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Panacea Journal of Medical Sciences

Journal homepage: https://pjms.in/

Original Research Article

Prevalence of non-alcoholic fatty liver disease and left ventricular diastolic dysfunction in newly diagnosed type II diabetes mellitus: an observational, cross-sectional study

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Abstract

Introduction: Diabetes mellitus with its micro and macro vascular complication is one of the most researched topic in diabetology, but emergence of non-alcoholic fatty liver disease (NAFLD) and left ventricular diastolic dysfunction (LVDD) as its major complications has been given due consideration recently. Several workers have studied NAFLD and LVDD in diabetes separately.
Aim and Objective: In our current study we estimated the prevalence of NAFLD and LVDD in patients of type II diabetes mellitus.
Materials and Methods: The study was carried out in the department of internal medicine, IGMC Shimla during July 2017 to June 2018. All patients underwent laboratory investigations, abdominal ultrasound for fatty liver and 2D Echocardiography for LVDD.
Results: A total of 208 newly diagnosed type II diabetic patients were enrolled. Among these 179 (86.05%) had NAFLD on ultrasound, 107 (51.4%) had LVDD on 2D ECHO and 107 (51.44%) had metabolic syndrome. Out of 107 patients with diastolic dysfunction, 100 (93.41%) had fatty liver, which was significant statistically (p-0.002).
Conclusion: It was concluded that prevalence of NAFLD and LVDD was alarmingly high in patients of type II diabetes mellitus, who had normal blood pressure (Normotensive). As NAFLD and LVDD are linked to high cardiovascular risk in diabetic patients, these patients should be screened for the same at the time of diagnosis of diabetes so that steps for cardiovascular risk modification can be taken.

Keywords: Diabetes mellitus, Non-alcoholic fatty liver disease, Left ventricular diastolic dysfunction.

Received: 20-05-2024; **Accepted:** 27-12-2024; **Available Online**: 19-08-2025

1. Introduction

Diabetes mellitus is amongst the most common non communicable disorders attaining epidemic proportions worldwide. According to the International Diabetes Federation, by 2030 number of people with diabetes will rise to 552 million all over the world.[1] The burden of diabetes is also increasing in India. In the year 2015, India constituted second highest number of people (69.2 million people) with diabetes, which is expected to increase to 109.5 million by the year 2030.[1] Patients of type II diabetes are mostly overweight or obese.[2] Excess weight itself contributes to insulin resistance. Diabetes and obesity are associated with excess deposition of fat in liver parenchyma, which is known as non-alcoholic fatty liver disease (NAFLD).[3] Diabetes mallitus with its micro and macro vascular complication is one of the most researched topic in diabetology, but emergence of non-alcoholic fatty liver disease (NAFLD) and left ventricular diastolic dysfunction (LVDD) as its major complications has been given due consideration recently.

Historically, Ludwig et al first described Non Alcoholic Steato Hepatitis (NASH) as new and indistinct liver disease when they studied 20 patients at Mayo Clinics in 1980. Histologically it was similar to alcoholic hepatitis, though in

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https://doi.org/10.18231/pjms.v.15.i.2.433-437

the absence of alcohol abuse.[4] After excluding alcohol, medications and hereditary disorders as reasons for secondary fat depositions, any evidence of fat accumulation in liver supported by imaging or histology, has been defined as NAFLD.[5] The prevalence of NAFLD is 9-32% among the general population and as high as 70% among diabetics in India.[6] NAFLD has been emerged as one of the manifestation of metabolic syndrome now. NAFLD has been associated with more occurrence of cirrhosis, hepatocellular carcinoma, micro and macro-vascular complications of diabetes especially cardiovascular disease.[7] Though, liver biopsy has been considered as gold standard for diagnosis of NAFLD but ultrasonography is an easily available, non-invasive modality for assessment of fatty liver. It has a specificity of 93.6% and sensitivity of 84.8% in diagnosing fatty liver.[8]

