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ORIGINAL RESEARCH ARTICLE

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Cardiac dysfunction in a cohort of biopsy proven nonalcoholic steatohepatitis in comparison to nonalcoholic fatty liver

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Abstract

Introduction NAFLD (non-alcoholic fatty liver disease) is increasing worldwide. Inflammation, fibrosis, and steatosis are the three components of NAFLD. Cardiac events are the most common cause of death in NAFLD. It is believed that there is an association between the inflammatory component of NAFLD and cardiac dysfunction. The gold standard for diagnosis of NAFLD is liver biopsy. Based on histology, NAFLD is categorized into two, nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). As biopsy is an invasive procedure, studies comparing cardiac dysfunction in NAFL and NASH are few. The aim of our study is to compare cardiac dysfunction in patients with NAFL and NASH.

Materials and method This is a cross-sectional study in which all patients who were biopsy proven for NAFLD without stage 4 fibrosis were included. Cardiac dysfunction in these patients was assessed by 2 D ECHO.

Results Out of the 92 patients, 52 were males and 40 were females (53.5 vs 46.5 %). Among these patients, 48 had NAFL, whereas 48 had NASH. Among the variables analyzed for the study SGOT, SGPT, ALP, Ferritin, ANA, TSH, LVEF, LA diameter, E/e, NAS score, lobular inflammation, ballooning, and steatosis statistically correlated with cardiac diastolic dysfunction. Majority of the patients with NASH had cardiac dysfunction (32/44) while only a few patients with NAFL (4/48) had cardiac dysfunction (p value = 0.002). Among the variables that can cause diastolic dysfunction, i.e., coronary artery disease, dyslipidemia, diabetes mellitus, and hypertension, only diabetes mellitus had an independent association. By binary logistic regression, it was seen that NASH was an independent risk factor for predicting cardiac dysfunction.

Conclusion The prevalence of cardiac dysfunction is more in NASH than NAFL in patients with NAFLD. NASH is an independent risk factor for cardiac dysfunction. There is no correlation between fibrosis and diastolic dysfunction.

Keywords NASH, NAFL, Cardiac dysfunction

Summary box

- What is already known about this subject?
- Cardiac dysfunction is a known complication of cirrhosis. Those patient with cirrhosis has more cardiac dysfunctions than healthy controls.
- What are the new findings?
- In NAFLD, patient's cardiac dysfunction can develop even before progression to cirrhosis. Cardiac dys-

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function is more with the NASH subgroup compared to non-NASH NAFL.
- How might it impact on clinical practice in foreseeable future?
- Screening for cardiac dysfunction in NAFLD patients with NASH even in the absence of cirrhosis can improve the outcome and can result in better patient care.

Background

NAFLD (non-alcoholic fatty liver disease) is increasing worldwide. Non-alcoholic fatty liver disease (NAFLD) has become a major cause of chronic liver disease [1]. Though NAFLD leads to liver-related morbidity and mortality, it is well known that the leading cause of death in NAFLD is cardiovascular disease (CVD), especially coronary artery disease (CAD) [2, 3]. NAFLD is not only associated with cardiovascular disease but it also independently contributes to its pathogenesis [4].

Patient with NAFLD who progress to cirrhosis has increased risk of cardiac dysfunction. Liver biopsy is the gold standard investigation to diagnose NAFLD. But only a handful of studies have evaluated biopsy proven NAFLD without cirrhosis and its association with cardiac dysfunction [5]. Based on those studies, NASH has more propensity to cause cardiac dysfunction than NAFL. The three components of NAFLD are inflammation, fibrosis, and steatosis. The most common cause of death in NAFLD patients is a cardiac event. It is believed that there is an association between the inflammatory component of NAFLD and cardiac dysfunction. Our aim is to compare cardiac dysfunction in NAFL and NASH.

AIMS and objectives

1. To find out the association of steatosis, inflammation, and fibrosis in biopsy proven NAFLD with sonographic markers of cardiac dysfunction: E/e' ratio, E/A ratio, LVEF, and LA diameter.

