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GENDER DIFFERENCES IN LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NORMOTENSIVE TYPE 2 DIABETIC PATIENTS

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All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: To determine the pattern and severity of left ventricular diastolic dysfunction in normotensive type 2 diabetic males and females patients.

Methodology: This descriptive study was performed in Department of Cardiology, Lady Reading Hospital, Peshawar, from March 2007 to February 2008. Total of 60 patients were enrolled. Glycemic status was defined on the basis of HbA1c level. Detailed history and physical examination was performed on every patient. Exercise tolerance test was performed on every patient to exclude major ischemia. Echocardiography was performed in left lateral position. Main outcome measure was left ventricular diastolic dysfunction.

Results: We enrolled 60 normotesive type 2 diabetic patients in the study that fulfills the inclusion criteria. Left ventricular diastolic dysfunction was found in 50% (30/60). There were 12 males (40%) and 18 females (60%) among subjects presenting with diastolic dysfunction. In male gender impaired relaxation was found in 75% (9 males) and in female gender it was found in 66.6% (12 females) ($p=0.58$). Pseudonormal pattern was found in 25% in male gender (3 males) and in 33.3% in female gender {6 females} ($p=0.003$). Males subjects with diastolic dysfunction the mean age were 54 ± 8.8 and mean age of females' subject were 60 ± 13.2 ($p=0.17$).

Conclusion: Left ventricular diastolic dysfunction is more common in female gender and is more severly impaired in female gender than in male gender.

Key Words: Type 2 diabetes mellitus, Left ventricular diastolic dysfunction, Gender.

INTRODUCTION

The main reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure (diabetic cardiomyopathy).[1,2] Diabetes mellitus is a well-recognized risk factor for developing heart failure.[2] The Framingham Heart Study showed that the frequency of heart failure is twice in diabetic men and five times in diabetic women compared with age matched control subjecs.[3] This increase incidence of heart failure in diabetic patients persisted despite correction for age, hypertension, obesity, hypercholesterolemia, and coronary artery disease.[3] Studies using independent population databases have provided similar results, revealing increased heart failure rates in subjects with diabetes mellitus in cross sectional analyses and increased risk for developing heart failure in prospective analyses, even after correction for confounding variables.[4, 5]

Diabetic cardiomyopathy in humans also is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction.[6,7] Echocardiography perform in 87 patients with type 1 diabetes mellitus without known coronary artery disease revealed diastolic dysfunction with a reduction in early diastolic filling, an increase in atrial filling, an extension of isovolumetric relaxation, and increased number of supraventricular premature beats.[8] In patients with type 1 diabetes mellitus that had not develop microvascular or macrovascular complication, the researchers reported early structural and functional cardiac alterations such as increased LV wall thickness and LV mass index, an age related decline in ejection fraction, and an age related increase in diastolic diameter.[9] Similar approaches in well-controlled subjects with type 2 diabetes have revealed a prevalence of diastolic dysfunction of up to 30%.[10] The use of flow and tissue doppler technique suggests even higher prevalence of diastolic dysfunction (as high as 40% to 60%) in community surveys and in smaller studies of individuals with type 1 and type 2 diabetes mellitus without overt coronary artery disease.[11-14]

Diastolic dysfunction has been described as an early sign of the diabetic cardiomyopathy before systolic dysfunction.[15] Diastolic dysfunction comprises about 30 to 50% of all patients hospitalized for heart failure.[16] The dramatic increase in hospitalisation for heart failure among the elderly can be largely attributed to this condition.[16] Diabetes mellitus is considering an important independent factor in developing diastolic dysfunction.[17]

Doppler echocardiography is one of the most useful clinical tools for the assessment of left ventricular diastolic function.[18] Doppler indices of left ventricular filling are use not only for diagnostic purposes but also for establishing prognosis and evaluating the effect of treatment.[18]

