36 (63.2 %)	
Signs of aut. Dysfunction		7 (17.5 %)	27 (47.4 %)	
Signs of vascular affection				
Abnormal cardiac function				
LVH		2 (5 %)	19 (33.3 %)	0.001
Abnormally low FS		5 (11.5 %)	35 (61.4 %)	0.001
Echocardiographic parameters				
Mean LVMI (Gm /m^2)	67.3	76.7	102.9	<0.001
Mean FS (%)	36.5	34.2	29	<0.001
Mean PW thickness (cm)	0.8	0.9	1	<0.001
Mean IVS thickness in diastole (cm)	0.9	0.4	1.1	<0.001
Mean LVD dimension	4.2	4.4	4.7	<0.001
Mean left atrial dimension	2	2.9	3.1	<0.001

(Table-2)

Multiple Regression Model with LV Mass Index as the Dependent Variable Showing the Age, Gender and the BMI Adjusted Effect of Type I & Type II DM Compared to the Healthy Control

		Standardized ß	ß	P
Type I DM (compared to healthy control)		12.0	0.19	0.04
Type II DM (compared to healthy control)		30.8	0.53	< 0.001
Body mass index (BMI)		0.3	0.02	0.81
Male gender (compared to female)		- 1.5	- 0.02	0.75
Age in years		0.8	0.14	0.23
r^2 = 0.31				
P (model) < 0.001				

(Table- 3)

Multiple Regression Model with Lv Mass Index as the Dependent Variable among Diabetics and Evidence of Autonomic Dysfunction and Vascular Affection as Independent Variables

	Standardized ß	ß	P
Having retinopathy	18.4	0.31	0.007
Positive symptoms of autonomic dysfunction	11.2	0.19	0.05
Positive signs of autonomic dysfunction	7.4	0.12	0.26
Diminished peripheral pulses	3.6	0.05	0.64
Positive signs of peripheral neuropathy	-8.8	-0.15	0.17
r^2 = 0.20			
P (model) < 0.001			

(Table -4)

Multiple Regression Model with Lv Mass Index as the Dependent Variable among Diabetics and Evidence of Autonomic Dysfunction Together with Age, Gender, Type and Duration of Dm as Independent Variables.

	Standardized ß	ß	P
15 + years duration of DM (compared to < 15 years)	18.9	0.30	0.004
Type II DM (compared to type I DM)	13.0	0.26	0.15
Positive symptoms of autonomic dysfunction	9.9	0.17	0.11
Having retinopathy	9.5	0.16	0.16
Age in years	0.2	0.09	0.64
Positive signs of autonomic dysfunction	3.6	0.06	0.56
Male gender (compared to females)	-3.8	-0.06	0.54
Diminished peripheral pulses	-5.8	- 0.07	0.44
Positive signs of peripheral neuropathy	-15.4	-0.22	0.23
r^2 = 0.34			
P (model) < 0.001			
Forward stepwise selection method for the same independent variables			
Type II DM (compared to type I DM)	21.9	0.37	<0.001
15+ years duration of DM (compared to < 15 years)	15.4	0.25	0.01
r^2 = 0.25			
P (model) < 0.001			

References

1. Harris MI Hadden WC Knowler WC *et al* Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S population aged 20-74 years. *Diabetes* 1987; 36: 523-34

2. Nathan DM Meigs J Singer DE *et al*: The epidemiology of cardiovascular disease in type 2 diabetes mellitus.*Lancet*1997; 350:4-9.

3. Frier BM Truswell AS Shepherd J: Diabetes mellitus, and nutritional and metabolic disorders .In: Christopher H., Edwin R.C (eds) Davidson principles of medicine 18th (Ed.). Edinburgh, *Churchill Livingstone*,1999:480-52rundySM,BenjaminIJ,BurkeGL*etal*,Diabetes mellitus, and cardiovascular disease: a statement for health professionals from the American Heart Association. Criculation.1999; 100: 1134-1146.

4. Galderis M, Anderson KM, Wilson PWF *et al*. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart study) Am J cardiol.1991; 68:85-9.

5. Panja M, Sarkar C, Kumar S et al. Diabetic cardiopathy. JAPI 1998; 46(7): 635-9.

6. Mittal SR, Bharadwaj A, Gupat VD Et Al. Non invasive assessment of pre clinical left ventricular dysfunction in young diabetics. *Ind Heart J* 1985; 35(4): 204-6.

7. Thanikachalam S, Lakshminathan C, Vishwanathan M *et al.* Subclinical diabetic cardiomypathy, Assessment by systolic time intervals. J Assoc Phy Ind 1981; 29:267-72.

8. Ahmed SS, Jaferi GA, Narang RM *et al.* Pre clinical abnormality of left ventricular function in diabetes mellitus. *Am Heart J* 1975; 89 (2): 153-8.

9. Kannel WB, Hjortland M, Castelli WP, Role of diabetes in congestive heart failure: Framingham Study. *Am J Cardio*l1974; 34:29-34.11.

10. Fein FS. Diabetic cardiomyopathy. Diabetes Care.1990; 13:1169-1179.

11. Berg TJ. Snorgaard O, Faber J, *et al*: Serum levels of advanced glycation end products are associated with left ventricular diastolic function in patients with type 1 diabetes. Diabetes Care 22:1186-1190.1999.

12. Avendano GF, Agrawal RK, Bashey RI. *et al:* Effect of glucose intolearnce on myocardial function in and collagen linked glyction. Diabetes.48: 1443-1447, 1999.

13. Schaffer SW, Mozaffari M: abnormal mechanical function in diabetes: Realtion to myocardial calcium handling. Coron Artery Dis.7:109-115,1996.9

14. Allo SN, Lincolin TM, Wilson GL *et al*: Non-insulin dependent diabetes induced defects in cardiac cellular calcium regulation. AM J Physiol.260: C1165-C1171, 1990.

15. Scognmiglio R, Avogaro A, Casara D. *et al*: Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin dependent diabetes mellitus .***J Am Coll Cardiol*** 31: 404-412, 1998.

16. Savage DD, Garrison RJ, Kannel WB *et al*. Considerations in the use of echocardiography in epidemiology. The Framingham study.Hypertension.1987; 9 (Suppl 2): 40-4.

17. Engstrom JW, Martin JB: Disorders of autonomic nervous system. Harrison's principles of internal medicine McGraw-Hill, Inc 15th Ed.2001; 366:2417.

18. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J cardiol* 1986; 57:450-458.

19. Roman MJ, Pichering TG, Schwartz JE *et al*. Relation of atrial structure and function to left ventricular geometric patterns in hypertensive adults. *J Am Coll. Cardiol* 1996; 28:751-756.

20. Vanninen E, Mustonen J, Vainio P *et al*. Left ventricular function and dimension in newly diagnosed NIDDM. *Am J Cardiol* 1992; 70:371-8.

21. Lee M, Gardin JM, Lynch JV *et al.* Diabetes mellitus and Echocardiographic left ventricular function in free-living elderly men and women (the cardiovascular health study). *Am Heart J* 1997; 133:36-43.

22. Robillon JF, Sadoul JL, Jullien D *et al*. Abnormalities suggestive of rdiomyopathy in patients.

AL- Kindy Col Med J 2007; Vol .4(1) P: 18

****College of Medicine University of Baghdad*.**
Address Correspondence to:
Dr. Hilal B. shawki
E-mail: *Crescent 1957@ yahoo.com*
Received at 7th March 2006, Accepted at 16th Oct.2006