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Original Research Paper

General Medicine

A STUDY ON THE CORRELATION BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction Type 2 diabetes mellitus (T2DM) patients are at increased risk for heart failure, following cardiac abnormalities including LV hypertrophy and diastolic dysfunction, collectively termed as diabetic cardiomyopathy. The pathogenesis of diabetic cardiomyopathy encompasses an array of metabolic derangements mainly attributable to insulin resistance. NAFLD - and especially NASH - is highly prevalent in persons with T2DM and is considered a hepatic manifestation of insulin resistance. However, it is unclear whether NAFLD or NASH in patients with T2DM conveys an independent risk for heart failure, aside from contributions by diabetes mellitus and insulin resistance. **Aim:** To study the correlation between Non-alcoholic fatty liver disease and left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus. **Methodology:** Between November 2020 and October 2022 a prospective study was conducted at 100 patients with Non-alcoholic fatty liver disease presenting to the Medicine outpatient department, Rajah Muthiah Medical College and Hospital, Chidambaram are included to the study. Doppler echocardiogram was done for all the patients to estimate the LV diastolic dysfunction. **Results:** Our study consists of 100 newly diagnosed diabetic patients comprising 56(56%) males and 44(44%) females. Diastolic dysfunction was present in 33(78.57%) in group A with Non-alcoholic fatty liver disease and 9(21.42%) in group B without Non-alcoholic fatty liver disease with P value of 0.04 which was statistically significant. **Conclusion:** This cross-sectional study from Type 2 diabetes mellitus patients with results from liver ultrasound, and echocardiography demonstrated a significant association between NAFLD and LV diastolic dysfunction. Moreover, in the presence of Type 2 diabetes mellitus, individuals with simple fatty liver should be aware of the progression to Non-alcoholic fatty liver disease and subsequent cardiac dysfunction.

KEYWORDS : Non-Alcoholic Fatty liver disease, Non-Alcoholic Steatohepatitis, Diabetes Mellitus. HBA1c, Left Ventricular Diastolic Dysfunction.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in many parts of the world[1]. Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) often coexist. The prevalence of NAFLD is 59.67% in T2DM patients. This results in adverse outcomes such as higher rates of mortality due to cirrhosis[2]. The NAFLD spectrum ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), a progressive necro-inflammatory form that can lead to liver cirrhosis and hepatocellular carcinoma[3].

Notwithstanding, the leading cause of death in persons with NAFLD is cardiovascular disease (CVD)[4], presumably due to shared risk factors composing obesity and metabolic syndrome[5,6]. Previously NAFLD was linked to a higher prevalence of coronary artery disease[7] and subclinical atherosclerosis, demonstrated by increased carotid artery wall thickness and impaired endothelial flow-mediated vasodilatation[8]. In addition, persons with NAFLD had altered left ventricular (LV) geometry and early features of LV diastolic dysfunction by echocardiography[9-14]. Another study demonstrated decreased LV energy metabolism in subjects with newly diagnosed NAFLD, despite normal LV structure and function[15]. The presence of concomitant liver fibrosis poses an even greater risk for cardiovascular mortality.[16] Recently, biopsy-proven NASH was associated with altered diastolic indices[17,18], although studies with histopathologic assessment of liver fibrosis were limited in size, owing to the invasive nature of liver biopsy.

MATERIALS & METHODS

Study design

This is a prospective Cross-Sectional study conducted among patients presenting in the medicine OPD of Rajah Muthiah Medical College & Hospital, Chidambaram with diabetes mellitus. The study period is between November 2020 and October 2022. The study protocol was approved by the Institutional Research and Ethical Committee and written informed consents were received from the study population.

