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A Clinical Study of Cardiological Dysfunction in Non-Alcoholic Fatty Liver Disease in a Tertiary Care Hospital

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a term used to describe the accumulation of fat in the liver of people who drink little or no alcohol. Previous studies have shown a higher prevalence of left ventricular remodelling and diastolic dysfunction in patients with NAFLD but they all include patients with obesity, diabetes and/or hypertension, which are by themselves well known risk factors for cardiovascular dysfunction. Our aim was to find out the cardiological dysfunction in non alcoholic fatty liver disease patients without conventional cardiovascular risk factors as diabetes and hypertension. We performed a cross-sectional study in 70 non alcoholic fatty liver disease patients without hypertension, diabetes and 30 controls without NAFLD, with an aim to find out any cardiological dysfunction, its occurrence, nature and correlation, with simple and cost-effective means, such as echocardiography, electrocardiography and some relevant biochemical parameters. Cases and controls were subjected to detailed echocardiography examination, including tissue Doppler imaging. CRP, uric acid, lipid profile, liver function tests were done. Results were compared between cases and controls and suitable statistical analysis were done. Cases had higher waist circumference compared to controls, though BMI and body weight were not different. Blood pressure, blood sugar was similar between two groups. Serum triglyceride was more in NAFLD group. Though diabetes, hypertension was excluded,20 out of 70 patients met the criteria for metabolic syndrome. Left ventricular end diastolic diameter and left ventricular mass index were more in NAFLD group suggesting cardiac structural alteration. NAFLD patients also showed lower early diastolic velocity (E) and lower early to late diastolic flow (E/A), thus demonstrating diastolic dysfunction. Our study also showed a sensitive and specific cutoff value for LVMI, which can be very useful in Indian scenario.
So, our study demonstrated cardiological structural and functional alteration in NAFLD patients independent of conventional risk factors of diabetes, hypertension and obesity in Indian perspective, where it is recently emerging as a booming epidemic.

Keywords: NAFLD, LVMI, Diastolic Dysfunction

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a term used to describe the accumulation of fat in the liver of people who drink little or no alcohol. The spectrum of this disease [1] encompasses simple fatty liver and steatosis in one side; non-Alcoholic steatohepatitis (NASH), cirrhosis and liver failure on the other side. NAFLD probably is the most common liver disorder in the world [2], affecting 2.8% to 24% of the general population [3, 4, 5] with an equal sex prevalence and possible yet inexplicable familial clustering. Many different agents

and conditions have been associated with NAFLD e.g., Obesity (69-100%), Diabetes mellitus (36-75%), Hyper lipidaemia, Kwashiorkor and marasmus, Starvation (Acquired Metabolic Disorders); Methotrexate, Tetracycline, Gluco-corticoids, highly active antiretroviral therapy (Cytotoxic Drugs); Abetalipopro-teinemia, Galactosemia, Glycogen storage disease (Inborn Errors of Metabolism); Inflammatory bowel disease, Total parenteral nutrition (Miscellaneous Conditions).

Obesity is the condition most commonly associated with NAFLD [6]. The frequency of NAFLD may be as high as 80% in obese persons, with advanced disease (i.e., NASH) seen in 9% to 30% [7]. There is direct correlation between the severity of obesity and severity of NAFLD [8] e.g., body mass index (BMI) & severity of liver injury; waist-to-hip ratio & degree of hepatic steatosis, etc. as shown in different studies [9]. 20 - 80% of patients with NASH have hyperlipidemia in the form of high blood cholesterol level and/or high triglyceride levels. NAFLD has been associated with insulin resistance and hyperinsulinemia, even in lean subjects with normal glucose tolerance [10].