   Study setting: Department of Medical Gastroenterology, Medical College Thiruvanthapuram

   Study duration: 6 months

Inclusion criteria

1. Liver biopsy proven NAFLD patients who were willing to give consent.

Exclusion criteria

1. Competing etiology in liver biopsy
2. Cirrhosis in liver biopsy
3. Acute coronary syndrome or coronary artery disease in the past

Materials and methods

All patient who underwent liver biopsy and diagnosed to have biopsy proven NAFLD without stage 4 fibrosis who were willing to give consent were taken up for the study.

Indications of liver biopsy were as follows:

- Transaminitis with other etiological work ups negative
- Positive autoantibodies to distinguish between autoimmune hepatitis or epiphenomenon associated with NAFLD
- High-ferritin level to determine the extent of liver injury and iron accumulation
- Competing etiologies with NAFLD were suspected

Liver biopsy was taken using 16G liver biopsy needle under ultrasound guidance. One core biopsy was taken with length of 1–1.5cm. At least 8 portal tracts were considered as adequate biopsy specimen. All biopsies were analyzed by single pathologist who had experience of more than 15 years in liver histopathology to avoid inter-observer variability.

All patients undergoing liver biopsy with biopsy proven NAFLD without competing etiologies in liver biopsy were taken up for the study.

2D Echo was done by a cardiologist who had experience of doing more than 2000 2D echocardiography. All 2 D echocardiography were done by the same person to avoid inter observer variability. NAS (NAFLD activity score) score was used to define NASH. Those with score more than or equal to 5 were considered as NASH and without that as NAFL (Table 1).

Ethical consideration

Ethical clearance was obtained from the Institutional Ethical Committee (Humans Ethics Committee Medical College Trivandrum) (HEC.NO.05/24/2019/MCT). Written informed consent were obtained from all the study subjects in English and local language (Malayalam). All expenses were met by investigators. Confidentiality was maintained.

Table 1 NAS score (NAFLD activity score)

Histological feature	Description	Score
Steatosis	≤5	0
	5–33	1
	33–66	2
	>66	3
Lobular inflammation	No	0
	<2	1
	2–4	2
	>4	3
Hepatocellular ballooning	None	0
	Moderate	1
	Evident	2

Results

Ninety-two patients were recruited for the study of which 44 had NASH and 48 had NAFL. Forty of the included patients were females while 52 were males (46.5 vs 53.5%).

Among the 44 NASH patients, ANA was found to be positive in 20, while none of the patients with NAFL were positive for ANA (p value 0.008)

Twenty-four out of 44 patients with NASH had diabetes mellitus, while only 4 out of 48 with NAFL had the disease (p value 0.016).

Taking hypertension into consideration, it was seen that 20 out of 44 patients with NASH had hypertension while only 16 out of 48 patients NAFL had the disease (p= 0.552).

Twenty-eight out of 44 patients with dyslipidemia had NASH, while 32 out of 48 patients with NAFL had dyslipidemia (p value 0.879).

Comparing CAD in both groups, it was seen that 4 out of 44 patients with NASH had CAD while two of the NAFL patients had CAD (p value 0.286).

Thirty-two patients among the 44 patients with NASH were having diastolic dysfunction while only 4 among the 48 patients with NAFL had diastolic dysfunction (p value 0.002). It was also seen that there was no correlation between the stage of fibrosis and cardiac dysfunction (p value 0.495) (Table 2, Figs. 1 and 2).

Among the variables analyzed for the study SGOT, SGPT, ALP, Ferritin, ANA, TSH, LVEF, LA diameter, E/e, NAS score, lobular inflammation, ballooning, and steatosis statistically correlate with cardiac diastolic dysfunction by t test (Table 3).

Among the variables that can independently cause diastolic dysfunction, CAD, DLP, and hypertension were not statistically significant. Only diabetes mellitus was identified to be an independent predictor by binary logistic regression (Table 4).

Discussion

Among the 92 patients were recruited for the study 48 patients had NAFL, while 44 had NASH. There were 40 females and 52 in the study population (46.5 vs 53.5%). In a study by Peter et al., 33 patients were included. The mean age is 48.8±10.8 years, 61% is male, 48% is Caucasian, 36% is diabetic (T2DM), and 18% is with coronary artery disease (CAD) [5].

