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COMPARISONOFLEFTVENTRICULARHYPERTROPHYAMONGNORMOTENSIVETYPE 2 DIABETES MELLITUSPATIENTS WITHTHAT OF AGE-ANDGENDER-MATCHEDNON-DIABETICPATIENTS.

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ABSTRACT

Background: Adverse cardiac outcomes like morbidity and mortality are eventually associated with Type 1 or Type 2 DM. The cardiovascular risk may eventually be increased with increased LVM. LVM is a life-threatening prognostic sign because of developing ventricular arrhythmia, myocardial ischemia, CHD, and HF.

Aim: This cross-sectional study aimed to evaluate the prevalence and risk factors for the development of LVH in age-and gender-matched normotensive population with T2DM and comparison of LVH among diabetic and non-diabetic normotensive patients

Methods: A total of 300 populations were included in this study.150 who were non-hypertensive with known T2DM and a similar number of healthy age- and gender-matched, non-diabetic, and normotensive controls. All the subjects of known diagnosed with T2DM with on oral or injectable anti-diabetic medication or patients with fulfilling the American Diabetic Association criteria for DM without any medical therapy. The baseline data were collected and LVM and LVMi were calculated by using echocardiographic parameters and BSA.

Results: LVM and LVMI were significantly higher in T2DM patients compared with the age-and gender-matched control population (231.7±30.38 vs 190.8±25.18 g/m^2 with all P<0.0001) and (134.1±25.43 vs 70.61±14.57 with P<0.0001) respectively.

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Conclusion: LVM and LVMIwas significantly higher in T2DM patients without HTN, IHD, and other diseases. The prevalence of LVH is almost the same in both genders. Prevalence of left ventricular mass in T2DM patients were high without other major complications. It's important to rule out the prognosis of LVM in the diabetic population to overcome cardiovascular adverse events and morbidity and mortality.

Keywords: Left ventricular hypertrophy, Diabetes mellitus, left ventricular mass, left ventricular mass index,

INTRODUCTION

In the last century, DM is becoming a rising epidemic more pressing in the last few decades and with the exponential cause in obesity and become a leading cause of death worldwide. As compared with non-diabetic, those with T2D carry a higher mortality risk of cardiovascular disease (CVD) across different ethnic groups and sex. The most common CVD manifestation with T2D is heart failure, peripheral arterial, and coronary artery disease (CAD) [1]. Framingham's study shows that there is a risk increase from one- to fivefold of peripheral arterial disease (PAD), myocardial infarction (MI) congestive heart failure (CHF), and coronary disease (CAD) in DM. There is the highest mortality of cardiovascular complications in diabetic patients, mainly due to coronary artery disease and congestive heart failure (CHF). With other independent known cardiovascular risk factors such as hypertension, microalbuminuria, and dyslipidemia, diabetes is associated with a high prevalence. Diabetes is associated with an increased incidence of cardiovascular death even in a population with low cardiac risk factors [2]. LVH, which is a menacing and independent risk factor for adverse cardiac events and is often associated with T2D patients[3]. The underlying cause of LVH due to possible contributions of high insulin and glucose level in blood have been suggested in hypertensive and normotensive patients without DM but there are limited studies that suggest the possible cause of LVH in T2D subjects without HTN.

LVH is an important predictor of cardiovascular events detected by ECG [4]. In the Framingham study of all cardiovascular deaths preceded by LVH, 45% were detected by ECG-LVH [5]. Echocardiography has proven to be a more sensitive and reliable non-invasive tool for the detection of LVH than other tools.

Therefore, the purpose of this cross-sectional study was (i) to evaluate the prevalence and risk factors for the development of LVH in an age-and gender-matched normotensive population with T2D without anti-HTN medication. (ii) Comparison of LVH among diabetic and non-diabetic normotensive patients. (iii) To evaluate the risk factors for the development of high LVH in T2D normotensive patients.