The majority of NAFLD patients are asymptomatic, some may complain of vague right upper quadrant abdominal pain, fatiguability and weight gain. They are generally diagnosed incidentally during the course of assessment of unrelated diseases or evaluation of metabolic syndrome. Diagnosis of NAFLD is based on three criteria [11]: (i) establishing the presence of a fatty liver or steatohepatitis, (ii) establishing the non-alcoholic nature of the disease Process and (iii) exclusion of another etiologist. Radiologic imaging of the liver with sonography, computed tomography (CT) or magnetic resonance imaging (MRI) has an adequate threshold for detection of fatty infiltration of the liver, used either singly or in combination [12]. Liver biopsy is the gold standard for diagnosis of NAFLD/NASH.NAFLD has been regarded as the hepatic manifestation of Metabolic Syndrome [13]. Previous studies have shown a higher prevalence of left ventricular (LV) remodelling and diastolic dysfunction in patients with the metabolic syndrome but they all include patients with obesity, diabetes and/or hypertension, which are by themselves well known risk factors for cardiovascular dysfunction [13,14,15,16]. It is unclear, however, whether impaired diastolic function and changes in cardiac structure are, only the consequence of hypertension, diabetes, obesity - individually or collectively; or whether any other factors such as insulin resistance state has a negative impact on` the heart [17,18,19] to produce such CVS disease. Very little is known regarding the alteration of LV structure and function in patients with metabolic syndrome without obesity, diabetes and hypertension. In a prospective study, 14-year risk of mortality from cardiovascular causes was doubled in patients with biopsy-proven NAFLD compared with a reference population [20]. In the Hoorn Study, raised alanine aminotransferase (ALT) at baseline increased the 10-year risk of CHD events, even after adjustment for the components of the metabolic syndrome. Therefore, studying young, nondiabetic, normotensive patients with NAFLD may serve as a good model for evaluating LV geometry and function in this novel population before conventional risk factors appear and any cardiological abnormality if found, may give an opportunity, to find out the independent etiological factor(s) responsible for developing cardiovascular disease and also to halt its development or progression at a very early stage.

NAFLD is also characterized by a low-grade inflammatory state[20] in liver and adipose tissue , that may affect coronary vasculature as well as myocardial metabolism giving rise to endothelial dysfunction as shown by Targher et al in a study showing greater carotid intima media thickness and decreased endothelial flow mediated vasodilatation in a population,

independent of obesity and other conventional metabolic syndrome components[21].They also proposed in the same study , that similar pathogenesis, as observed in the progression of liver damage in NAFLD, may play a pivotal role here, as there may be significant myocardial steatosis , contributing to LV overload and hypertrophy, impairment of energetics and mechanical inefficiency, leading to diastolic dysfunction, and advanced atherosclerosis risk potential.

So, it is important in future studies to determine what specific structural and functional cardiovascular alteration occurs in NAFLD patients, what is the correlation between degrees of NAFLD and CVS disease, if at all present, whether routine assessment of CVS risk is required on incidental diagnosis of NAFLD and also, whether therapies that correct abnormal myocardial and hepatic substrate metabolism will translate to a lower prevalence of CVS disease. Though many studies are undergoing in the West, a comprehensive study regarding the cardiovascular structural and functional alterations in NAFLD patients without hypertension, diabetes, is lacking in the Indian literature, in spite of the booming epidemics of NAFLD in India. With this background, our study aimed at assessing the cardiovascular status in patients of NAFLD without diabetes, hypertension, by simple and cost-effective means, as, two-dimensional echocardiography, electrocardiography, and other relevant biochemical parameters and finding out any changes and its possible etiology, at an earlier stage, before conventional CV risk factors appear, so that early prevention can be arranged.

Aims & objectives

Our aim was to find out the cardiological dysfunction in non alcoholic fatty liver disease patients without conventional cardiovascular risk factors as diabetes and hypertension. We first selected patients having NAFLD without hypertension and diabetes, depending upon clinical profile, some biochemical parameters as liver function test, radiological parameters namely USG whole abdomen, and if possible, liver biopsy H/P study. Next, we performed Echocardiography, Electrocardiography and some relevant biochemical parameters to assess their functional and structural cardiological status. Any significant outcome will find out the cardiological dysfunction and, its nature, if any, in NAFLD patients.

