Left ventricular mass assessment in normotensive type 2 diabetic patients

Mohamed Kamal, Gamal A .Badr, Mohamed M.Hashem, Essam M. Ghamry, Moussa A. Hussin, Ibrahim Gh. Ramadan and Wael M.Attia*

Departments of General Medicine and Cardiology*, Faculty of Medicine, Al-Azhar University, Egypt.
esamghamry@yahoo.com

Abstract: Introduction: Cardiovascular disease is increased in individuals with type 1 or type 2 diabetes mellitus (DM). Increased left ventricular mass may contribute to the increased cardiovascular risk because left ventricular hypertrophy which is an ominous prognostic sign and an independent risk factor for sudden death, ventricular dysarrhythmia, myocardial ischemia, coronary heart disease and heart failure, is often present in type 2 DM patients. The present study was performed to evaluate the prevalence of LVH, and risk factors for its development, in normotensive type 2 diabetic patients without antihypertensive. **Subjects and methods:** A total of 100 age- and sex-matched subjects were selected (50 cases, diabetic normotensive and 50 controls, nondiabetic normotensive). The study was performed at El- Hussein Hospital, Al-Azhar University, between October 2011 and May 2012. All patients were suspected to full history taking, complete physical examination, full lab, resting twelve leads ECG, plain x-ray chest and heart p-A view, transthoracic echocardiography (including 2D, M-mode, pulsed Doppler imaging) with standard views have been taken. LVM and left ventricular mass index (LVMI) were calculated using Echocardiographic parameters and body surface area. **Results:** FBS, 2HPPBS, B. urea, S. creatinin, HbA1C, TG, total cholesterol, LDL-cholesterol) were significantly higher in group I than group II (p <0.05) while HDL-cholesterol were significantly higher in-group II when compared to group I) (p <0.05). LV posterior wall thickness at end diastole (LVPWTD), and interventricular septal thickness at end diastole (IVSTD) were higher in group I than group II (p <0,001), while there were no statistical difference between the two groups as regard males and females and left ventricular internal dimension at end diastole (LVIDD). LV mass (LVM) correlated with weight (r=0.465), BMI (r=0.351), BSA(r=0.427), 2hppBS (r=0.357), HBA1C(r=0.666) and duration of diabetes (r=0.645) but not correlated with other studied parameters. LVM index (LVMI) correlated with 2hppBS (r=0.363), HbA1C (r=0.644) and duration of diabetes(r=0.654). It is recommended that all patients of type 2 diabetes should be routinely and repeatedly subjected to 2D-guided M-mode echocardiography for early detection of high LVM. This is because increased LVM is associated with increased cardiovascular morbidity and mortality and its early diagnosis and prevention is important, drug therapy can cause improvement in left ventricular function and can decrease cardiovascular morbidity.

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1. Introduction

Cardiovascular complications account for the highest mortality in diabetic patients, mainly due to coronary artery disease and congestive heart failure. Diabetes mellitus is associated with a high prevalence of hypertension, dyslipidemia and microalbuminurea, all known independent cardiovascular risk factors. Even in populations with low cardiovascular risk, diabetes is associated with an increased incidence of cardiovascular death **(Chen *et al.*, 1999).**

Increased left ventricular mass may contribute to the increased cardiovascular risk because left ventricular hypertrophy is an ominous prognostic sign and an independent risk factor for sudden death, ventricular dysarrhythmia, myocardial ischemia, coronary heart disease and heart failure. The possible contributions of hyperinsulinemia and hyperglycemia to left ventricular mass (LVM) have been suggested in the normotensive type 2 diabetic patients **(Felicio *et al.*, 2000).**

Many factors such as diabetic nephropathy, obesity, hyperinsulinemia, disautonomia, hypertension, and genetic abnormalities are suggested that contribute to increase LVM in DM **(Suzuki *et al.*, 2001).** In previous studies, the relation of DM, microalbuminurea, creatinine clearance, and HbA1c with LVH have been evaluated and they found the correlation between these variables and increased LVM **(Kuperstein *et al.*, 2001).** Echocardiography provides a reliable noninvasive estimation of LVM and has been proven to be a more sensitive tool for the detection of LVH than other techniques **(Sukamal *et al.*, 2011).**

The present study was performed to assessment of left ventricular mass in normotensive

type 2 diabetic patients in comparison to normotensive, nondiabetic populations.

