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Original Research Article

Prevalence of Proteinuria and Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients with Left Ventricular Diastolic Dysfunction.

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Abstract: To study the prevalence of proteinuria and diabetic retinopathy in Type 2 Diabetes Mellitus patients with left ventricular diastolic dysfunction.

Methods: After ethical consideration, Observation based Cross–Sectional study was done on 41 cases of type 2 diabetes mellitus with left ventricular diastolic dysfunction (LVDD). All the patients were subjected for routine investigations along with HbA1c and 2D echocardiography for evaluation of the left ventricular function and fundus examination.

Results: The cases with left ventricular diastolic dysfunction had a mean HbA1c of 8.48. There was significant correlation of left ventricular diastolic dysfunction with HbA1c (p value of 0.001). Out of forty-one (100%) cases fifteen (36.6%) were having nil urine Protein and eight (19.5%) were having 1+ and eight (19.5%) were having 2+ and eight (19.5%) were having 3+ and two (4.9%) were having 4+ urine Protein out of the 41 cases, fifteen (36.58%) cases were having diabetic retinopathy and twenty-six (63.42%) without diabetic retinopathy.

Conclusions: This study concludes that proteinuria, diabetic retinopathy and myocardial damage occurs before the appearance of clinical manifestations. Proteinuria and diabetic retinopathy is having high prevalence in patient with LVDD signifying early manifestations of the disease. Early intervention and strict control of diabetes should be advised to all diabetes patients to prevent the early involvement of the kidney, eyes and myocardium.

Keywords: Left Ventricular Diastolic Dysfunction (LVDD), HBA1C, Advanced glycation end products

Introduction

Diabetes is defined as a group of disorders which share the common phenotypic pattern of hyperglycaemia. [1]

The sweet urine symptom of diabetes is evident in the Chinese name for diabetes, táng niǎo bìng (糖 尿 病), meaning "sugar-urine disease". This name has also been borrowed into Korean and Japanese. [2]

The primary defect in diabetes lies in carbohydrate metabolism which may be a result of various factors. As the knowledge in this field is increasing day by day and with the advent of new technology and further research the disease appears to be more complex as it was thought eons ago. It is not merely a disease but a complex

metabolic disorder characterized by hyperglycaemia primarily because of defect of carbohydrate metabolism associated with disruption of fat and protein metabolism. [3]

India will have the highest number of diabetic patients in the world by 2025 becoming the Diabetic capital of the world. [4]

The delayed micro vascular and macrovascular complications of diabetes include retinopathy, nephropathy, cardiomyopathy and neuropathy; an increased risk of peripheral vascular disease and cerebrovascular accidents. [5]

The pathogenesis of these complications is multifactorial, although persistent hyperglycaemia ("glucotoxicity") seems to be a key mediator; apart from hyperglycaemia other factors are also responsible for the long-term complications of diabetes, such as insulin resistance, and co morbidities like obesity.

Diabetic cardiomyopathy

The existence of a primary myocardial disease "Diabetic cardiomyopathy" has been proposed in the absence of ischemic, valvular or hypertensive disease. [6]

Epidemiological and clinical and pathological data suggests association of a specific cardiomyopathy in diabetes mellitus.

In 1974, Framingham study showed that heart failure was more common in diabetes due to diabetic cardiomyopathy. This study was a prospective study comprising of 5000 study subjects over a follow up period of 18 years. The incidence of heart failure was more than twice in diabetic males when compared with the non-diabetic cohort while it was five times more in diabetic women.

These all results were after accounting for the other factors that commonly coexist with diabetes. [7]

Three distinct metabolic pathways have been implicated in the deleterious effects of persistent hyperglycaemia on peripheral tissues.

The pathways are

1. Formation of Advanced Glycation End Products. [8,9]

Advanced glycation end products (AGEs) are produced as a result of nonenzymatic reactions between intracellular glucose-derived dicarbonyl precursors (glyoxal, methylglyoxal, and 3deoxyglucosone) with the amino groups of both intracellular and extracellular proteins. In the presence of hyperglycaemia, the natural rate of AGE formation is greatly accelerated and these AGEs bind to a specific receptor (RAGE), which is expressed on inflammatory cells (macrophages and T cells), vascular smooth muscle and the endothelium. The detrimental effects of the AGE-RAGE signalling axis within the vascular compartment include

(a) Release of pro-inflammatory cytokines and growth factors from intimal macrophages;

(b) Generation of reactive oxygen species in endothelial cells;

(c) Increased procoagulant activity on endothelial cells and macrophages; and

(d) Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix.

2.Activation of Protein Kinase C.

Activation of intracellular protein kinase C (PKC) by Ca^{2+} ions and the second messenger diacyl glycerol (DAG) is an important signal transduction pathway in many cellular systems. The activation of PKC by intracellular hyperglycaemia stimulates the de novo synthesis of DAG from glycolytic intermediates, which leads to numerous changes and include the following.