ANA was found to be positive in 20 patients with NASH. However, none of the patients with NAFL was positive ANA (NAFL, p value= 0.008, Table 2).

Among the various comorbidities that were taken into consideration, only diabetes was found to be significant (p value= 0.016). Twenty-four out of 44 patients with NASH had diabetes while only 4 out 48 patients with NAFL had diabetes. We also compared the prevalence of hypertension and dyslipidemia in both subgroups. In the NASH group, 20/44 had hypertension and 28/44 had dyslipidemia. In the NAFL group, it was seen that out of the 48 patients, 16 had hypertension and 32 had dyslipidemia. Neither the prevalence of hypertension (p= 0.552) nor dyslipidemia was statistically significant (p = 0.879). Four out of the 44 patients with NASH had CAD, while none of the patients with NAFL had CAD (p=0.286). Peter et al. had conducted a study on 17 patients with NAFL and 16 patients with NASH. Forty-four percent of NASH patients had advanced fibrosis. There were statistically significant non-cardiac differences between patients with NAFL and NASH, with NASH patients

Table 2 Diastolic dysfunction among NASH and NAFL

Diastolic dysfunction	NASH				Total		χ^2	df	p
	Present		Absent						
	N	%	*N*	%	*N*	%			
Yes	32	72.7	4	8.3	36	39.1			
No	12	27.3	44	91.7	56	60.9	9.991	1	0.002
Total	44	100	48	100	92	100			