METHODS

Population and study design

A total of 9 months (from September 2017 to June 2018) hospital-based cross-sectional observational study was conducted in Lady reading hospital of Khyber Medical University Peshawar. A total of 300 populations were included in this study from diabetic OPD, Medicine OPD, and Echocardiography sections. 150 who were non-hypertensive with known T2D and a similar number of healthy age- and gender-matched, non-diabetic, and normotensive controls. The inclusion criteria were (i) subjects of known diagnosed T2D with on oral or injectable anti-diabetic medication. (ii) patients with fulfilling the American Diabetic Association criteria for DM without any medical therapy. The exclusion criteria were (i) subject with known HTN with or without antihypertensive medication;(ii) patient with known IHD, Cardiomyopathy, congestive heart failure, COPD, renal impairment, and thyroid disorders: (iii) Known case of T1D and dyslipidemia. All subjects provided inform consent.

Main Parameters

Subject's characteristics like age, gender, height, body surface area (BSA), weight, Body mass index (BMI), and blood pressure were measured. The routine and relevant examinations like fasting blood sugar (FBS), with at least 6 to 8 hours fasting, Random blood sugar (RBS), HbA1c, Urine R/E, serum urea, and creatinine, lipid profile, thyroid profile, ECG, and echocardiogram were also performed.

Body surface area (m^2).

Body surface area (BSA) was measured using the standard formula by Dr. Mosteller and DuBois; BSA (m^2) =SQRT ([Height (cm) x Weight (kg)]/3600).

Body mass index (BMI)

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For BMI, weight was taken by using a balance scale; the height was recorded in cm and used the standard formula for calculating BMI as BMI = Weight (kg)/Height (m^2).

Blood pressure

The blood pressure was measured by using the standard tools. The JNC 7 blood pressure classification was used for the exclusion and inclusion criteria. The subject with blood pressure between 120-139/80-89 which is categorized as normal and prehypertension range respectively were included in our study. The patient with blood pressure beyond this range was excluded.

Lab investigations.

Fasting blood glucose (FBS).

Venous blood sample in the morning following an overnight (6 to 8 hour) fast. The blood sample was sent to the laboratory and was estimated the FBS level by using the standard tools.

Random blood glucose (RBS)

Random blood glucose level was measured after 2 h after the ingestion of standard 75 g of anhydrous glucose.

Other lab tests

Serum urea was measured by using the kinetic UV method and serum creatinine was measure by Jaffe's method which involves SCrMJ and SCrMS chemistry. Serum lipid profile was measured by using Hitachi 912 analyzer. Urine R/E and microscopic examination were performed in all cases.

Urinary albumin level

UACR evaluation method was used for the estimation of microalbuminuria. The albumin level in urine less than 30mg/g was considered normal.

Electrocardiogram

The 3-Chenal ECG-UN8003 machine was used for electrocardiogram. The leads were properly attached to ensure any fault in the recording. The classical Sokolow-Lyon electrocardiogram criteria were used for the determination of LVH.

Echocardiography

For the LVH the M-mode and pulsed doppler were used by using the Philip echocardiography system (EPIQ 7C, X5-1 probe, Philip healthcare, Andover, MA, USA). All the subjects were put into a lift semi-recumbent position with ECG leads attached properly. The LV wall motion was observed in the entire 16 segments. All echocardiographic examinations were performed by the same experienced sonographer.

Left ventricular dimensions

Form 2D-guided M-mode echocardiography of the LV dimensions was measured at the level of mitral valve leaflets tips using the parasternal view. The thickness of LVPW and IVS were measured. The obtained value was used for the calculation of LV mass. The LV end-diastolic dimensions and end-systolic dimensions were obtained during diastole and systole respectively with the help of the attached ECG.

Left ventricular parameters

The left ventricle was measured at end-diastole and end-systole according to the recommendation of ASE[6]. Left ventricular mass was calculated by using the equation based on necropsy validation studies [7]: LV mass= 0.80 (ASE-cube LV mass)+0,6 g, where ASE-cube LV mass = 1.04 {$(IVSd+LVIDd+PWd)^3$ - $LVIDd^3$ },1.04 is specific gravity and 0.8 is the correction factor. For the comparison, LV mass index (LWMI) was calculated by dividing the left ventricular mass by surface area.

The normal upper range limit for left ventricular mass was 224g in males and 162g in females and the upper limit for LV mass normalized to body surface area was 113g.m^2 in men and 95g/m^2 in women[3,8].

Data collection in the controls group.

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Age- and the gender-matched healthy controlled group followed by all measurements as FBS, RBS, serum urea, and creatinine, urine R/E, albuminuria, ECG, lipid profile, thyroid profile, and left ventricular parameters were measured through the Echocardiography by the same method and observer as for diabetic subjects.

