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Study of Correlation Between Insulin Resistance and Left Ventricular Diastolic Dysfunction In Patient of Type 2 Diabetes Mellitus

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by hyperglycaemia and insulin resistance (IR). IR has also been reported as an independent predictor for Left ventricular diastolic dysfunction (LVDD) but with limited research evidence. Therefore, the present study aims to find correlation between insulin resistance and LVDD in patients with T2DM.

Materials And Methods: Patients aged 18-65 years, of either gender, meeting the diagnostic criteria for T2DM were included. The calculated sample size was 104. The following variables were evaluated and compared; age (years), gender, basal metabolic index (BMI; kg/m2), waist circumference (cm), fasting blood sugar (FBS; mg/dl), HbA1c (%), fasting insulin (µU/ml), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score, and LVDD grade.

Results: The mean age of the patients was 58.55 ± 10.75 years with male: female ratio of 1.53 :1. The mean ± SD values of BMI, waist circumference, FBS, HbA1c, fasting insulin, and HOMA-IR score among all the enrolled patients were 24.45 ± 2.10 kg/m2 , 83.38 ± 5.02 cm, 144.08 ± 16.45 mg/dl, 7.23 ± 0.59%, 8.55 ± 6.11 µU/ml, and 2.53 ± 1.9, respectively. LVDD was absent in 60.6 % (n=63). The distribution of patients with LVDD Grade 1, 2, 3 and 4 were 13.5% (n=14), 15,4% (n=16), 6.7% (n=7) and 3.8% (n=4), respectively. LVDD grades showed statistically significant difference with fasting Insulin and & HOMA IR score.

Conclusion: In asymptomatic patients with T2DM without evidence of cardiac or systemic disorders, insulin resistance was independently associated with impaired left ventricular diastolic function. Future research is recommended to determine its exact mechanism.

Keywords: Nil

Introduction

Diabetes mellitus (DM) is a chronic community health issue with high morbidity and mortality. DM will cover approximately 9.9% of the world population by 2045 [1]. The number of diabetic cases will rise from 135 million in 1995 to 300 million in the year 2025 globally [2]. In India, 69.1 million people are suffering from DM, which is further moving to be the second- highest number of cases of DM in the world [3]. Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by hyperglycaemia and insulin resistance (IR) predisposes to cardiovascular risk factors. IR has also been reported as an independent predictor for the progression of cardiovascular disease in T2DM and predicted diastolic heart failure (HF) [4].

Left ventricular diastolic dysfunction (LVDD), increased left ventricular wall thickness, increased left ventricular mass and specific diabetic cardiomyopathies are some of the cardiovascular complications associated with diabetes [5]. Diastolic dysfunction is an early complication of DM and it is believed to be the initial step in Diabetic cardiomyopathy (DCM). It is characterized by a decrease in systolic and diastolic function without hypertension, coronary artery disease, and left ventricular hypertrophy [6].

Research suggests IR is directly and independently associated with worsening diastolic function and increased risk for LVDD [7,8]. It is also suggested that subclinical changes in diastolic function are present even before the onset of T2DM and are significantly associated mainly with the state of insulin resistance and not only with the duration of persistent hyperglycemia [7]. Multiple pathophysiologic mechanisms play a role in the causation of insulin resistance and LVDD in DM.

In the heart, insulin induces glucose uptake and increases fatty acid uptake, inhibiting fatty acid utilization for energy. These changes in substrate utilization from glucose to free fatty acids results in a reduction of myocardial energy supply in the situation of IR [9]. Other proposed

theories include increased afterload and impaired ventricular-vascular coupling due to arterial stiffness [10], increased myocardial oxidative stress [11] activation of sympathetic nervous system, endothelial dysfunction [12], or increased myocardial interstitial fibrosis [13]. Limited literatures are available about the associations between IR and LVDD in DM. So, the role of IR in cardiovascular diseases in people with diabetes deserves further investigation. Therefore, we aimed to study the correlation between insulin resistance and LVDD in patients with T2DM

Material & Method:

The present study was conducted in the Department of Medicine, Pt.J.N.M. Medical College and Dr. Bhim Rao Ambedkar Memorial Hospital, RAIPUR, CG, over two years from September 2019 to August 2021. The calculated sample size was 104. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from the participants.