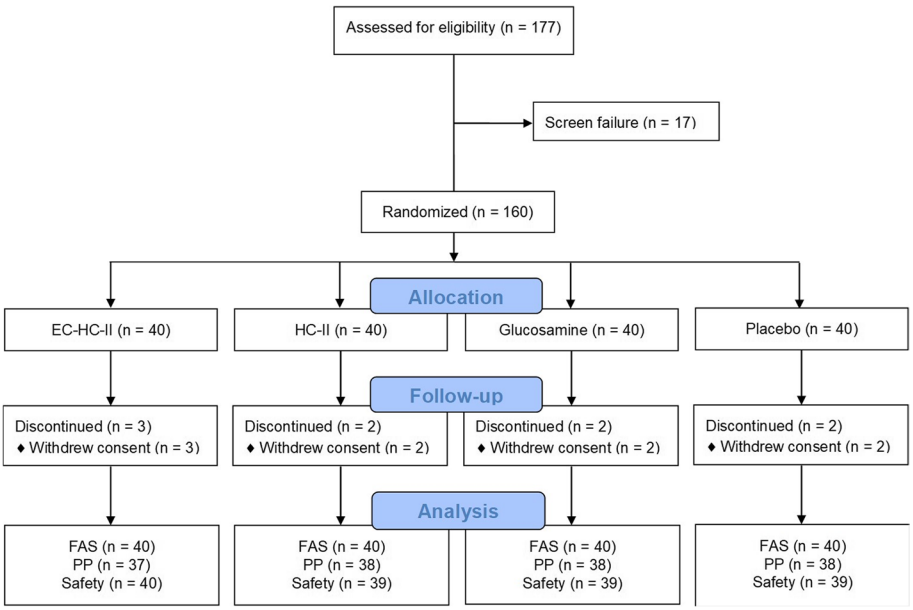

Fig. 1 Diastolic dysfunction among NASH and non-NASH

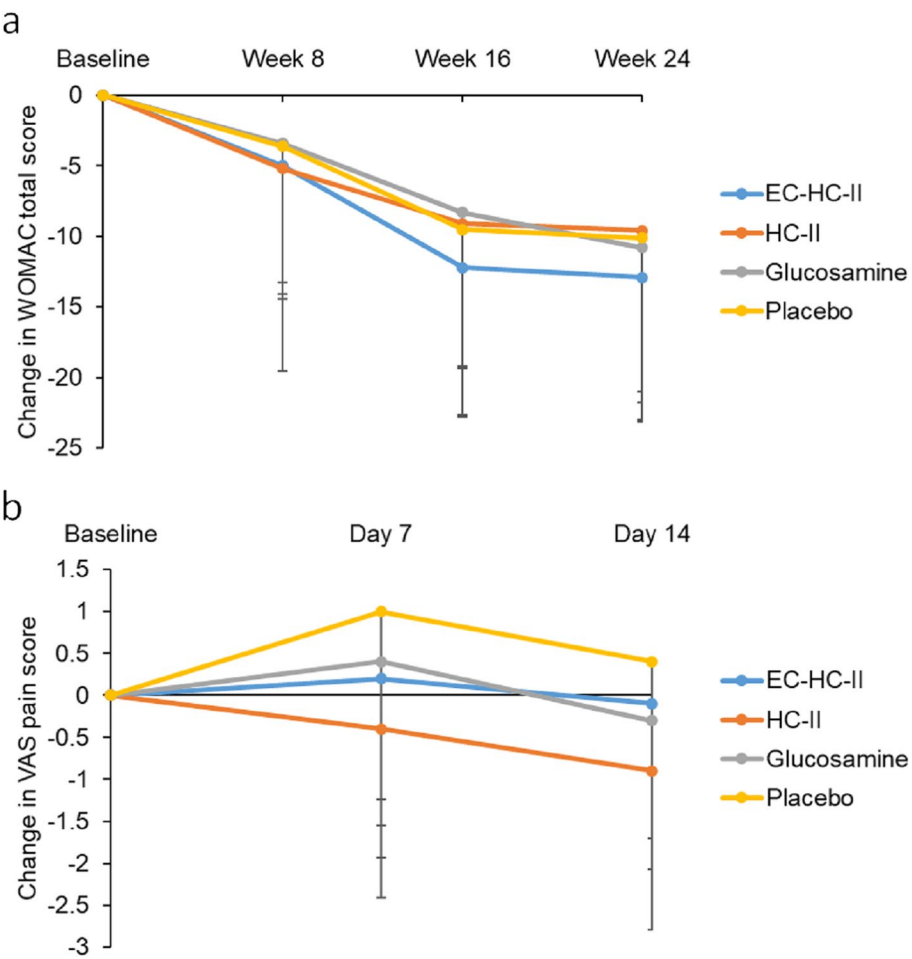

Fig. 2 Boxplot diagram describing E/e of NASH present group and absent group

Table 3 Correlation of various variables to diastolic dysfunction

	NASH				*t*	*p*
	Present		Absent			
	Mean	SD	Mean	SD		
Age	43.1	11.1	44.5	11.3	0.301	0.767
BMI	30.4	4.2	27.4	4.5	1.67	0.11
HB	13.5	2.0	13.8	1.3	-0.33	0.745
TC	6995.1	1329.9	8068.4	1023.7	-2.18	0.041
PLT	2.06	0.48	2.51	0.26	2.848	0.01
PCV	41.4	6.0	41.8	4.2	0.181	0.858
MCV	86.7	3.4	86.2	2.8	0.435	0.668
Bilirubin	0.98	0.47	0.78	0.29	1.256	0.223
SGPT	162.7	78.6	80.7	43.9	3.129	0.005
SGOT	97.4	49.5	49.5	22.0	3.041	0.006
ALP	100.2	17.6	75.8	15.6	3.511	0.002
Albumin	4.1	0.4	4.4	0.3	1.752	0.094
T. cholesterol	187.8	31.2	202.8	43.9	0.932	0.362
TAG	127.2	19.0	131.2	41.7	-0.29	0.775
HDL	38.4	9.2	42.3	8.9	1.029	0.315
LDL	116.9	28.2	136.3	38.5	1.364	0.187
FBS	101.6	10.5	96.0	6.5	1.546	0.137
HBA1C	6.91	1.43	5.90	0.37	2.359	0.028
NAS	5.45	0.52	3.75	0.45	8.388	<0.001
E/A	1.058	0.374	1.184	0.141	1.088	0.289
E/e	13.85	3.28	9.62	0.60	4.394	<0.001
LA diameter	3.79	0.31	3.43	0.35	2.63	0.016
LVEF	63.3	4.8	69.3	3.1	3.567	0.002
Ferritin	436.7	438.7	152.8	95.2	2.191	0.04
Ceruloplasmin	37.1	15.5	32.9	13.3	0.695	0.495
TSH	4.67	4.99	1.64	0.40	2.096	0.048