Statistical analysis

Continuous variables were presented as mean ± SD, or median and IQR, while categorical variable was presented as frequency. For the test of normality and log-normality, the Shapiro-Wilk test was used. For comparing one set of data with another Unpaired student t-test was used by using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA). A two-sided P-valve <0.05 was considered to be significant.

To study the relationship between T2DM and LVM the Chi-square test was used. The null hypothesis, that the two factors are independent of the relationship between two factors is accepted. If the calculated P-value <0,05 then the null hypothesis was rejected and vice versa. GraphPad Prism 8.0 (GraphPad Software, San Diego, CA) was used for the Chi-square test.

RESULTS

Study population

The entire study population was observed 150 cases (T2DM) while 150 control all with normotension. For the effect of age on LVM, all the populations were selected from the same age. The age range was from 46-61 years with a mean age of 53 years. There general clinical characteristics are presented in **Table 1.** Among the 150 T2DM case population there was 78 Male which contributes 52% of the study population and 72 (48%) females. The same trend was kept in control.

Table 1: Clinical characteristics and laboratory data of study population.

Variable	Case (n=150)	Control (n=150)	t-value	P-value
Age (years)	54.3±7.33	53.96±7.35	0.432	0.665
gender (male/female)	78/72	78/72	-	-
Height (m)	1.64±0.081	1.65±0.08	0.417	0.676
Weight (kg)	81.10±10.25	81.2±10.19	0.016	0.986
BMI	30.05±3.92	29.92±3.89	0.295	0.767
BSA kg/m2	1.75±0.25	1.72±0.24	1.079	0.281
FBS mg/dl	154.9±37.0	76.88±12.5	24.42	<0.0001
RBS mg/dl	268.1±56.7	137.7±22.27	26.21	<0.0001
HbA1C	10.33±1.39	5.97±1.04	30.61	<0.0001
SBP (mmHg)	126.7±5.18	125.2±4.96	2.572	0.052
DBP (mmHg)	79.88±5.05	78.89±4.05	1.877	0.061

BMI: Body mass index, BSA: Body surface area, FBS; Fasting blood sugar, RBS; Random blood sugar, SBP; Systolic blood pressure, DBP; Diastolic blood pressure.

Main Parameters

The subject main parameters like weight, height, and other parameters are shown in table 1. The observed height and weight in T2DM subjects were observed 1.64±0.081m and 81.10±10.25 kg respectively. While in the control group height and weight was found 1.65±0.08 m and 81.2±10.19 kg respectively.

Body surface area (BSA m2) and body mass index (BMI)

The observed body surface area (BSA) was in case and control group was 1.75±0.25 and 1.72±0.24 respectively with no significant difference (p = 0.281) while the observed body mass index in case and control group was 30.05±3.92 and 29.92±3.89 respectively with a p-value 0.767.

Blood pressure (mmHg)

The systolic and diastolic blood pressure (mmHg) in both case and control was almost similar with no significant p-value. For the case and control group, the measured SBP was 126.7±5.18 and 125.2±4.96 respectively while DBP was 79.88±5.05 and 78.89±4.05.

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Lab investigations

Blood glucose level.

The fasting and random blood glucose level was higher and found significant in case group versus control, (FBS; 154.9±37.0 vs 76.88±12.5, RBS; 268.1±56.7 vs 137.7±22.27 respectively with all P<0.0001) same trend was observed in case of HbA1C.

Echocardiography

All measurements of left ventricle like interventricular symptom (IVS cm) left ventricular posterior wall (LVPW cm) LV diastolic dimensions (LVDD cm), left ventricular mass, and left ventricular mass index were found higher in T2DM vs control subject Table 2. The observed left ventricular mass in T2DM subjects was 231.7±30.38 g/m^2 which was much higher than control subjects 190.8±25.18 g/m^2 with all P<0.0001. a similar trend was observed in the left ventricular mass index.

Table 2: Echocardiographic parameters of T2DM (case) and healthy (control) subjects.