Patients aged 18-65 years, of either gender, meeting the diagnostic criteria for type 2 diabetes mellitus (clinical symptoms like polyuria, polydipsia, and polyphagia) were included. Patients with type 1 diabetes mellitus or major systemic diseases like hypertension, hypothyroidism, infiltrative, valvular heart diseases or pregnant/lactating women were excluded. The following variables were evaluated in the study; age (years), gender, basal metabolic index (BMI; kg/m2), waist circumference (cm), fasting blood sugar (FBS; mg/dl), HbA1c (%), fasting insulin (µU/ml), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score, LVDD grade. IR was assessed by using HOMA-IR score. The HOMA-IR was calculated with the formula: HOMA-IR = glucose (in mmol/L) x insulin (in µU/mL) / 22.5 [14]. LVDD was assessed using Transthoracic Echocardiography. The LVDD was compared with the variables described above.

Data were expressed as a percentage and mean ± SD. Kolmogorov-Smirnov analysis was performed for checking the linearity of the data. Pearson correlation analysis was performed to assess the correlation between two categorical variables. The Chi-square test was used to analyze the significance of the difference between frequency distribution of the data. P-value

<0.05 was considered statistically significant. All statistical analysis was done in Microsoft Excel and SPSS 17.0.

Results:

The mean age of the patients was 58.55 ± 10.75 years. The majority of patients (38.5%) belonged to age group ≥61 years. Male predominance was observed with a male: female ratio of 1.53:1. About 61% were males and the rest 39% cases were females. The mean ± SD values of BMI (kg/m2), waist circumference (cm), FBS (mg/dl), HbA1c (%), fasting insulin (µU/ml), and HOMA-IR score among all the enrolled patients were 24.45 ± 2.10 kg/m2, 83.38 ± 5.02 cm, 144.08 ± 16.45 mg/dl, 7.23 ± 0.59%, 8.55 ± 6.11 µU/ml, and 2.53 ± 1.9, respectively. LVDD was absent in 60.6 % (n=63) (Table 1). The distribution of patients with LVDD Grade 1, 2, 3 and 4 were 13.5% (n=14), 15,4% (n=16), 6.7% (n=7) and 3.8% (n=4), respectively (Table 2). The correlation between LVDD grade and the following parameters; age, gender, BMI, waist

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circumference, FBS and HbA1c, did not show statistically significant differences among the patients. There was a statistically significant difference between LVDD & fasting Insulin (Figure 1) and LVDD grade & HOMA IR score (Figure 2).

Discussion:

Diabetes mellitus, including both insulin-dependent and non-insulin dependent are risk factors for cardiac diseases. One of the common precursors in the aetiology of diabetic cardiomyopathy is LVDD, while IR is a pre-disposer in the aetiology of T2DM [5]. Multiple pathophysiologic mechanisms play a role in the causation of insulin resistance and LVDD in DM. In the heart, insulin induces glucose uptake and increases fatty acid uptake, inhibiting fatty acid utilization for energy. These changes in substrate utilization from glucose to free fatty acids results in a reduction of myocardial energy supply in the situation of IR [9][15]. Heart failure in diabetic patients is caused by various factors that are unknown [16]. Doppler echocardiography was used to study the left ventricular diastolic dysfunction in this research and correlated these findings with IR estimated by HOMA-IR score.

The prevalence of LVDD among total patients (n=104) in our study was 39.4% (n=41). These findings were comparable with other studies that report the prevalence of LVDD among asymptomatic T2DM patients as 30.76% [17], 54.33% [18] and 64% [19]. Diastolic dysfunction in diabetic patients is believed to represent an earlier stage in the natural history of diabetic cardiomyopathy. Its timely recognition may help avoid or significantly delay the onset of CHF [20]. Studies have shown that DM causes structural and functional abnormalities independent of the effect of atherosclerosis, and these abnormalities contribute significantly to adverse cardiovascular events. Left ventricular diastolic dysfunction has been proposed as the first stage of diabetic cardiomyopathy [21].