SPECIFIC OBJECTIVES OF THE STUDY:

(a)To study the echocardiographic and electro cardio graphic parameters in NAFLD patients and to find out - any cardiological dysfunction in NAFLD patients.

(b)To find out the nature of cardiological dysfunction, if any, in NAFLD patients.

MATERIALS & METHODS

1.STUDY AREA: Medical College & Hospital, Kolkata.

2.STUDY POPULATION: Non alcoholic fatty liver disease patients, attending MOPD or liver clinic or admitted in MCH, Kolkata.

3.STUDY PERIOD: One year

4.SAMPLE SIZE:70 patients with NAFLD were compared to 30 age and sex matched controls without NAFLD.

5.SAMPLE DESIGN: Nonalcoholic fatty liver disease patients, attending medicine department, who satisfy inclusion and exclusion criteria and give written informed consent for our study, were made part of this study.

INCLUSION CRITERIA OF SAMPLE:

i. Patients of Non-alcoholic fatty liver disease, documented by clinical, biochemical, radiological and /or histological evidence.
ii. Age between 15-60years, in either sex.

EXCLUSION CRITERIA OF SAMPLE:

i. Chronic liver disease due to other etiologies as - alcoholic liver disease,

hepatitis B, hepatitis C, autoimmune liver disease, drug induced or other known causes of liver diseases.

ii. Frank cirrhosis patients, irrespective of its etiology.

iii. Known diabetic patients (according to ADA guideline).

iv. Known valvular heart disease and ischemic heart disease patients.

v. Known hypertensive patients (BP>=140/90).

vi. Patients taking chronic medications known to cause cardiological

vii. dysfunction (glucocorticoid, tetracycline, methotrexate, etc.)

6. STUDY DESIGN: Hospital based observational study.

7.PARAMETERS TO BE STUDIED:

A. Tests to diagnose non-alcoholic fatty liver disease and association:

- Clinical parameters (anthropometric measurements)
- Biochemical- LFT (Total, direct, indirect bilirubin; total protein, albumin, globulin; SGOT, SGPT, ALP), fasting venous blood glucose, fasting venous blood insulin.
- Radiological – USG W/A
- Histological-liver biopsy (wherever feasible)

B. Tests to rule out other etiologies of liver disease-

HBsAg, anti HCV antibody (wherever feasible).

C. Tests to find out incidence and severity of cardiological dysfunction-

Echocardiography and electrocardiography.

D. Other tests to asses systemic disease status, associated metabolic status and comorbidities -

- Fasting venous blood lipid profile; Post glucose blood sugar; HbA1C; P time (in sec), INR; Complete hemogram;
- Serum uric acid, CRP, TSH, urinary albumin
- Urea, creatinine; upper GI endoscopy (in selected group).

E. Other relevant investigation reports.

8. STUDY TOOLS:

a. Preformed pre structured checklist.
b. Laboratory/investigation reports
c. BHT/OPD ticket
d. Routine study tools.

9. STUDY TECHNIQUE:

We examined all patients, within the age range of 15 to 60 years, who attended our MOPD, or liver clinic of medical college hospital, Kolkata for investigation of either elevated liver enzymes or an ultrasound finding of fatty liver. All patients underwent a thorough medical history and physical examination. All subjects satisfying inclusion and exclusion criteria signed an informed consent, which was approved by our Institutional Review Board and were made part of our study. Baseline Measurements Weight (kg) and height (m) were measured and BMI (kg/m2) was calculated and categorised according to WHO criteria. Blood pressure was measured in both of patient's arms using the first and the fifth phase of Korotkoff sounds by column mercury sphygmomanometer at rest in the sitting position. The diagnosis of NAFLD was made on the basis of fatty liver on ultrasound by accepted criteria of at least 2 of the following: increased contrast of the hepatic compared with the renal parenchyma, vascular blurring, focal sparing, or narrowing of the lumen of the hepatic veins. The grading system of NAFLD according to Rumacks Diagnostic ultrasound was used in our study. Mild/grade 1—Minimal diffuse increase in hepatic echogenicity with normal visualization of diaphragm and intrahepatic vessel borders. Moderate/grade 2 — Moderate diffuse increase in hepatic echogenicity with slightly impaired visualization of intrahepatic vessels and diaphragm. Severe/grade 3 — Marked increase in echogenicity with poor

penetration of posterior segment of right lobe of liver and poor or no visualization of hepatic vessels and diaphragm. Other etiologist was excluded by clinical examinations and relevant investigations.