There is a higher incidence of heart failure in diabetes even without hypertension and coronary artery disease. This has been attributed to diabetic cardiomyopathy, which causes diastolic dysfunction before systolic dysfunction.[9] Moreover, structural changes that occur in NAFLD result in remodelling of left ventricle and diastolic dysfunction. Subclinical LVDD is a predictor of heart failure and long term mortality.[10] Studies have shown LVDD to be an early indicator of myocardial involvement in diabetes.[11]

Several workers have studied NAFLD and LVDD in diabetes separately. In our current study we estimated the prevalence of NAFLD and LVDD in patients of type II diabetes mellitus and their association in diabetes. Early diagnosis of NAFLD offers a window of opportunity to modify cardiovascular risk factors. Since ultrasonography is more easily accessible at most centres in India, screening for NAFLD can help stratify which patients to be referred to cardiologist for LVDD screening.

2. Materials and Methods

2.1. Patient population

Two hundred and eight patients, diagnosed first time as type II diabetics, presenting to department of medicine (both outdoor and indoor) were enrolled. Newly diagnosed type II diabetes mellitus patients fulfilling the inclusion criteria of age more than 18 years, non-pregnant female patient, alcohol consumption less than 20 g/day in males and less than 10 g/day in females with no clinical evidence of cardiovascular disease or heart failure were enrolled. Diabetes was diagnosed by the following criteria.[12] Fasting blood sugar ≥ 126 mg/dl or 2 hours post prandial sugar ≥ 200 mg/dl after 75 gm anhydrous glucose in water or HbA1c ≥ 6.5% or random blood sugar ≥ 200 mg/dl with constitutional symptoms of hyperglycaemia. Patients with alcohol intake of more than 20 g/day, prior hepatic disease, hepatitis B, hepatitis C, hepatotoxic drug intake, coronary artery disease, hypertension, valvular heart disease, cardiomyopathy and known heart failure patients were not included. Patients with history of angina and ECG changes were also excluded. All patients gave informed consent and approval for study was taken from the institutional ethical committee.

2.2. Study design

It was a cross sectional, observational study

2.3. Study duration

We conducted this study between 1st July 2017 and 30th June 2018.

2.4. Data collection

The relevant history, physical examination and demographic details of all patients were recorded, with focus on BMI and waist circumference. Laboratory parameters namely FBS and 2 hour - PPBS, HbA1c, Lipid profile, LFTs, RFTs, haemogram and viral hepatitis markers were recorded. All patients underwent abdominal ultrasound for diagnosis of fatty liver. Fatty liver was graded as.[13]

Grade I- Increased echogenicity of liver
Grade II – Echogenicity of portal vein branches obscured by liver echogenicity.
Grade III - Diaphragmatic outline obscured by liver echogenicity

All patients underwent 2D ECHO with Philips i33 X-Matrix echocardiography machine. It was performed both in supine as well as in left lateral position. It was performed as per the guidelines issued by American Society of Echocardiography.[14] Trans mitral early diastolic filling wave (E), late diastolic filling velocity (A), E/A ratio, isovolumetric relaxation time (IVRT) and deceleration time (DT) were assessed. Following were the criteria to consider any patient with LVDD, E/A ratio<1 or >2, DT < 150 or>220 ms, IVRT< 60 or >100 ms, or E/e' ratio > 15.

Adult Treatment Panel (ATP) III has given criteria to diagnose metabolic syndrome. These are as follows: (1) Waist circumference more than 102 cm in men or more than 88 cm in women; (2) Triglyceride level more than 150 mg/dL or drug treatment for raised triglycerides; (3) High-density lipoprotein (HDL) level less than 40 mg/dl in men and less than 50 mg/dL in women or on drug treatment for low HDL; (4) Systolic blood pressure≥130 mm Hg or diastolic pressure≥85 mm Hg or treatment for hypertension; (5) Fasting plasma glucose level≥110mg/dL or drug treatment for elevated plasma glucose.[15] As per ATP III, presence of three or more of the above criteria are essential to diagnose patients with metabolic syndrome.

2.5. Statistical analysis

Discrete values were expressed as percentage and continuous variables as mean ± SD. Student t test and chi-square test was applied to assess the significance of the difference in mean values and between groups respectively. 'P' value < 0.05 was considered statistically significant.