In this study, HOMA-IR score and Fasting Insulin were significantly correlated with LVDD grade. The mean HOMA-IR score was 2.53 ± 1.9, with 48.1% of patients having a score between 0 to 2. A study suggested individuals in the highest HOMA-IR quartile were more likely to have LVDD, even after adjustment for age, sex, blood pressure and body mass index.

They concluded that HOMA-IR score and metabolic syndrome were independently associated with LVDD. Changes in diastolic function are already present before the onset of diabetes, being mainly associated with the state of insulin resistance [7].

Our findings were also in accordance with the study by Ayalon et al.[22] which suggested that IR can lead to the development of diastolic dysfunction through mechanisms independent of hypertrophy. Also, in a study by Matthews et al.[14], they found that IR, as estimated by the HOMA-IR, was strongly associated with LVDD in patient without a history of overt diabetes.

Another study was conducted to assess whether IR and glucose metabolism abnormalities are related to LVDD. The prevalence of LVDD was 92% in subjects with IR vs. 72% in patients without IR (n = 113), respectively (p = 0.013). HOMA-IR seems to be a reliable diagnostic tool and practicable alternative in the clinical setting in the assessment of IR [8].

Also, in relation to our findings, Bajraktari et al. reported that in subjects with impaired glucose tolerance and patients with type 2 diabetes, insulin resistance is associated with the impaired diastolic function of the left ventricle [23].

The exact mechanism of association between IR and LVDD is still not fully understood. Impaired relaxation is well established as one of the first signs of cardiac involvement in various disorders. Metabolic disturbances in the pre-diabetic of type 2 diabetes cause left ventricular fibrosis, elicited in recent clinical research [24]. Furthermore, elevated levels of transforming growth factor beta-1 receptor were found in rat left ventricular myocytes, implying that metabolic disorders and IR may play a role in the beginning of cardiac fibrosis [24]. Insulin stimulates the proliferation of cardiac myocytes and enhances collagen synthesis in fibroblasts, also claimed in other research [25,26].

However, the mechanisms by which IR increases left ventricular diastolic dysfunction remain largely unknown. Our results also demonstrate, Insulin resistance and Fasting Insulin were

significantly correlated with LVDD and hence can be used as a predictor of left ventricular diastolic dysfunction.

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Conclusion:

In asymptomatic patients with T2DM without hypertension and evidence of cardiac or systemic disorders, insulin resistance is independently associated with impaired left ventricular diastolic function. Future research is recommended to determine the exact mechanism behind it and determine if improving insulin resistance using insulin sensitizers or lifestyle changes can improve diastolic function.

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Tables And Figures:

Table 1: Demographic characteristics of the study population

S.no	Parameter	Mean	SD	P-value obtained after correlation with LVDD
1	Age (years)	58.55	10.75	0.965
2	BMI (kg/m^2)	24.45	2.10	0.848
3	Waist circumference (cm)	83.38	5.02	0.178
4	FBS (mg/dl)	144.08	16.45	0.081
5	HbA1c (%)	7.23	0.59	0.562
6	fasting insulin (µU/ml)	8.55	6.11	0.001**
7	HOMA-IR score	2.53	1.9	0.001**

Table 2: Distribution of patients according to Grading of Left ventricular diastolic dysfunction (n=104)

LVDD Grade	Frequency (N=104)	Percentage
Absent	63	60.6
Grade 1	14	13.5
Grade 2	16	15.4
Grade 3	7	6.7
Grade 4	4	3.8

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Figure 1: Scattered Diagram between LVDD grades and fasting insulin showing regression line representing the correlation between the variables.