2. Patients And Methods

This study was carried out on 100 Egyptian subjects at El- Hussein Hospital, Al-Azhar University, between October 2011 and May 2012. The studied population classified into two groups: **Group (1):** included 50 normotensive cases with type 2 diabetes on oral or insulin therapy. They were 26 males and 24 females, their age range between (40-60 years) with mean (51±4.9). **Group (2):** included 50 normotensive nondiabetic subjects with age and sex matched. They were 26 males and 24 females, their age range between (40-60 years) with mean (50.3±5.1).

Patient's known to be hypertensive or accidentally discovered during examination to be hypertensive, patients with clinical evidence of cardiac disease, ischemic heart disease, CHF, cardiomyopathy, valvular heart disease, patients with renal involvement especially albuminuria, patients with BMI >30, patients with COPD were excluded from the study.

All patients and control group were subjected to full clinical examination including the following: Detailed medical history including age and sex with special emphasis to diabetes duration and complete clinical examination with special emphasis to resting ECG, plain X-ray, measurements of blood pressure, BMI and body surface area that calculated by Mosteller formula, $BSA_{(m2)} = (height_{(cm)} \times weight_{(Kg)} / 3600)^{1/2}$ (**Musarò *et al.*, 1999).**

Laboratory investigations including; fasting and postprandial plasma glucose, S. creatinin & blood urea, Lipid profile (total cholesterol, LDL, HDL and triglycerides), HbAlc% and albuminuria were performed to all subjects.

Echocardiography: Routine full echo-Doppler analysis to all participants was performed to exclude any cardiac disease. M-mode echocardiography was performed according to the recommendations of the American Society of Echocardiography using Vingmed CFM725 equipped with a 3.25-MHz transducer.

Left ventricular dimensions: LV dimensions were measured from 2D-guided M-mode echocardiograms of the LV at the level of mitral leaflet tips or the papillary muscle using the para-sternal view. The thicknesses of the left ventricular posterior wall and the ventricular septum (from the leading edge to the trailing edge) were measured. These values were used to calculate the LV mass. The LV end-diastolic and end-systolic dimensions were measured at the level of tips of the mitral leaflets as the largest and the smallest LV dimensions, respectively.

Left ventricular mass: The following equation provides a reasonable determination of LVM in grams: LV mass (ASE method) = 0.8 (1.04([LVID+PWT+IVST] 3 – [LVID] 3) + 0.6 g**,** where LVID is the left ventricle internal dimension, PWT is the posterior wall thickness, IVST is the interventricular septal thickness, 1.04 is the specific gravity of the myocardium and 0.8 is the correction factor. All measurements were made at end-diastole (at the onset of the R wave) in centimeters **(Devereux *et al.*, 1986).**

For comparison, the LVM index (LVMI) was calculated by dividing the LVM with the body surface area (BSA).The upper limit of LVM was 162 g in females and 224 g in males. The upper limit of the LVMI was 95 g/m2 in females and 115 g/m2 in males. Left ventricular wall motion was inspected in each of the 16 segments defined by the American Society of Echocardiography. All measurements were averaged over five cycles **(Lang *et al.*, 2005).**

Statistical analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, chi-square and Linear Correlation Coefficient by SPSS V17. Unpaired Student T-test was used to compare between two groups in quantitative data. A *P* value <0.05 and r value >0.300 were considered significant.

3. Results

The following items were statistically significant higher in-group I when compared to group II; (FBS, 2HPPBS, B. urea, S. creatinin, HbA1C, TG, total cholesterol, LDL-cholesterol) (p <0.05) while HDL- cholesterol were significantly higher in-group II when compared to group I) (p <0.05). On the other hand there were no statistical significant difference between the two groups as regard Age, Sex, BMI, BSA, SBP, DBP ECG and X-ray finding (Table 1).