Relevant biochemical parameters were studied in both case and control groups, especially liver function test, fasting lipid profile, CRP, uric acid and fasting insulin level.

Metabolic syndrome was defined according to the International Diabetes Federation as: Central obesity (defined as waist circumference ≥90 cm for South Asian men and ≥80 cm for South Asian women, with ethnicity specific values for other groups) Plus, any two of the following four factors:

Raised TG level: >150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality ; Reduced HDL cholesterol: <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females, or specific treatment for this lipid abnormality ; Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mm Hg , or treatment of previously diagnosed hypertension ; Raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes .

Fasting levels of insulin greater than 15 µU/ml, or more than 75 µU/ml at 120 min of OGTT are hyper insulinemic levels, which infer IR. Insulin sensitivity was assessed by Homeostasis model assessment (HOMA) by the equation: HOMA-IR= Fasting Insulin(µU/ml) × Fasting Plasma Glucose (mg/dl) / 405. HOMA-IR value more than 2, were considered diagnostic of insulin resistance.

Complete echocardiography including colour M-mode and TDI at rest was performed on all our NAFLD patients and 30 age sex matched controls in the left lateral decubitus position from the standard views. LV internal dimensions and wall thickness were measured from 2-dimensional guided M-mode echocardiographic tracings obtained at mid-chordal levelling the parasternal long axis view.

Left ventricular ejection fraction (LVEF) will be calculated from left ventricular end-diastolic internal diameter (LVIDD) and left ventricular end-systolic internal diameter (LVIDS) using the following formula:

LVEF = $(LVIDed^3) - (LVIDes^3) / (LVIDed^3)$.

End-diastolic LV dimensions will be used to calculate LV mass by an anatomically validated formula

LV mass = 0.8 (1.04 ([LVIDD ± PWTD ± IVSTD]3- [LVIDD]3)) ± 0.6 g and indexed per metre square of body surface area. Where: LVIDD = Left Ventricular Internal Diameter in Diastole; PWTD = Posterior Wall Thickness in Diastole; IVSTD = Interventricular Septum Thickness in Diastole. All measurements were performed according to the guidelines of the American Society of Echocardiography. Reference range for left ventricular mass index is as follows.

Reference Range(gm/m^2)	**Female**	**Male**
Normal	43-95	49-115
Mildly Abnormal	96-108	116-131
Moderately Abnormal	109-121	132-148
Severely Abnormal	≥122	≥149

From the apical four-chamber view, pulse-wave Doppler recordings of the mitral inflow were acquired with the sample volume placed at the tips of the mitral valve leaflets. The following parameters were measured by pulse-wave Doppler: peak velocities of early (E) and late (A) diastolic filling, deceleration time (DT), isovolumic relaxation time (IVRT). The ratio of early diastolic to late diastolic mitral inflow velocities was calculated (E/A). The TDI program was set to pulse-wave Doppler mode. The TDI of the diastolic velocities was obtained from the apical 4-chamber view. Analysis was performed for early (E') and late diastolic velocity (A'). The Doppler pattern of diastolic dysfunction is characterized by a prolonged IVRT (Isovolumetric relaxation time), decreased peak E velocity, prolonged DT (Deceleration time), and an E/A ratio < 1, decreased E', increased E/E'. Diastolic

dysfunction was graded using standard formula. All Doppler signals were recorded with a chart recorder set at 100 mm/s. The averages of 3 cycles were used. Two experienced echocardiographers performed the examination and measurement and were blinded to the clinical and metabolic data.