Table 4 Binary logistic regression model for NASH

	B	S.E.	Wald	df	*p*	OR	95% C.I. for OR	
							Lower	Upper
Diastolic dysfunction	2.849	1.375	4.295	1	0.038	17.264	1.167	255.345
T2DM	1.115	1.52	0.538	1	0.463	3.05	0.155	59.97
Constant	−6.527	2.881	5.134	1	0.023	0.001		

having lower platelets and higher AST and ALT. Patients with NASH were also significantly more likely to have T2DM, CAD, and hypertension [5].

Diastolic dysfunction was more prevalent in patients with NASH (32/44) than NAFL (4/48) in our study (p value = 0.002). Fibrosis stage had no correlation with cardiac dysfunction (p value 0.495. In a study by Peter et al., the E/e' ratio, a sonographic marker of left ventricular diastolic dysfunction, was significantly higher in NASH compared to NAFL (p=0.004). It was also seen that diastolic dysfunction was more common in advanced-stage NASH than early-stage NASH (stages 1–2) plus NAFL (p=0.021), and high-grade NASH than low-grade NASH plus NAFL (p=0.004). The presence of diastolic dysfunction trended toward significance when comparing NAFL to NASH, advanced-stage NASH compared to early-stage NASH plus NAFL, and high-grade NASH compared to low-grade NASH plus NAFL [5].

A study by Tracey et al. showed that NASH patients had increased median left atrial (LA) volume (28.6mL/m^2 vs. 24.8mL/m^2, p<0.0001) and LV mass (82.6 g/m_2 vs. 78.6 g/m^2, p<0.0001), indexed for height [6].

In our study, SGOT, SGPT, ALP, Ferritin, ANA, TSH, LVEF, LA diameter, E/e, NAS score, lobular inflammation, ballooning, and steatosis statistically correlated with cardiac diastolic dysfunction. Markers of diastolic dysfunction including E/A ratio, LVEF, LV mass index, LA volume index, average strain, TR velocity, and estimated PASP were not significantly different among study population of Peter et al. [5].

Among the variables that can independently cause diastolic dysfunction, CAD, DLP, and hypertension was not statistically significant among 2 groups. Only diabetes mellitus was significant. By binary logistic regression, NASH was proven to be an independent risk factor in predicting cardiac dysfunction.

Conclusion

- Cardiac dysfunction was more common in NASH than NAFL.
- NASH was found to be an independent predictor of cardiac dysfunction.
- Further studies are required to confirm the same.
- Short coming of the study is small sample size.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
ANA	Anti-nuclear antibody
CAD	Coronary artery disease
CVA	Cerebrovascular accident
LA diameter	Left atrial diameter
LVEF	Left ventricular ejection fraction
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatits
NAS Score	NAFLD activity score
T2DM	Diabetes mellitus
TSH	Thyroid-stimulating hormone

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Authors' contributions
1 Jijo Varghese: conceptualization and analysis and wrote the study. 2 Krishnadas Devadas: conceptualization. 3 Neeraj Vinayakumar: data collection. 4 Nibin Nahaz: data collection. 5 Atul Hareendran: data collection. 6 Tharun Tom Oommen: data collection. 7 Bony George: data collection. The author(s) read and approved the final manuscript.

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Availability of data and materials
All data generated during the study is incorporated to this article.

Declarations

Ethics approval and consent to participate
Ethical clearance was obtained from the Institutional Ethical Committee (Humans Ethics Committee Medical College Trivandrum) (HEC. NO.05/24/2019/MCT).

Consent for publication
Written informed consent was obtained from all the study subjects in English and local language (Malayalam). All expenses were met by investigators. Confidentiality was maintained.

Competing interests
The authors declare that they have no competing interests.

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