3. Results

A total of 208 patients (132 male and 76 female) participated in the study. Amongst them, 49 (23.6%) were incidentally diagnosed to have diabetes, while 34 (16.4%) had polyuria and/or polydipsia as presenting complaint. However on specifically asking, 116 (55.8%) patients reported osmotic symptoms at diagnosis. Distribution of patients on the basis of presenting complaints has been detailed in (**Table 1**).

Table 1: Presenting complaints in study population (n=208)

Presenting complaint	No of patients	Percentage
Incidentally diagnosed	49	23.6%
Generalised body ache	34	16.3%
Weight loss	33	15.9%
Fatigue	23	11.1%
Polyuria	20	9.6%
Burning feet	15	7.2%
Polydipsia	14	6.7%
Burning micturation	8	3.8%
Increased appetite	4	1.9%
Blurring of vision	5	2.4%
Foot ulcer	3	1.4%

In our study, mean age of the study participants was 51.29 ± 9.96 years and mean weight was 70.27 kg. Out of 208 patients studied, 127 (61.1%) patients were obese (BMI ≥ 25), 41 (19.7%) patients were overweight (23 ≥ BMI ≤ 24.9), 39 (18.8%) patients had normal BMI (18.5 ≥ BMI ≤ 22.9) and one patient was underweight (BMI <18.5). Mean HbA1c at diagnosis was 9.73% with a maximum value of 15.3% and a minimum of 6.7%. The mean systolic and diastolic blood pressure was 115.8 mmHg and 75.8 mmHg respectively. A total of 179 (86.1%) patients had fatty liver on ultrasonography. On comparing the characteristics between NAFLD and non-NAFLD group, the mean age of study population in NAFLD was 50.67 years, while it was 49.86 years in patients without NAFLD. Prevalence of smoking in the NAFLD group was 18.4% (33 patients) and 3.4% (1 patient) in the non-NAFLD group. The mean BMI (Kg/m^2) of people with NAFLD was 25.88 and in patients without NAFLD it was 25.30. Out of the 208 people studied, mean HbA1c among patients with NAFLD was 9.81% and among patients without NAFLD was 9.22%. In our study age, body mass index and HbA1c were comparable among NAFLD and non-NAFLD groups. Statistically there was no significant difference among two groups (**Table 2**).

Table 2: Comparison of demographic profile between NAFLD and Non-NAFLD

Characteristic	NAFLD	Non-NAFLD	p-value
Age (years)	50.67	49.86	0.906
BMI (Kg/m^2)	25.88	25.30	0.16
HbA1c (%)	9.81	9.22	0.64

We observed that total cholesterol, LDL and triglyceride levels were higher in NAFLD patients in comparison to non-NAFLD patients, a statistically significant difference. However, HDL levels were comparable between both the groups (**Figure 1**).

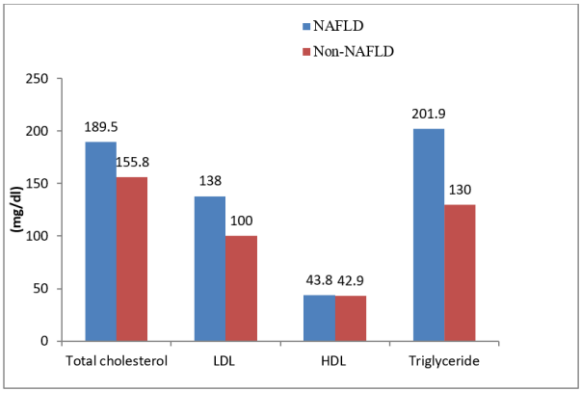

Figure 1: Comparison of lipid profile among NAFLD and Non-NAFLD

Out of 179 patients with fatty liver, 161 (89.9%) had normal AST levels and 157 (87.7%) had normal ALT values. On 2 dimensional ECHO, out of 208 patients 107 (51.4%) had left ventricular diastolic dysfunction (LVDD) and 101 (48.55%) were not having LVDD. The mean age was higher in the LVDD group than those without LVDD. Diabetics with LVDD also had a higher mean HbA1c and higher BMI than those without (**Table 3**).