Variable	Case (n=150)	Control (n=150)	t-value	P-value
Interventricular septum	1.201±0.279	1.017±0.263	5.86	<0.0001
LV posterior wall	1.177±0.271	1.028±0.278	4.68	<0.0001
LV diastolic dimension	4.471±0.618	4.333±0.402	2.292	<0.0001
Left ventricular mass	231.7±30.38	190.8±25.18	12.69	<0.0001
Left ventricular mass index	134.1±25.43	70.61±14.57	26.53	<0.0001

LV: Left ventricle

Prevalence of LVM and LVMi

Among the T2DM group for male subjects, the prevalence of high LVM was observed at 42.8% while found normal with 57.2%. For the control group, the LVM was high at 18.5% while normal at 81.5%. in the case of the left ventricular mass index (LVMi), the prevalence of high LVMi in T2DM subjects was 59.0% while found normal in 41.0%. same as in the control group the prevalence of high LVMi was observed at 19.77% and normal LVMi was 80.23% Figure 1 &2, Table 3.

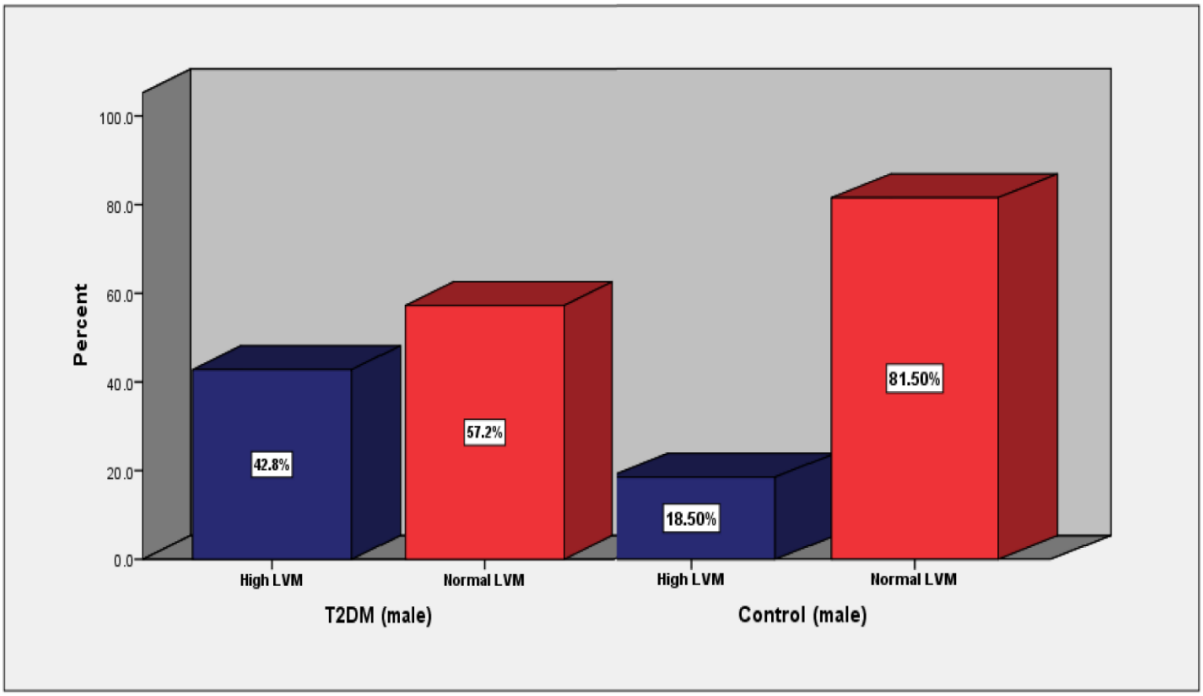

Figure 1: *Bar diagram showing the prevalence of left ventricular mass in the male in type 2DM (case) and healthy (control) subjects.*