10. ANALYSIS OF DATA:

Data were shown as mean ± SD. The t test was used to compare the continuous variables describing the 2 groups. Chi-square analysis was used to compare the categoric data of the 2 groups. Variables with P<0.05 were considered significant. Regression models were estimated to determine the independent predictors of NAFLD using the stepwise method. Analyses were performed using SPSS 17 statistical software.

RESULT

A total of 70 patients with NAFLD and 30 patients without NAFLD were included in our study as case and control. The demographic characteristics of the study population are shown in table 1 and figure 1. The two groups were age and sex matched (40.51±0.90 vs. 41.8±1.5 with P value0.4665). Male: female ratio was 27:43 vs. 12:18 (P value 0.99).

Figure 3 and Table 2 shows, there was no significant difference in BMI between case and control group [mean 22.01± 0.26 vs. 21.45 ± 0.355 with P value 0.2331]. Range was between 18 and 26.7. But waist circumference was significantly more in NAFLD cases than in control [mean 77.1 ± 0.935 vs. 73.57 ±0.95, with P value 0.0097]. Female NAFLD patients having waist circumference value above cutoff level (80 cm) were 25 in number in comparison to 18 below cutoff; and 27 male NAFLD patients, all had WC values below cutoff (90 cm) level.

Table 2 and 3 also shows there is no significant difference in Blood Pressure (120.9±1.136 vs. 120.5±1.73, P value 0.8494) and Blood Sugar levels (91.84±1.2 vs. 88.23±1.38, P value 0.053) between the two groups.

The patients with NAFLD had a significantly higher level of SGOT (46.54±2.01 vs. 34.03±1.45, P value <0.0001) and SGPT (70.34±4.225 vs. 33.23±1.98, P value <0.0001).

Fasting Insulin level was significantly more in NAFLD cases than in control group [13.55±0.3729 vs. 6.708± 0.46] with P value <0.0001]. Insulin resistance (IR) as calculated by HOMA-IR (fasting Insulin in µU/ml * fasting blood glucose in mg/dl / 405) was also significantly higher in NAFLD cases (3.044±0.093 vs. 1.163±0.1355, P value <0.0001). 51 out of 53 NAFLD (96.26%) patients were having Insulin resistance (calculated HOMA-IR >2) in our study. Maximum Insulin resistance value (HOMA-IR) in our study was 4.84. There were 5 patients with IR values higher than 4.

Serum Uric Acid and CRP levels were not significantly different in case and control group.

Serum Triglyceride level was significantly more in NAFLD patients than in control group [167.9±3.079 vs. 137.3 ± 2.612 with P value < 0.0001]; though total cholesterol (195.3±2.393 vs. 192.1±3.915, P value 0.482), HDL (39.36±0.698 vs. 41.67±0.94, P value 0.493), LDL (122.4±2.452 vs. 123±3.575) values were not significantly different in these two groups (Table 4).

ECG shows left ventricular hypertrophy in 10 out of 70 NAFLD patients.

Echocardiographic assessment of LV geometry and both systolic and diastolic function were performed in all patients and controls. The results were shown in Table 5. Left ventricular end-diastolic diameter (LVIDD) was more in NAFLD patients (47.09±0.824 vs. 43.1±0.9795, P value 0.0027). But posterior wall thickness PWD (10.97±0.1842 vs. 10.60±0.233, P value0.215), Intraventricular septal thickness IVSD (11.01±0.1842vs. 11.20±0.3195) and left ventricular end-systolic diameter LVIDS were not statistically different in case and control. LV

Mass Index (g/m^2) was more in NAFLD patients than in control group with a P value < 0.0001(108.8±3.68 vs. 88.43±3.313). Raised LVMI were present in 42 out of 70 patients of NAFLD, i.e., in 60% cases. In our case group of70 NAFLD patients, 17 (24.3%) patients had mild alteration of LVMI, 11 had moderate alteration (15.7%) and 14 patients were of severe alteration (20%), as shown in Table 6. We used ROC curve as shown in Figure 11 and Table7 which shows acceptably high sensitivity and specificity of LVMI > 96.5 $g/m^{2.}$ This can also serve as a cut off value for Indian population. Considering this cut off level, 43 out of 70 NAFLD cases, i.e. 61.4 % have increased LVMI. No significant difference was found in relation to LV Ejection Fraction (63.4±0.007 vs. 63.53±1.182, P value 0.9231).