Inclusion and exclusion criteria

All patients presenting in the medicine OPD of Rajah Muthiah Medical College & Hospital, Chidambaram with All newly diagnosed Type 2 diabetes mellitus patients, who clinically had no cardiovascular symptoms (age more than 30 years according to who criteria). Patient undergoing treatment of type 2 DM (HI and OHA) and History of any heart disease (ischemic heart disease, valvular disease, chronic heart failure including hypertension), History of Alcohol intake(more than one drink in women and 2 drink in men per day), History of chronic Liver disease, History of Kidney disease, Patient on OHA (pioglitazone), Type 2 DM with complication, History of thyroid disorder, BMI >40, Postmenopausal women without hormone replacement therapy, Drugs causing steatohepatitis (glucocorticoids, amiodarone, tamoxifen, valproic acid , zidovudine) were excluded from the study.

Patients enrolment

100 patients of Type-2 DM attending the medicine outpatient department of Rajah Muthiah Medical College & Hospital, were enlisted for Doppler echocardiography and HbA1clevels were included in the study. Subjects were enrolled in the study based on the inclusion and exclusion criteria. The selected subjects were briefed about the nature of the study and a written informed consent was obtained before the subject was enrolled in this study.

Study protocol

Demographic data like gender, age etc. was collected along with the relevant history and recorded in predesigned

proforma. A thorough clinical examination was conducted and findings were also recorded and relevant investigation (including complete blood count, RFT, urine routine,viral markers, fasting lipid profile, TFT, FBS, PPBS, HBA1C, ECG, ultrasound, echo for diastolic dysfunction) Then the correlation between NAFLD and diastolic dysfunction in patient with type 2 diabetes mellitus is studied using statistical analysis.

Following were USG and ECHO parameters:

Usg Abdomen And Pelvis (parameters for fatty liver)

- Liver echo genecity, Periportal echogenicity, Diaphragm echogenicity

ECHO (parameters for calculating diastolic dysfunction)

- E/A ratio (E-early diastolic filling, A-late diastolic filling)
- D (deceleration time),
- IVRT (isovolumetric relaxation time)

Based On Ultrasound Findings Of Nafld Patients Were Catagorized Into Two Groups	
GROUP A includes 37 patient with NAFLD	GROUP B includes 63 patients without NAFLD

Statistical analysis

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

RESULTS

In our study of 100 participants, 63 participants without NAFLD and 37 had NAFLD.

Table 1: Age range vs NAFLD

NAFLD		Age range				Total
		30-40 years	41-50 years	51-60 years	>60 years	
NAFLD	GROUP A	5	19	12	1	37
		13.5%	51.4%	32.4%	2.7%	100.0%
	GROUP B	20	28	9	6	63
		31.7%	44.4%	14.3%	9.5%	100.0%
Total		25	47	21	7	100
		25.0%	47.0%	21.0%	7.0%	100.0%

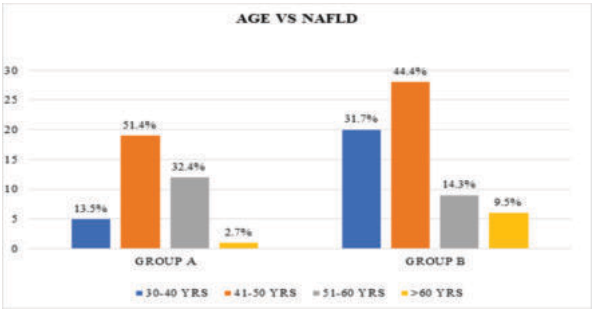

Fig 1: Age range vs NAFLD

In our study, the Mean age is 49±7 years in NAFLD positive group. Mean age is 46±9 years in NAFLD negative group. There is a significant association between age and people having NAFLD with p-value <0.05 i.e, 0.036.

Table 2: Sex vs NAFLD

NAFLD		Sex		Total
		Female	Male	
NAFLD	GROUP A	15	22	37
		40.5%	59.5%	100.0%
	GROUP B	29	34	63
		46.0%	54.0%	100.0%
Total		44	56	100
		44.0%	56.0%	100.0%