Endothelial dysfunction is aggravated by hyperglycemia.[19] A gradual increase in abnormalities of diastolic function according to the frequency and severity of diabetic microvascular complications was demonstrated.[19] Diabetic microangiopathy is a background factor for diabetic heart muscle disease.[15] Chronic hyperglycemia contributes to diabetic complications through the formation of advanced glycosylation end products, which are irreversibly formed biochemical end products of non enzymatic glycosylation.[19] AGEs play a key role in the pathogenesis of cardio-myopathy.[19]

Left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy reinforcing the importance of the early examination of diastolic function in individual with diabetes.[12,20] Left ventricular diastolic abnormalities reported in diabetes mellitus contain a component of reversibility and can be prevented by aggressive treatment.[21] Intensive blood glucose control by either sulphonylureas or insulin decreases the risk of microvascular complications in patients with type 2 diabetes mellitus.[22] Early and accurate detection of left ventricular diastolic dysfunction in type 2 diabetic patients might have therapeutic implication.[20]

Diastolic dysfunction in women differs in many aspects from that of men. Some of these differences may have a pathophysiological basis. These sex differences may have widespread implications in the field of heart failure with normal ejection fraction. Elucidation of a pathophysiological basis of sex differences, together with clinical trials designed to study the impact of treatments in women, could lead to some aspects of diastolic dysfunction management being sex based. Until now, little investigation of sex influence on pathophysiology has been carried out. The large and consistent difference in the yield of left ventricular diastolic dysfunction in women versus men with suspected heart failure is puzzling and requires explanation. We conducted this study to determine the pattern and severity of left ventricular diastolic dysfunction in normotensive type 2 diabetic males and females patients.

METHODOLOGY

This descriptive study was conducted from March 2007 to February 2008. Normotensive type 2 diabetic patients that full fill the inclusion criteria were included. Patients were selected from out patient department of Lady Reading Hospital, Peshawar. Patients were excluded from the study if they had a history of myocardial infarction (previous or recent), congestive heart failure, valvular heart disease, hypertension, cardiomyopathy, known coronary artery disease, connective tissue disease, thyroid dysfunction and renal disease. Informed consent was taken from all patients. Complete history and full physical examination was done on every patient included in the study.

Diabetic status was defined on the basis of HbA1c level. Resting ECG and Exercise tolerance test was performed on every patient to exclude ischemia. The study patients underwent echocardiography (using Acuson CV70 Siemens system). All patients were examined in the left lateral position.

From apical four-chamber view pulse wave Doppler Mitral inflow velocities was recorded by placing sample volume at the tips of the Mitral valve. The transmitral peak early diastolic velocity (E), peak late diastolic velocity (A), E wave deceleration time (DT) and E/A ratio were measured. Isovolumic relaxation time (IVRT) was recorded from apical 5- chamber view by simultaneously recording of the mitral and aortic flows.

The normal cut-off values for Doppler echocardiography adopted from the guidelines of American Society of Echo-cardiography.

Diastolic dysfunction on conventional Doppler echo-cardiography:

Impaired relaxation: This was defined as deceleration time >220msec, Isovolumic relaxation time > 100 msec, E/A < 1.

Pseudo normal: It was defined as deceleration time 150-200msec, Isovolumic relaxation time 60-100msec, E/A > 2.

Restrictive filling: It was defined as deceleration time <150msec, Isovolumic relaxation time <60msec, E/A ratio >2.

Data were analysed using SPSS version 10. The variables were age, sex, duration of diabetes mellitus, Ejection fraction, Fractional shortening, mitral inflow velocities, Isovolumic relaxation time and Mitral E wave deceleration time on Doppler Echocardiography. Data were expressed as mean ± standard deviation and in percentage. Student t test was applied for numerical variables and chi square test was applied for categorical variable. P value < 0.05 was considered significant.