1. Production of proangiogenic vascular endothelial growth factor (VEGF),

implicated in the neovascularization characterizing diabetic retinopathy
2. Elevated levels of the vasoconstrictor endothelin-1 and decreased levels of the vasodilator NO, due to decreased expression of endothelial nitric oxide synthase
3. Production of profibrogenic factors like TGF-β, leading to increased deposition of extracellular matrix and basement membrane material
4. Production of PAI-1, leading to reduced fibrinolysis and possible vascular occlusive episodes
5. Production of pro-inflammatory cytokines by the vascular endothelium

Proteinuria and Diabetes

The ADA defines albuminuria as a persistently increased urinary albumin-to-creatinine ratio >30 mg/g on a spot specimen. the albuminuria can regress with improvement in glycaemic control if it is of short duration, or if the blood pressure is under control by the use of angiotensin-aldosterone system blockade and/or SGLT-2 inhibitor drugs. Diabetic kidney disease refers to albuminuria and reduced GFR (<60 mL/min per 1.73 m2); Once there is marked albuminuria and a reduction in GFR, the pathologic changes are likely irreversible. There may be significant albuminuria when type 2 DM is diagnosed, reflecting its long asymptomatic period, and hypertension more often contributes to albuminuria and reduced GFR. [10,11]

Eye and Diabetes

Diabetes as we say involves head to toe; eyes are also affected because of the vascular damage; the growth factors play an important role and their production is increased by most of the proposed pathways. the vascular endothelial growth factor A (VEGF-A) is main culprit implicated in diabetic ocular involvement manifesting as diabetic retinopathy. The progressive diabetic retinopathy, leads to vision loss because of significant macular edema and new blood vessel formation. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of hyperglycaemia and is marked by retinal vascular microaneurysms, blot haemorrhages, and cotton-wool spots. Mild nonproliferative retinopathy may progress to more extensive disease, characterized by changes in venous vessel calibre, intraretinal microvascular abnormalities, and more numerous microaneurysms and haemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which can lead to retinal ischemia. The neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy. [12,13]

Aims and Objectives: To study the prevalence of proteinuria and diabetic retinopathy in patients with left ventricular diastolic dysfunction

Material & Methods: This Observation based Cross–Sectional study was done on 41 cases of Type 2 Diabetes Mellitus with Left ventricular diastolic dysfunction.

Inclusion Criteria

- Diabetic Patients in the age group 30-60 years with left ventricular diastolic dysfunction.
- Without prior history or symptoms suggestive of hypertension, coronary artery disease, valvular heart disease or congestive cardiac failure.

Exclusion Criteria

- Patients without Left ventricular diastolic dysfunction.
- Past history of Myocardial infarction, unstable angina.
- Patients with Rheumatic Heart disease.

Observation & Results

In the present study the mean age is 50.41 yrs. with a standard deviation of 8.02. The result of mean age of cases in was statistically significant p value = 0.004.

In the present study twenty-two (53.6%) cases were males while nineteen (46.34%) were females whereas in the male: female ratio was 1.15:1

In the present study out of forty one (100%) cases twenty one (51.21%) were having nil urine sugar and five (12.19%) were having 1+ and nine (21.95%) were having 2+ and five (12.19%) were having 3+% and only one (2.4%) was 4+ urine sugar.

In the present study out of the forty one cases studies, fifteen (36.58%) cases were having diabetic retinopathy and twenty six (63.42%) without diabetic retinopathy. The result of Diabetic Retinopathy of cases was statistically not significant p value = 0.7.

Madhumathi R, Prakash Kikkeri Gowdaiah et al [14] their study in 2014, observed high prevalence of diabetic retinopathy in patients with LVDD was 61.5%. (Eight patients out of thirteen) as compared to that of present study. [15]

In the present study out of forty one (100%) cases fifteen (36.6%) were having nil urine Protein and eight (19.5%) were having 1+ and eight (19.5%) were having 2+ and eight (19.5%) were having 3+ and two (4.9%) were having 4+ urine Protein

Table 1: Mean age with SD of patients with LVDD

No of patients	41
Mean age	50.41
Std. deviation	8.02
t value	3.013
p value	0.004

Table 2:

Gender	No. of cases	Percentage
Males	22	53.66
Females	19	46.34
	41	100
Chi-square	df	p value
0.2	1	0.6

Table 3: Prevalence of Glycosuria in cases

Urine Sugar	No	%
Nil	21	51.21
1+	5	12.19
2+	9	21.95
3+	5	12.19
4+	1	2.4
	41	100
Chi-square	df	p value
1.86	4	0.76

Table 4: Diabetic Retinopathy in patients with LVDD

	No	%
Diabetic Retinopathy+	15	36.58
Diabetic Retinopathy-	26	63.42
Total	41	100
Chi-square	df	p value
0.15	1	0.7