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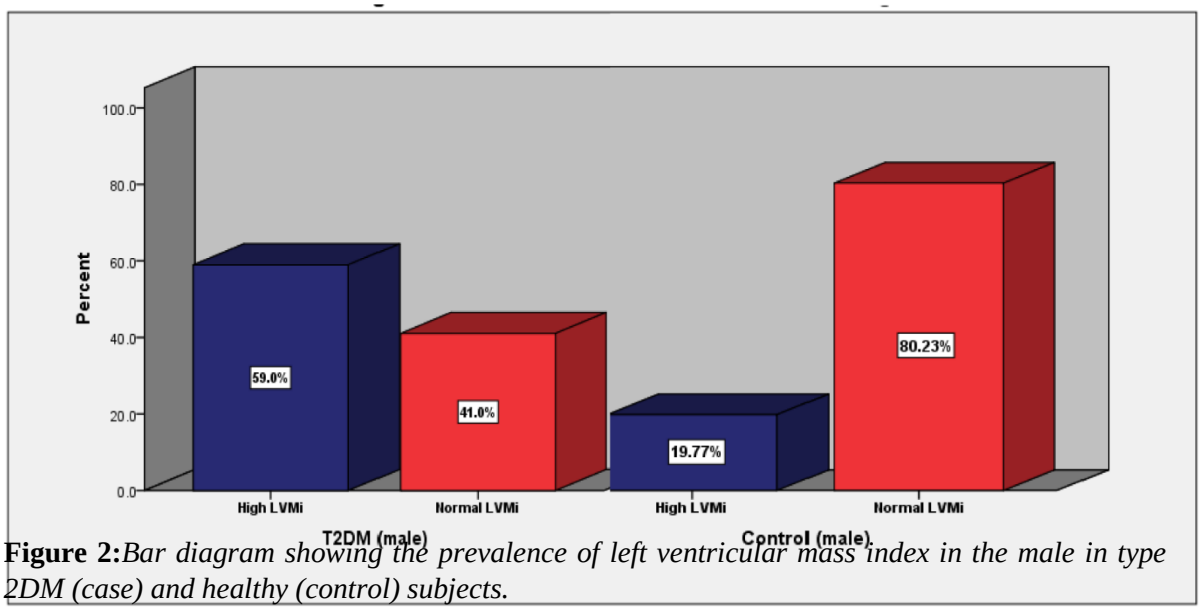

Figure 2:*Bar diagram showing the prevalence of left ventricular mass index in the male in type 2DM (case) and healthy (control) subjects.*

Table 3:Frequency of LVM and LVMI in T2DM and control subjects in male.

Variable	Type 2DM	Control
Left ventricular mass (LVM)		
High	42.80%	18.50%
Normal	57.20%	81.50%
Left ventricular mass index (LVMI)		
High	59.00%	19.77%
Normal	41.00%	80.23%

T2DM: Type 2 diabetes mellitus

In female subjects, the prevalence of high LVM in T2DM subjects was found 48.55% with a normal LVM of 51.45%. For the control group, the high LVM was observed in 20.23% and with a normal LVM of 79.77%. In the case of LVMi, the observed prevalence was 61.63% for high LVMi and 38.37% for normal LVMi in T2DM subjects. Same as in the control group the high LVMi was 20.23% and normal LVMi was 79.77 % Figure 3 & 4, Table 4.

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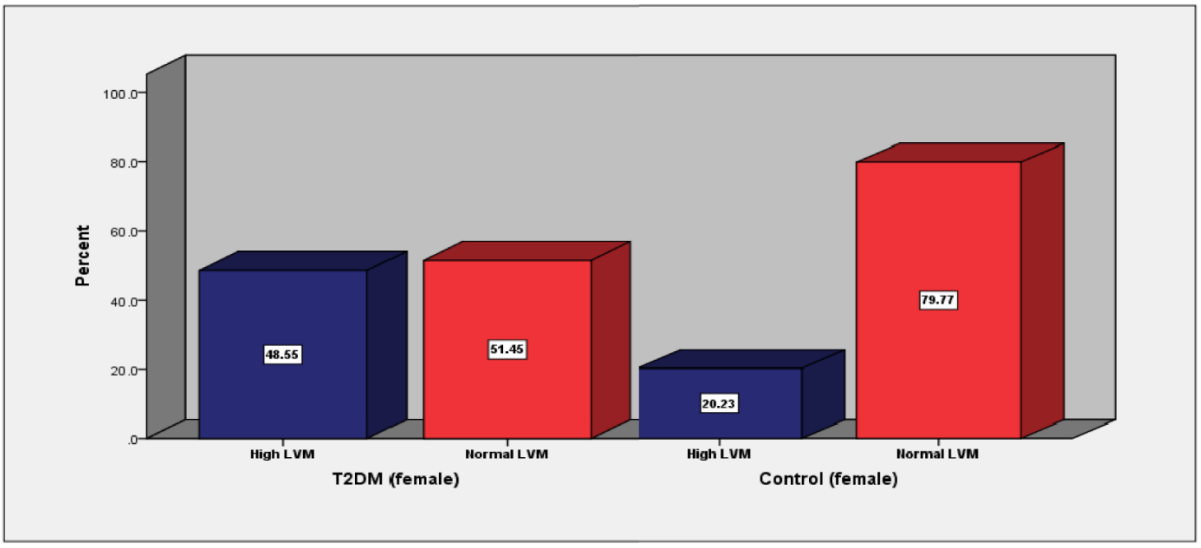