RESULTS

We enrolled 60 normotensive type 2 diabetic patients that fulfill the inclusion criteria. The basic characteristics of the patients were shown in Table 1. Males were 32 in number and females were 28. Fifty percent (30/60) had left ventricular diastolic dysfunction. There were 12 (40%) males and 18 females (60%) subjects presenting with diastolic dysfunction. Basic clinical characteristics were similar between all patients. All patients had normal systolic functions (Table 2).

Mean Peak E velocity was lower in female patients than male patients. Peak A velocity was higher in female subjects than male subjects. E/A ratio were lower in female subjects than male subjects. The deceleration time was longer than in male subjects by a mean of 08 ms in female subjects (Table 3).

In this study the mean E velocity of early filling was lower in female gender having left ventricular diastolic dysfunction than in male gender with left ventricular diastolic dysfunction (Table 4). Mean A velocity was higher in females gender than in males. Regarding mean E/A ratio there was a significant difference between male gender and female gender (p=0.0001). Deceleration time is longer in males than in females. Isovolumic relaxation time is longer in female gender than in male gender with statistical significance difference (Table 4).

In male gender Impaired Relaxation was found in 75% (9 males) and in female gender it was found in 66.6% (12 females) with no statistical significant (p=0.58). Pseudonormal pattern was found in 25% in male gender (3 males) and in 33.3% in female gender (6 females) with statistical significant (p=0.003) {Table 5}.

Table 1: Basic Characteristics of all Patients

Characteristic	Male Gender (32)	Female Gender (28)	P-value
Age (years)	53±8.7	57±11	0.11
Heart rate (min)	72	75	0.2
Systolic blood pressure (mmHg)	120±5	118±8	0.56
Diastolic blood pressure (mmHg)	70±5	72±6	0.5
Duration of diabetes	10.2±2.7	10.3±3.5	0.96

Table 2: Echocardiographic Characteristics of all Patients

Characteristics	Male Gender (32)	Female Gender (28)
LVESD	2.70	2.75
LVEDD	4.36	4.4
IVS	0.81	0.86
PW	0.80	0.83
EF%	61	60
LA size	3.6	3.9

P-value is >0.05

Table 3: Doppler Echocardiographic Characteristics of all Subjects

Characteristics	Male Gender (32)	Female Gender (28)	P-value
E wave	0.64±0.06	0.54±11	0.001
A wave	0.55±0.13	0.65±0.15	0.02
E/A ratio	1.23±0.36	0.91±0.04	0.000
IVRT	97±8.7	103±10.8	0.009
DT	214±13	222±15	0.02

Table 4: Diastolic Filling Parameters of Patients having LV Diastolic Dysfunction

Characteristics	Male Gender	Female Gender	P-value
E wave	0.59±0.06	0.46±0.07	0.0001
A wave	0.72±0.03	0.75±0.07	0.15
E/A ratio	0.80±0.11	0.62±0.11	0.0001
DT	229±2.1	232±3.5	0.24
IVRT	108±2.9	110±4.7	0.01

Table 5: Pattern of Left Ventricular Diastolic Dysfunction

Characteristics	Male Gender	Female Gender	P-value
Impaired relaxation	75% (9)	66.6% (12)	0.58
Pseudonormal pattern	25% (3)	33.3% (6)	0.003

DISCUSSION

The objective of this study was to investigate gender-related patterns of left ventricular diastolic dysfunction in normotensive type 2 diabetic patients. On average, male subjects were characterized by a slightly lower LV diastolic dysfunction as compared to female subjects. In males LV diastolic dysfunction was found in 40% and in females LV diastolic dysfunction was found in 60%. Klapholz et al, showed that 73% patients present with diastolic dysfunction are women and 82% of these patients were suffering from type 2 diabetes mellitus.[23] Persson et al, demonstrates that 34% females present with diastolic dysfunction.[24]

Impaired relaxation was common in both gender it was 75% in males and 66.6% in female gender. More severe form of diastolic dysfunction in the form of pseudonormal is slightly more common in females (pseudonormal pattern is 33.3%) than in males (pseudonormal pattern is 16.6%). Persson et al, showed that 67% patients had impaired relaxation while 44% patients had moderate and sever form of LV dysfunction in the form of pseudonormal and restrictive pattern.[24]