Diastolic dysfunction was present in 59 out of 70 NAFLD patients, i.e., in 84.28%. In NAFLD group, grade 1 diastolic dysfunction were present in 53 patients (75.7%) and grade 2 in 6 patients, i.e., in 8% (Table6). Patients with NAFLD had lower early diastolic velocity E (67.8±1.298 vs. 71.17±1.378, P value 0.0793, though not achieving statistical significance); significantly lower early to late diastolic velocity E/A ratio (0.953±0.0229 vs. 1.072±0.255, P value 0.0009); although E' (9.263±0.239 vs. 1.072±0.255, P value 0.456), E/E' ratio (8.534±0.42 vs. 8.361±0.355, P value 0.7565) were not different in case and control (Figure 4).

As the patients with NAFLD had higher waist circumference, serum triglyceride and insulin resistance; linear regression analysis was employed to determine whether the differences in cardiac geometry and parameters of diastolic function between NAFLD patients and controls were related to higher waist circumference, serum triglyceride or insulin resistance (HOMA-IR). No significant correlation was found between LVM index, LVIDD, early diastolic velocity (E) and waist circumference (r=0.111, P=0.359; r=0.12, P=0.319; r=0.01, P=0.909; respectively) in the NAFLD patients (Fig.5,6,7,8,910). No significant correlation was found between LVMI and serum triglyceride level also, in linear regression analysis (r=0.174, P=0.149). Analysis between LVMI, early diastolic velocity (E) and Insulin resistance revealed no statistically significant relation (r=0.135, P=0.333; r=0.74, P=0.599 respectively).

Table 1: Demographic profile of study populations

Parameters	***Case (with NAFLD). N=70***	***Control (without NAFLD). N=30***	***P value***
Age	*40.51 ± 0.90*	*41.8 ± 0.90*	*0.4665*
Sex (M: F); F %	*27:43; 61.4 %*	*12:18; 60 %*	*0.99*