Table 3: Comparison of demographic profile between LVDD and non-LVDD group

Characteristic	LVDD	Non-LVDD	p-value
Age (years)	53.8	47	0.000
BMI (Kg/m^2)	26.10	25.47	0.154
HbA1c (%)	9.81	9.65	0.282

It was found that levels of both LDL and triglyceride were higher in LVDD group as compared to non-LVDD group, a statistically significant difference (**Figure 2**).

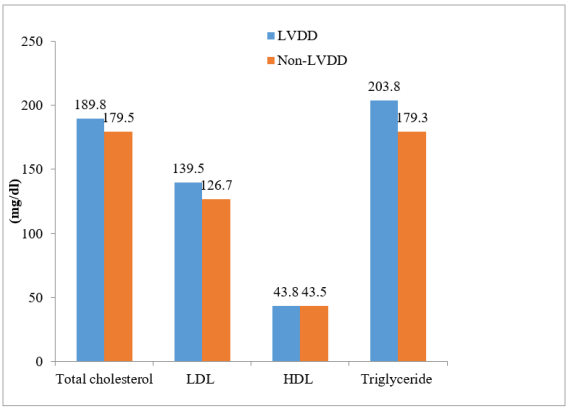

Figure 2: Comparison of lipid profile among LVDD and Non-LVDD

Out of the 107 diabetic patients with LVDD, 100 (93.4%) patients had fatty liver and 7 (6.54%) did not have fatty liver on USG (p value-0.002). Out of 101 diabetics without LVDD, 79 (78.21%) had fatty liver and 22 (21.78%) patients had no fatty liver (**Table 4**).

Table 4: Prevalence of NAFLD among LVDD and Non-LVDD diabetics

Variable		LVDD (n=107)	Non-LVDD (n=101)
NAFLD	Yes	100 (93.45%)	79 (78.21%)
	No	7 (6.54%)	22 (21.78%)

Out of 208 patients, 107 (51.44%) had metabolic syndrome while, 101 (48.56%) patients did not fall under the category of metabolic syndrome. The number of patients with metabolic syndrome were higher in NAFLD group 100 (93.45%) versus 7 (6.54%) in non-NAFLD group. Similarly, it was higher in LVDD group 65 (60.74%) as compared to those without LVDD 42 (39.25%). Thus, it was observed that NAFLD and LVDD were associated with higher prevalence metabolic syndrome in comparison to non-NAFLD and non-LVDD (p value – 0.002 and 0.006 respectively) (**Table 5**)

Table 5: Association of metabolic syndrome with NAFLD and LVDD

Variable		Metabolic Syndrome		p-value
		Yes (n=107)	No (n=101)	
NAFLD	Yes	100 (93.45%)	79 (78.21%)	0.002
	No	7 (6.54%)	22 (21.78%)	
LVDD	Yes	65 (60.74%)	42 (39.26%)	0.006
	No	42 (39.25%)	59 (60.75%)	

In patients with metabolic syndrome, triglyceride level was high both in NAFLD and LVDD group in comparison to their non-NAFLD and non-LVDD counterparts.