Poirier et al, showed that LV diastolic dysfunction appears to be quite common in well-controlled type 2 diabetic patients without clinically detectable heart disease; in 46 well-controlled type 2 diabetic patients who had no evidence of diabetic complications, hypertension, coronary artery disease, congestive heart failure, or thyroid or overt renal disease, and no overt systolic dysfunction, LV diastolic dysfunction was present in 28 subjects (60%), of whom 13 (28%) had a pseudonormal pattern of ventricular filling (indicating raised filling pressure), and 15 (32%) had impaired relaxation (a milder form of diastolic dysfunction).[12] Diabetes is associated with left ventricular hypertrophy and, with different patterns of left ventricular structural abnormalities between genders.[12]

The prevalence of DM is growing fastest in women. Women with diabetes, regardless of menopausal status, have a 4 to 6 fold increase in the risk of developing cardiovascular diseases whereas men with diabetes have a 2 to 3 fold increase in risk. Women with type 2 DM experience more symptoms of hyperglycemia than do their male counterparts. Obesity, an important contributor to type 2 DM, is more prevalent in women. Women with diabetes have an increased risk of hypertension compared with men with diabetes.[25]

Women have a more severe type of dyslipidemia than do men (low levels of high-density lipoprotein cholesterol, small particle size of low-density lipoprotein cholesterol, and high levels of triglycerides), and these risk factors for CAD have a stronger influence in women. Oxidative stress may confer a greater increase in the risk of cardiovascular risk for women with diabetes than for men with diabetes.[25]

Many other sex differences in DM are due to women's reproductive physiology. Women are less likely than men to receive aggressive treatment. Critical recommendations for women include exercise, testing for cardiovascular diseases, daily aspirin to counteract the prothrombotic state, depression screening, careful treatment to avoid weight gain, long-term follow-up of children of women with GDM, control of risk factors for CAD, and aggressive treatment with coronary angioplasty for CAD. Disease management programs for patients with diabetes have been shown to save money and improve outcomes, and should continue to incorporate information about sex-specific differences in DM as it becomes available.[25]

Heart failure with normal ejection fraction (HF-NEF) is frequently believed to be more common in women than in men. However, the interaction of gender and age has rarely been analyzed in detail, and knowledge of the distinction between pre- and postmenopausal women is lacking. Some of the epidemiological investigations agreed on the greater prevalence of HF-NEF in women.[26]

Major risk factors for HF-NEF include hypertension, aging, obesity, diabetes, and ischemia. Aging, obesity, and diabetes affect myocardial and vascular stiffness differently and lead to different forms of myocardial hypertrophy in women and men.[26]

Gender differences in ventricular diastolic distensibility, in vascular stiffness and ventricular/vascular coupling, in skeletal muscle adaptation to HF, and in the perception of symptoms may contribute to a greater rate of HF-NEF in women. The underlying molecular mechanisms include gender differences in calcium handling, in the NO system, and in natriuretic peptides. Estrogen affects collagen synthesis and degradation and inhibits the renin-angiotensin system. Effects of estrogen may provide benefit to premenopausal women, and the loss of its protective mechanisms may render the heart of postmenopausal women more vulnerable. Thus, a number of molecular mechanisms can contribute to the gender differences in the development of diastolic dysfunction.[26]

Gender may be an independent factor in the development of left ventricular diastolic dysfunction.[27]

CONCLUSION

In conclusion, this observational study provides important new insight into gender-specific differences in left ventricular diastolic dysfunction in diabetic patients free from hypertension and ischemic heart disease. Left ventricular diastolic dysfunction is more common in female gender and is more severily impaired in female gender than in male gender.

Additional investigations are warranted to confirm these findings and to elucidate the biological under printings of these sexes' related differences.

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