The following structural measurements of the left ventricle, left ventricular posterior wall thickness at end diastole (LVPWTD), and interventricular septal thickness at end diastole (IVSTD) were higher in group I than group II (P<0,001), while there were no statistical difference between the two groups as regard left ventricular internal dimension at end diastole (LVIDD), (Table 2).

Among the (26) diabetic male patients there were (12) with high LVMI which represent (46.15%) of the total diabetic male patients and (14) with normal LVMI which represent (53.85%) of the total diabetic male patients. Among the (26) control males there were (4) with high LVMI which represent (15.38%) of the total control males and (22) with normal LVMI which represent (84.62%) of the total control males. There was statistical significant difference between male patients and control group

as regards LVMI, *P*-value 0.016 (<0.05). Among the (24) diabetic female patients there were (13) with high LVMI which represent (54.17%) of the total diabetic female patients and (11) with normal LVMI which represent (45.83%) of the total diabetic male patients. Among the (24) control females there were (5) with high LVMI which represent (20.83%) of the total control females and (19) with normal LVMI which represent (79.17%) of the total control females. There was statistical significance between female patients and control group as regard LVMI 0.017(<0.0s), (Table 3).

LV mass correlated with weight (r=0.465), BMI (r=0.351), BSA(r=0.427), 2hppBS (r=0.357), HBA1C(r=0.666) and duration of diabetes (r=0.645) but not correlated with other studied parameters. LVMI correlated with 2hppBS (r=0.363), HbA1C (r=0.644) and duration of diabetes(r=0.654), but not correlated with other studied parameters (Table 4).

Table (1): Clinical and laboratory characteristics of the studied subject

	Patients			Controls			T-test	
	Mean	±	SD	Mean	±	SD	t	*P*-value
Age (years)	51.409	±	4.952	50.3	±	5.14	1.099	0.274
wt (Kg)	72.02	±	6.635	73.04	±	5.364	-0.845	0.4
Ht (meters)	169.56	±	4.608	170.08	±	5.248	-0.526	0.6
BMI	24.858	±	2.057	25.155	±	1.8	-0.768	0.444
BSA (m2)	1.832	±	0.105	1.852	±	0.084	-1.042	0.3
FBS(mg/dl)	158.82	±	20.811	83.34	±	7.449	24.146	<0.001**
2hppBS(mg/dl)	258.8	±	33.35	129.02	±	5.527	27.147	<0.001**
B. urea(mg/dl)	30.66	±	5.738	27.68	±	7.104	2.308	0.023**
S. Creatinin (mg/dl)	0.816	±	0.226	0.674	±	0.243	3.023	0.003**
HBA1C %	9.029	±	2.376	4.338	±	0.614	13.516	<0.001**
UACR	18.558	±	5.334	11.348	±	5.007	6.97	<0.001**
TG (mg/dl)	146.16	±	13.125	111.46	±	33.613	6.8	<0.001**
cholesterol (mg/dl)	179.62	±	11.201	141.68	±	20.166	11.63	<0.001**
HDL (mg/dl)	38.64	±	3.193	47.66	±	6.527	-8.778	<0.001**
LDL (mg/dl)	147.34	±	8.243	101.82	±	11.923	22.207	<0.001**

**=highly significant

Table (2): Echocardiographic characteristics of all subjects

	Patients			Controls			T-test	
	Mean	±	SD	Mean	±	SD	t	*P*-value
LVIDD	4.661	±	0.543	4.595	±	0.522	0.622	0.535
PWTD	1.056	±	0.159	0.942	±	0.161	3.587	0.001**
IVSTD	1.133	±	0.228	0.943	±	0.167	4.768	<0.001**
LVM (g/m^2)	183.504	±	45.003	149.28	±	39.428	4.045	<0.001**
LVMI(g/m^2)	99.874	±	22.6	80.776	±	20.179	4.457	<0.001**
EF%	65.35	±	4.424	65.32	±	3.966	0.036	0.972
FS %	34.9	±	3.43	35.4	±	3.505	-0.721	0.473

**=highly significant

Table (3): Prevalence of left ventricular mass index in male and females subjects of Type 2 DM and control patients.