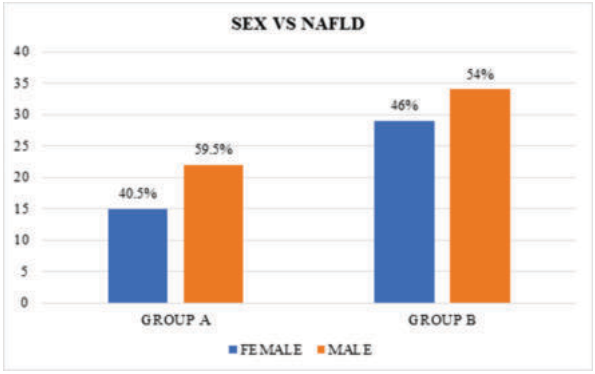

Fig 2: Sex Vs NAFLD

In the present study 56 patients were males out of which 22 had NAFLD. 44 patients were females out of which 15 had NAFLD. There is no significant difference between males and females when compared with people with NAFLD with p-value >0.05 i.e. 0.09.

Table 3: BMI vs NAFLD

		BMI			Total
		NORMAL	OVERWEIGHT	OBESITY	
NAFLD	GROUP A	2	15	20	37
		5.4%	40.5%	54.1%	100.0%
	GROUP B	11	35	17	63
		17.5%	55.6%	27.0%	100.0%
Total		13	50	37	100
		13.0%	50.0%	37.0%	100.0%

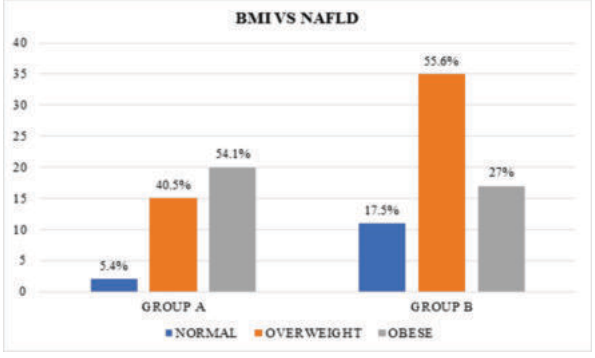

FIG 3: BMI VS NAFLD

In our study group A with NAFLD, 2 had normal weight, 15 had overweight, 20 had obesity and group B without NAFLD, 11 had normal weight, 35 had overweight, 17 had obesity. In NAFLD positive group compared to the NAFLD negative group is statistically significant as the p value is <0.05 i.e. 0.009 as per unpaired t- test indicating a true difference among study groups.

TAB 4: Total Cholesterol Vs NAFLD

NAFLD		T. Cholesterol range		Total
		Normal	Increased	
NAFLD	GROUP A	17	20	37
		45.9%	54.1%	100.0%
	GROUP B	42	21	63
		66.7%	33.3%	100.0%
Total		59	41	100
		59.0%	41.0%	100.0%

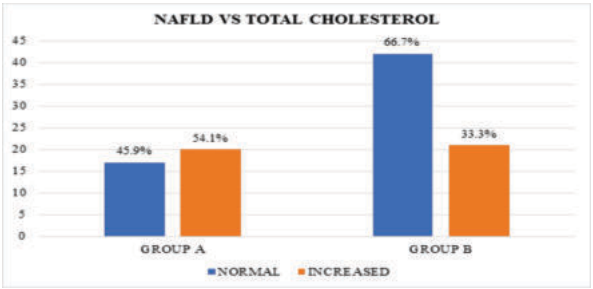

Fig 4: Total Cholesterol Vs NAFLD

In patients belonging to NAFLD negative group, the mean total Cholesterol levels are 147 mg/dl ±17. In NAFLD positive group, the mean total Cholesterol levels are 150 mg/dl ±17. There is significant difference between T. Cholesterol range when compared people with or without NAFLD, p-value <0.05 i.e. 0.03 which was statistically significant.