Figure 3:*Bar diagram showing the prevalence of left ventricular mass in females in type 2DM (case) and healthy (control) subjects.*

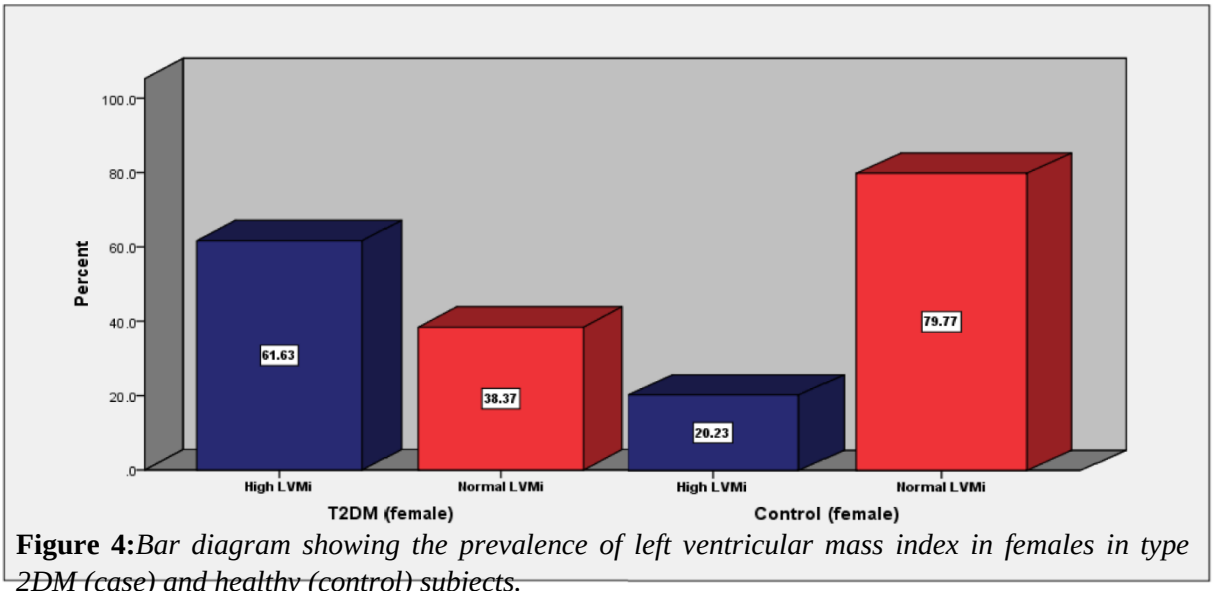

Figure 4:*Bar diagram showing the prevalence of left ventricular mass index in females in type 2DM (case) and healthy (control) subjects.*

Table 4: Frequency of LVM and LVMI in T2DM and control subjects in female

Variable	Type 2DM	Control
Left ventricular mass (LVM)		
High	48.55%	20.23%
Normal	51.45%	79.77%
Left ventricular mass index (LVMI)		
High	61.63%	20.23%
Normal	38.37%	79.77%

T2DM: Type 2 diabetes mellitus

DISCUSSION

Adverse cardiac outcomes like morbidity and mortality are eventually associated with T2DM[3]. The cardiovascular risk may eventually be increased with increased LVM. LVM is a life-threatening prognostic sign

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because of developing ventricular arrhythmia, myocardial ischemia, CHD, and HF. ACE inhibitors are effective both in controlling HTN and Left ventricular hypertrophy[9].