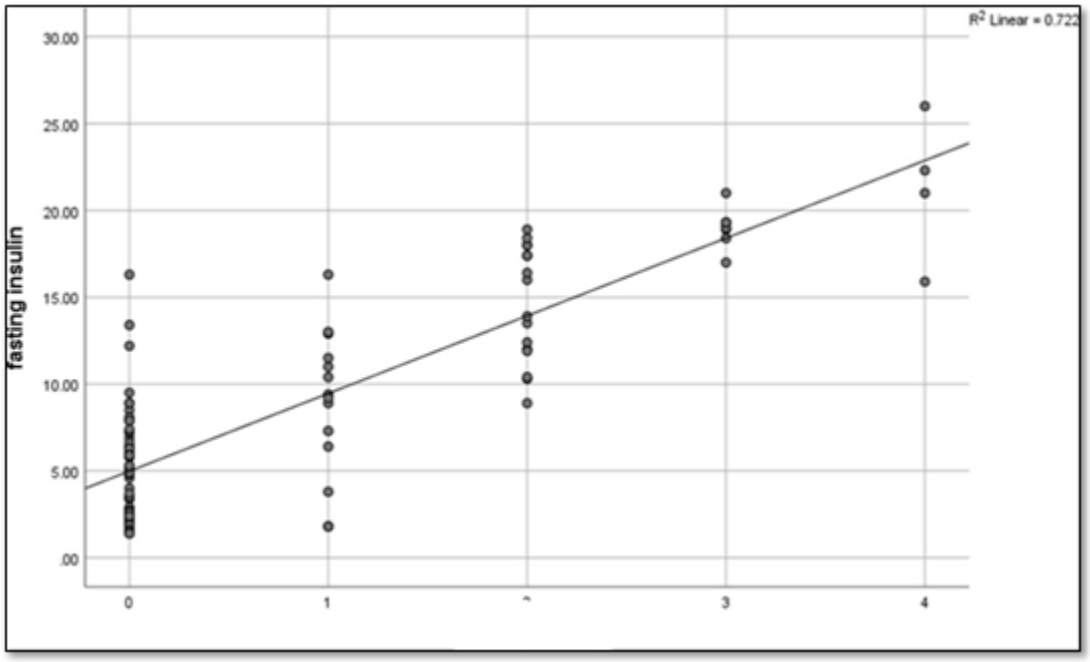
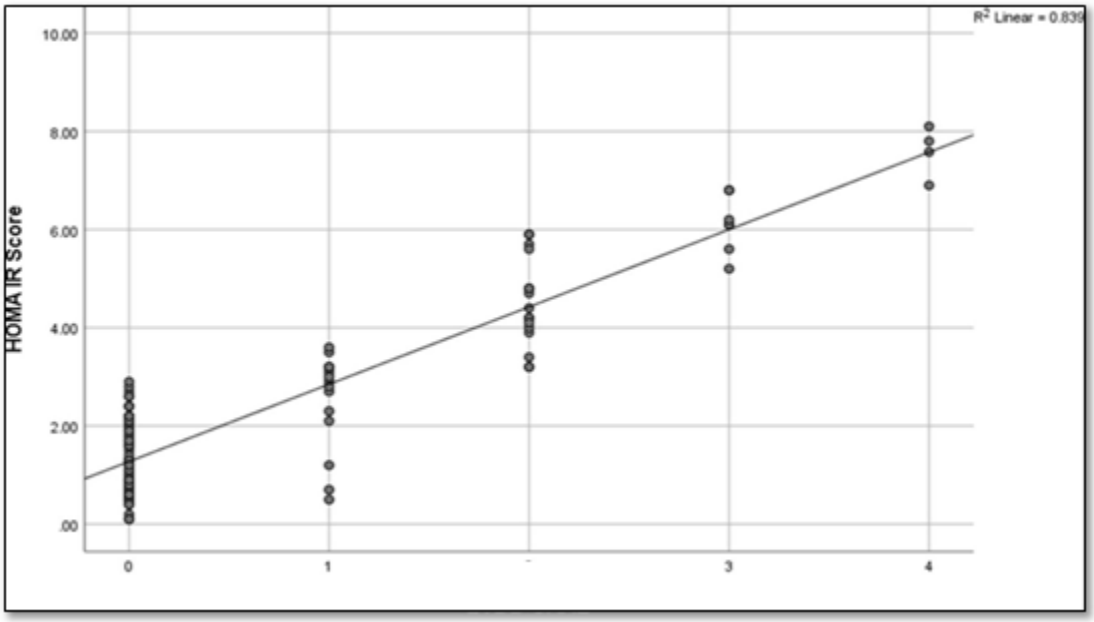


Figure 2: Scattered Diagram between LVDD grades and HOMA-IR score showing regression line representing the correlation between the variables.



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