LVMI Male	Groups						Chi-Square	
	Patients		Controls		Total			
	N	%	N	%	N	%	X^2	*P*-value
Normal	14	53.85	22	84.62	36	69.23	5.778	0.016**
High	12	46.15	4	15.38	16	30.77		
LVMI Female	Groups						Chi-Square	
	Patients		Controls		Total			
	N	%	N	%	N	%	X^2	*P* -value
Normal	11	45.83	19	79.17	30	62.50	5.689	0.017**
High	13	54.17	5	20.83	18	37.50		

**=highly significant

Table (4): Correlation between LVM & LVMI and all studied parameters

Correlations	LVM		LVMI	
	r-value	*P* -value	r-value	*P* -value
Wt (Kg)	0.465	0.001**	0.269	0.059
Ht (Meters)	0.227	0.112	0.090	0.533
BMI	0.351	0.012**	0.211	0.142
BSA (m^2)	0.427	0.002**	0.227	0.113
FBS (mg/dl)	0.198	0.168	0.199	0.166
2hppBS (mg/dl)	0.357	0.011**	0.363	0.010**
HBA1C%	0.666	<0.001**	0.644	<0.001**
Duration of DM (years)	0.645	<0.001**	0.654	<0.001**

4. Discussion

Cardiovascular complications account for the highest mortality in diabetic patients, mainly due to coronary artery disease and congestive heart failure. Diabetes mellitus is associated with a high prevalence of hypertension, dyslipidemia and microalbuminurea, all known independent cardiovascular risk factors. Even in populations with low cardiovascular risk, diabetes is associated with an increased incidence of cardiovascular death **(Chen *et al.*, 1999).**

Our study demonstrated LVH to be a common association in normotensive type 2 diabetic patients predominantly without hypertension compared to the age- and sex-matched, normotensive, nondiabetic control population. LVM was indexed to the BSA to avoid the effect of body weight over LVM. In this study, it was observed that the mean of LVM and LVMI was statistically significantly higher in diabetic patients in comparison to healthy control subjects. This indicates the association of high LVM in patients of DM without hypertension.

In accordance with our results**, Hirayama *et al.* (2000)** from Japan demonstrated in their study that LVM and LVMI were significantly greater in the normotensive type 2 DM patients than the normotensive control population**.** Also **Sukamal *et al.*(2011),** reported that LVM or LVM. Index was significantly higher in patients with type 2 DM who were normotensive when compared with age, sex, matched healthy population.

The prevalence of high LVM and high LVMI in all type 2 DM patients of our study was 50% and 50% respectively. The prevalence of high LVM and high LVMI in male subjects with type 2 DM was 46.15% and 46.15% respectively, while the prevalence of high LVM and high LVMI in female subjects with type 2 DM was54.17% and 54.17% respectively.

In this research, we found that there is a significant difference in LVM between normotensive, normoalbuminuric type 2 DM patients and the control group which must be noted because increased LVM is associated with increased cardiovascular morbidity and mortality and its early diagnosis and prevention is important; drug therapy can cause improvement in left ventricular function and can decrease cardiovascular morbidity. The high prevalence of LVH in diabetic patients supports this idea that early echocardiographic screening may be beneficial to these patients.

In the present study the urinary albumin excretion rate is strongly associated with the degree of LVM hypertrophy and has been demonstrated in several previous studies of nondiabetic and type 1 and type 2 diabetic patients with micro and macroalbuminuria. Furthermore, in hypertensive diabetic and nondiabetic patients with LVH, an increased urinary albumin excretion rate resulted in an increased risk for cardiovascular morbidity and mortality **(Wachtell *et al.*, 2003).**

In our study we reveal a significant correlation between duration of diabetes and poor control of diabetes (elevated HBA1C) and the increased LVM and increased LVMI. In agreement with **(Sato *et al.*, 1999)**, which reported a significant correlation between glycemic control, duration of DM, and severity of nephropathy and LVMI**?** Also **Sukamal *et al.* (2011),** reported that LVM or LVM.I was correlated significantly with duration of DM and poor control of DM. so our study is in agreement with that study.