TAB 5: TRIGLYCERIDES Vs NAFLD

NAFLD		Triglycerides range		Total
		Normal	Increased	
NAFLD	GROUP A	17	20	37
		45.9%	54.1%	100.0%
	GROUP B	48	15	63
		76.2%	23.8%	100.0%
Total		65	35	100
		65.0%	35.0%	100.0%

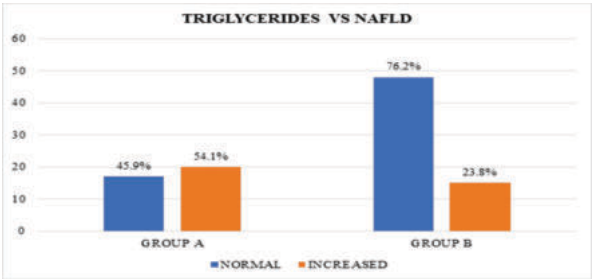

FIG 5: TRIGLYCERIDES Vs NAFLD

In patients belonging to NAFLD negative group, the mean triglycerides levels were triglycerides 217mg/dl ±43. In NAFLD positive group, the mean triglycerides levels are 239mg/dl ±46, with p-value <0.05 i.e. 0.001 which was statistically significant.

TAB 6: LDL Vs NAFLD

		LDL range		Total
		Normal	Increased	
NAFLD	GROUP A	14	23	37
		37.8%	62.2%	100.0%
	GROUP B	42	21	63
		66.7%	33.3%	100.0%
Total		56	44	100
		56.0%	44.0%	100.0%

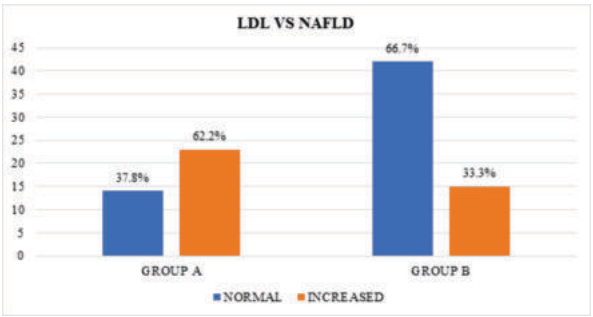

FIG 6: LDL Vs NAFLD

In patients belonging to NAFLD negative group, the mean LDL levels are 129mg/dl ± 20. In NAFLD positive group, the mean LDL levels are 139mg/dl ± 23. There is significant difference between LDL range when compared people with or without NAFLD with p-value <0.05 i.e. 0.02 which was statistically significant.

TAB 7: Comparison of ECHO VS USG

NAFLD		DIASTOLIC DYSFUNCTION IN ECHO		Total
		PRESENT	ABSENT	
NAFLD	GROUP A	33	4	37
		78.57%	6.89%	100.0%
	GROUP B	9	54	63
		21.42%	93.10%	100.0%
Total		42	58	100
		42.0%	58.0%	100.0%

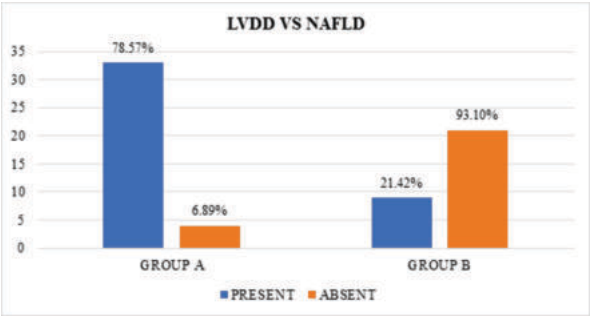

FIG 7: Comparison of ECHO VS USG

In 63 patients belonging to NAFLD negative group, 9 patients had LVDD. In 37 patients belonging to NAFLD positive group, 33 patients had LVDD. There is significant difference between LVDD when compared people with or without NAFLD, p-value <0.05 i.e. 0.04 which was statistically significant.

DISCUSSION

The prevalence of NAFLD in type 2 diabetic population is 37%. In our study the prevalence of non-alcoholic liver disease was made using imaging modality as per definition of AASLD. According to the study conducted by Browning J et al diabetic patients concomitantly had NAFLD upto 45% of the cases.