4. Discussion

In our study, out of 208 patients, 179 (86.1%) had fatty liver on abdominal ultrasound. The prevalence of NAFLD on histology was 87% in study by Prashanth M, et al.[16] On ultrasound, prevalence was found to be 56.5% in study done by Kalra, et al.[7] Agarwal, et al.[17] found a prevalence of 57.2% fatty liver. In our study prevalence of NAFLD increased with age with prevalence being 81% in age >40 years and 19% in age ≤40 years. The mean age was high in the NAFLD group as compared to non NAFLD (p=0.906). Similar results were observed in SPRINT study conducted by Kalra, et al.[6] We observed a high prevalence of NAFLD in males (62%) than in females (38%). This concurred in study by Agarwal, et al.[17] However, Prasanth, et al.[16] in their study showed higher prevalence among females than males. This was probably because their study population had more females (83) than males (28). Our study showed a higher level of total cholesterol, LDL and triglycerides in NAFLD than in non-NAFLD group (p value - 0.00 in all three variables). It was in concordance with the findings of a study conducted by Agarwal, et al.[17] who observed an statistically significant relationship between triglyceride and NAFLD. In the SPRINT study, Kalra, et al.[6] also demonstrated statistically significant association of NAFLD with dyslipidaemia. Various studies in the past as well found similar association of metabolic syndrome with the NAFLD. Thus, NAFLD has been considered as hepatic component of the metabolic syndrome.[19] Out of 208 patients in our study, 51.44% (n=107) patients had metabolic syndrome, as per the criteria given by ATP III. Amongst all NAFLD patients, 56% had metabolic syndrome however in LVDD patients only 42% patients had metabolic syndrome. It was concluded that prevalence of metabolic syndrome was high both in NAFLD and LVDD. This was in concordance with study by Kalra, et al.[6] who found close association of NAFLD with metabolic syndrome in their study participants. Similarly, 41.1% study participants had metabolic syndrome in a study conducted by Agarwal, et al.[17] In this study prevalence of metabolic syndrome was higher in patients with NAFLD (61.9%) than in non-NAFLD (13.2%) patients. A Study conducted by Targher, et al.[19] in 800 diabetic patients found that the metabolic syndrome and all its individual components were more frequent in NAFLD patients than those without NAFLD. It was concluded in our study that prevalence of obesity, dyslipidaemia and metabolic syndrome was high in patients of NAFLD than in non- NAFLD, the difference was statistically significant.

We found that 189 patients out of 208 (90.9%) had normal AST levels and 184 (88.5%) had normal ALT levels. In NAFLD group (n=179) 89.9% had normal AST and 87.7% had normal ALT levels. This was similar to studies by Prasanth, et al.[16] and Agarwal, et al.[17] in which majority of patients with NAFLD had normal amino transferases. However in SPRINT study by Kalra, et al.[6] mean ALT and AST in diabetics with NAFLD was higher, 55.6 ± 39.8 U/L and 54.8 ± 36.1 U/L, respectively. According to Stahl, et al.[20] most studies report >50% prevalence of NAFLD among diabetics with normal liver enzymes. Therefore liver enzyme measurement is not a reliable surrogate marker for NAFLD.

The HbA1c was high in patients of NAFLD than in non-NAFLD patients (p=0.64). Our study results were in concordance with the results of study conducted by Agarwal, et al.[17] and Prasanth, et al.[16] which demonstrated the higher HbA1c in diabetics with NAFLD than without NAFLD.

Amongst 208 enrolled patients, 107 (51.4%) had left ventricular diastolic dysfunction on 2D ECHO. Similar

results were observed in a study done by Patil VC, et al.[9] which showed prevalence of LVDD to be 54.33% among all study participants. In our study, LVDD increased with the age of the population, similar to study by Patil MB, et al.[21]

In our study, patients with LVDD had higher BMI, HbA1C and dyslipidaemia than non-LVDD group. This was similar to studies by Patil VC, et al.[9] Out of the 107 diabetic patients with LVDD, 100 (93.4%) had fatty liver on USG, while in 101 diabetics without LVDD, 79 (78.21%) had fatty liver. Out of the 179 patients who had fatty liver on USG, 100 (55.8%) had LVDD on 2D Echo. Thus, it was concluded that LVDD and NAFLD were strongly associated with each other.

5. Conclusion

It is recommended that diabetes mellitus patients should be screened for occurrence of fatty liver disease and for left ventricular diastolic dysfunction, presence of any such co-morbidity should be managed vigorously so that the development of cardiovascular disease can be minimized in patients of diabetes with non-alcoholic fatty liver.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Kaushal S, Ganju N, Mokta KK, Mokta JK, Gulepa R. Prevalence of non-alcoholic fatty liver disease and left ventricular diastolic dysfunction in newly diagnosed type II diabetes mellitus: an observational, cross-sectional study. *Panacea J Med Sci*. 2025;15(2):433-437.