This cross-sectional study reveals that LVM is to be a common association in T2DM patients with normotension predominantly without any complications and HTN vs age- and gender-matched non-diabetic and normotensive subjects. None of the subjects were receiving any hypertensive medicine. For the avoidance of the influence of obesity on LVM the subjects were indexed to BSA. In this study, it was observed that the mean of left ventricular mass (LVM) and left ventricular mass index (LVMi) was statistically significantly high in T2DM subjects vs the normal control group which indicates the association of high LVM in subjects with T2DM. These results are correlated with the study results of SantraSukamalet al. from India and Hirayama H et al. from Japan [3,10].

The prevalence of LVM and LVMi in our study was found higher than that of Sato A et al. study as their study demonstrated the LVH indexed by height was 43% (38-50%) and was similar in both genders of normotension and T2DM subjects[11]. In comparison to that study, they measure the LVH indexed by height instead of Left ventricular mass index and by using another (Penn) formula for left ventricular mass calculation.

Our study has shown that there is a significant difference in left ventricular mass and left ventricular mass index between normoalbuminuric and normotensive T2DM patients and control subjects which must be considered because high LVM is associated with adverse cardiac outcomes like cardiovascular morbidity and mortality. Initial consideration may decrease these adverse outcomes.

Another finding in our study is that left ventricular posterior wall thickness (LVPW) interventricular septum (IVS) and left ventricular diastolic dimensions (LVDD)are found significantly higher in age- and gender-matched normotensive T2DM than healthy control subjects. This shows that T2DM complicates heart muscle disease independently of HTN.

In the Framingham Heart Study, the prevalence of LVH assessed by echocardiography in a predominantly non-diabetic population was reported 16% in males and 21% in females. The study includes 42 females with diabetes and was characterized by a 22% increase in left ventricular wall thickness than their non-diabetic peers. In our study, the prevalence of LVM in age- and gender-matched normotensive T2DM and control subjects was 18.5% in males and 20.2% in female subjects (Figure 1 &2) which is somewhat consistent with the Framingham Heart Study.

Form our population none of the subjects fulfilled the Sokolow-Lyon ECG criteria for diagnosing left ventricular hypertrophy which is agreed with the Framingham Heart Study which reveals the electrocardiogram (ECG) left ventricular hypertrophy (LVH) of 0.5% by using the same method. In contrast with another study by Bruno G et al. which reported the prevalence of electrocardiogram left ventricular hypertrophy (ECG-LVH) of 17 in T2DM[12]. This was because of old age subjects with known long duration of DM and arterial hypertension as well as micro-and macroalbuminuria in half of the population.

In the non-diabetic population left ventricular mass is commonly associated with IHD, however, evidence suggests that IHD is a consequence despite left ventricular mass. One of the cohort studies by Lee M et al. investigated 5000 subjects and found that an increase in wall thickness in septum and LVPW was not associated with CHD[13]. Consequently, our results of increased thickness could not apply to such a phenomenon.

Urinary albumin excretion rate is highly associated with left ventricular mass demonstrated previously in non-diabetic and T1DM and T2DM patients with macro and microalbuminuria [9,14]. Along with this in diabetic and non-diabetic hypertensive subjects with left ventricular hypertrophy, and increased urinary albumin excretion results in increased cardiovascular morbidity and mortality[15]. For this purpose, we selected the subjects in both T2DM case and control groups having no micro or macroalbuminuria. So, in the study albuminuria is not the cause of LVH.

In addition to high BP, urinary albuminuria excretion rate, body mass index, and blood sugar [16] it has been also suggested that coronary microvascular disease, endothelial abnormalities, chronic inflammatory disease, and tissue disorders like the renin-aldosterone-bradykinin system might play role in the development of pathogenesis of left ventricular hypertrophy.

CONCLUSION

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The overall conclusion of this cross-sectional study can be summarizing as

I. As compared to healthy control subjects left ventricular mass (LVM) is significantly higher in T2DM patients without HTN, IHD, and other diseases.
II. The prevalence of developing left ventricular hypertrophy is almost similar in both genders.
III. Poor glycemic control, obesity, and long-duration diabetes increase the chances of left ventricular hypertrophy.
IV. This significant study reveals the prevalence of left ventricular mass in T2DM patients without other major complications like HTN, albuminuria, and other complications. It's important to rule out the prognosis of LVM in the diabetic population to overcome cardiovascular adverse events and morbidity and mortality.

Disclosure: None

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