According to our study, the prevalence of non-alcoholic liver disease among type 2 diabetes patients was high in the 41 to 50 years age group. The study conducted by Bellentai et al the prevalence and the severity of non-alcoholic liver disease increases with increasing age. Hu X et al reported that older age, male gender are the risk factors in the development of NAFLD. In our present study there is similar high prevalence of non-alcoholic liver disease in male sex (male (22) vs female (15)). The study conducted by Caruli et al the prevalence of non-alcoholic liver disease was high among men. This is because females are protected against non-alcoholic liver disease by female sex hormones.

In our study among 100 participants, obese individuals (37 participants) and overweight individuals (50 participants) had high frequency of getting NAFLD when compared with that of normal weight individuals (13 participants). According to Dionysos study the NAFLD was present in 94% of the obese individuals, 67% of the overweight individual. According to Angulo P et al the obese individuals are having high frequency of getting NAFLD and will have the severe form of disease. In our study among NAFLD patients, 40.5% are overweight, 54.1% are obese, 5.4% are normal weight.

In our study the diabetic NAFLD patient had high total cholesterol and high triglycerides level when compared without NAFLD patients which are statistically significant. So

dyslipidemic individuals are at high risk of getting NAFLD. According to Chatrath H et al NAFLD individuals often had altered lipid metabolism along with the characteristics of metabolic syndrome. The NAFLD individual usually will have increased triglycerides, increased LDL (non-type A) particles and decreased HDL. The altered lipid metabolism in NAFLD is due to overproduction VLDL by the liver and decreased clearance of lipid by the liver. According to David E Cohen NAFLD usually has an atherogenic lipid profile. The pathogenesis of atherogenic lipid profile in NAFLD is due to insulin resistance.

NAFLD has been linked to LV diastolic dysfunction and remodelling in a number of studies in which subjects with NAFLD had greater LV mass, lower E/A ratio, longer DT, and lower 'e', while having similar LVEF compared with normal controls. NAFLD was also associated with altered cardiac indices in small studies incorporating liver biopsy. Moreover, no study thus far has directly controlled for the effect of insulin resistance on cardiac dysfunction in patients with T2DM. In a previous study comparing T2DM, non-diabetic NAFLD without advanced fibrosis, and healthy controls, only the diabetes mellitus group exhibited diastolic dysfunction, indicating a significant relationship between glycemic control and cardiac function. These authors suggested that NAFLD-only subjects who had high liver fat demonstrated higher endocardial strain and structural compensation for maintaining cardiac function by first hit, and that progression to diabetes mellitus with hyperglycemia may lead to impairment in cardiac function by second hit. Prediabetes has also been associated with impaired myocardial glucose uptake; therefore, changes in glucose level and presence of diabetes mellitus itself may play a crucial role in altering cardiac function. However, in the present study, since glucose levels and HbA1c were comparable with or without NAFLD, and the effect of glucose level was controlled in logistic regression, we were able to assess the impact of hepatic steatosis or fibrosis on cardiac function in T2DM aside from glycemic control.

Therefore the present study demonstrates that, among persons with T2DM, those with NAFLD exhibited altered LV structure and diastolic function demonstrated by greater LV mass index, lower E/A ratio, and longer DT by echocardiography compared with non-NAFLD. Prevalence of LV diastolic dysfunction increased with severity of fatty liver.

CONCLUSION

In conclusion, this cross-sectional study from T2DM patients with results from liver ultrasound, and echocardiography demonstrated a significant association between NAFLD and LV diastolic dysfunction. Moreover, in the presence of T2DM, individuals with simple fatty liver should be aware of the progression to NASH and subsequent cardiac dysfunction. These findings, in light of current views on the effect of NAFLD on CVD pathogenesis in patients with T2DM, warrant further investigation of the mechanism and potential new targets to prevent CVD in T2DM with NAFLD.

Study Limitation

- The most important limitations of the study are the relatively small number of patients and its cross-sectional design, which precludes the establishment of causal and temporal relationships between NAFLD and diastolic dysfunction.
- Moreover, invasive measurements of LV filling pressure were not performed in this study. However, when compared with invasive reference methods, tissue Doppler imaging has been shown to accurately estimate LV filling pressure in patients with preserved systolic function.

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