The prevalence of LVH in the predominately nondiabetic population (95%) in the Framingham Heart Study assessed by echocardiography was reported to be 16% in men and 21% in women. In that study, 42 women had diabetes and were characterized by an increased left ventricular wall thickness and a 22% greater LVM than their nondiabetic peers **(Galderisi *et al.*, 1991).** In our study, the prevalence of LVH in the nondiabetic, normotensive control population was 15.38% in males and 20.83% in females which could

not be explained here but these findings are consistent with the Framingham Heart Study.

None of our patients fulfilled the classical electrocardiogram criteria for LVH. This is in agreement with the Framingham Heart Study which demonstrated on ECG a LVH prevalence of 0.5%, applying the same method. In contrast, a recent Italian study reported a prevalence of ECG-LVH of 17% in type 2 diabetic patients **(Bertoni *et al.*, 2004)**. These patients were, however, characterized by old age, long known duration of diabetes, arterial hypertension, and micro- or macroalbuminuria in nearly half of the population.

LVMI is more accurate than LVM because it is corrected by the body surface area (BSA) excluding the effect of body weight over the LVM **(Anderson *et al.*, 2005**). This is in agreement with our study, which demonstrates that LVM was correlated with body wt, BMI while LVMI was not correlated.

We reveal in our study that the women had higher LVMI (54.17%) than men (46.15%) and this is in agreement with **(Devereux *et al.*, 2000):** which reveal that Women with diabetes were noted to have significantly thicker LV walls and higher LVMI. While this trend was observed in men, it did not reach statistical significance. On multivariable analysis, diabetes remained independently associated with increased wall thickness (p = 0.008) and LVMI (p = 0.004) in women but not in men. These finding were supported by data from the CHS and the Strong Heart Study **(Cooper *et al.*, 1988).**

The exact mechanism of increased LVM and LVMI in normotensive type 2 diabetic patients is still unclear but could be explained by the long duration of diabetes, poor control of diabetes and many other mechanisms such as hyperinsulinaemia, and insulin has been shown to stimulate myocardial growth. The results concerning insulin and impaired insulin sensitivity in the development of LV hypertrophy are, however, conflicting **(Malmqvist *et al.*, 2001).**

Proinsulin levels are increased in patients with insulin resistance, and proinsulin has been shown to be more closely related to LV wall thickness than insulin levels **(Sundstro *et al.*, 2000).** Because of the similarities in the extracellular domains between the insulin receptor and the insulin-like growth factor (IGF) 1 receptor, increased levels of insulin can promote cellular hypertrophy by binding to the IGF-1 receptor, although binding would be with much less affinity **(Yoshimura *et al.*,2008).**

Insulin also stimulates cardiac hypertrophy through the same P13Kα/Akt-1 pathway by which it mediates glucose uptake. Akt-1 phosphorylates and inactivates glycogen syntheses kinase 3β, a well recognized inhibitor of nuclear transcription governing the hypertrophic process via the NFATC-3 **(Morisco *et al.*, 2005).** In rats, insulin stimulates an increase in myocardial mass Insulin may be a myocardial growth factor, increasing myocardial hypertrophy **(Holmang *et al.*, 1996).**

Hyperglycemia (glucose toxicity): LV hypertrophy might develop in diabetic patients as a result of higher glucose levels, which independently stimulated LV growth **(Morissette *et al.*, 2003).** This is in agreement with our study which show correlation between LVM,LVMI and PPBS (high blood glucose levels). Haemodynamic factors, such as increased afterload, are important for the development of LV hypertrophy. However, the relationship between LV mass and blood pressure is modest and LV hypertrophy can also be present in normotensive subjects **(Levy *et al.*, 1990).**

It is recommended that all patients of type 2 diabetes should be routinely and repeatedly subjected to 2D-guided M-mode echocardiography for early detection of high LVM. This is because increased LVM is associated with increased cardiovascular morbidity and mortality and its early diagnosis and prevention is important, drug therapy can cause improvement in left ventricular function and can decrease cardiovascular morbidity.

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