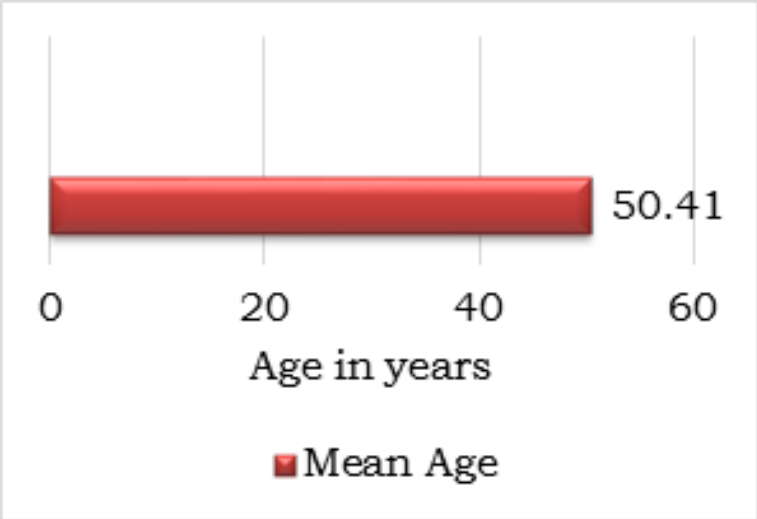

Figure 1: Bar Diagram of Mean Age of the cases with LVDD.

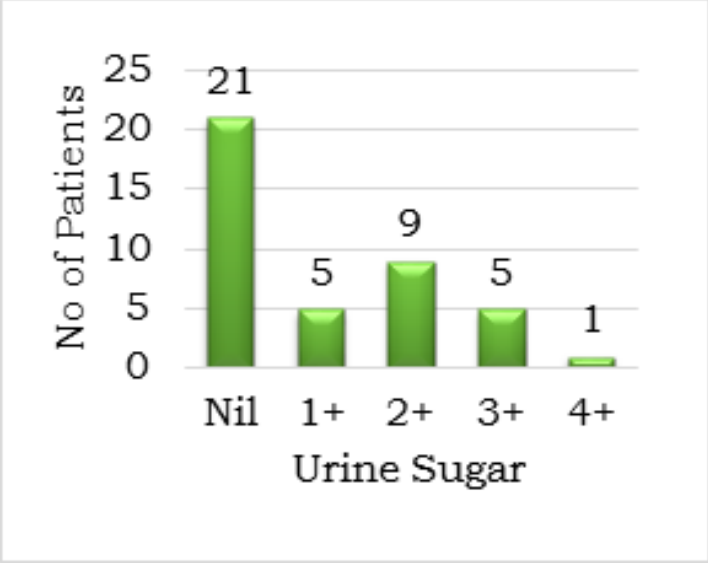

Figure 2: Bar diagram depicting the prevalence of urine sugar in cases with LVDD

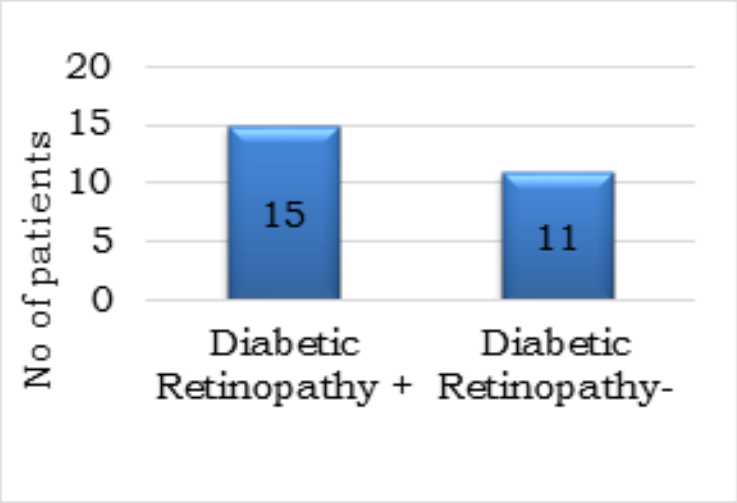

Figure 3: Bar diagram depicting the prevalence of Diabetic Retinopathy in cases with LVDD.

Conclusion

1. There is significant myocardial damage in diabetes which occurs before the clinical manifestations appear.
2. Left ventricular diastolic function is affected much earlier in type 2 DM patients than that in normal healthy population and is affected earlier than systolic function and is an early marker of Diabetic Cardiomyopathy.
3. Left ventricular diastolic Function was affected more or less equally in both genders
4. Diabetic retinopathy was prevalent in 36.58% in type 2 diabetes patients with left ventricular diastolic dysfunction.
5. Proteinuria was prevalent in 36.6% in type 2 diabetes patients with diastolic dysfunction.

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