Figure 1: Age distribution of study population

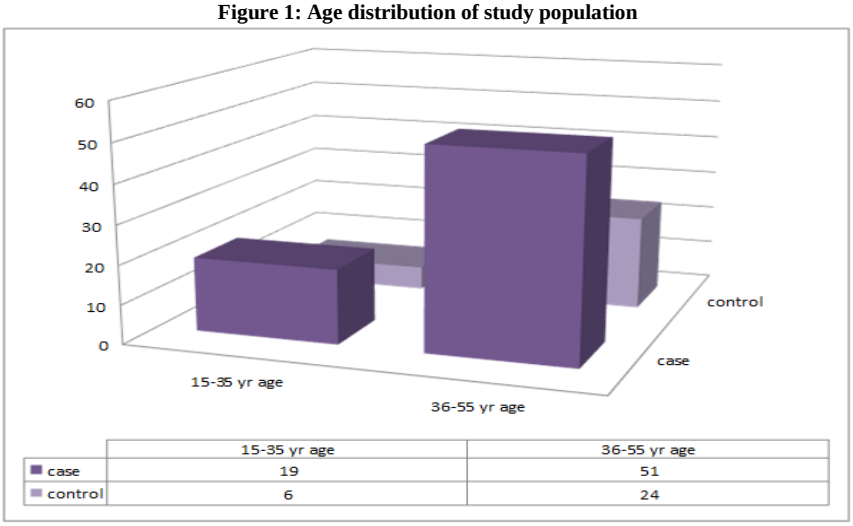

Figure 2: Distribution of study population according to Waist circumference

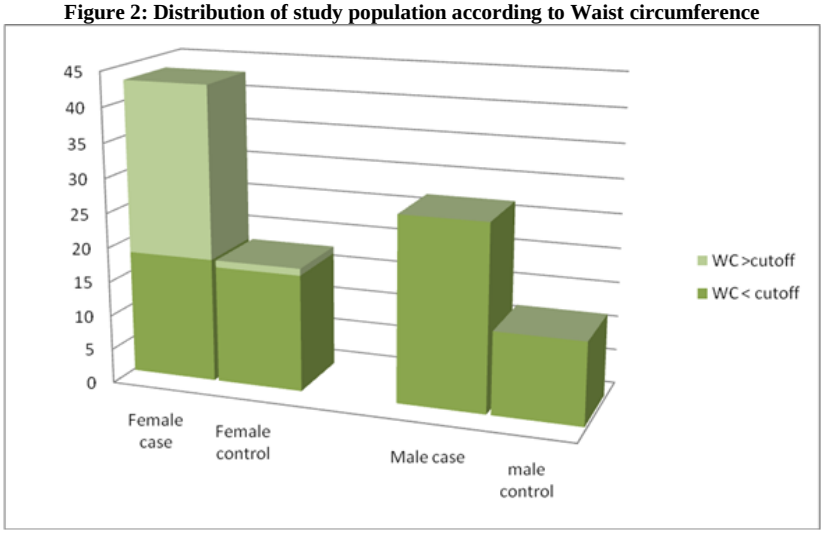

Figure 3: Bar diagram showing clinical parameters in study population

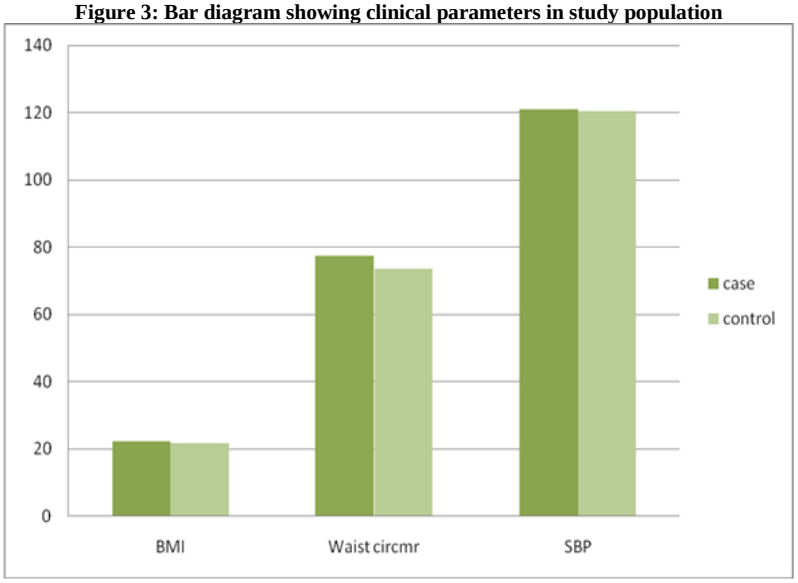

Table 2 : Clinical parameters in study population

Parameters	Case (with NAFLD). N=70	Control (without NAFLD). N=30	P value
BMI	22.01 ± 0.2685	21.45 ± 0.355	0.2331
Waist circumference	77.1 ± 0.935	73.57 ± 0.95	0.0097
SBP	120.9 ± 1.136	120.5 ± 1.732	08494

Table 3: Comparison of the various parameters between NAFLD cases and controls

Parameters	Case (with NAFLD). N=70	Control (without NAFLD). N=30	P value
FBS	91.84 ± 1.2	88.23 ± 1.384	0.053
SGPT	70.34 ± 4.225	33.23 ± 1.98	<0.0001
Fasting Insulin	13.55 ± 0.3729	6.708 ± 0.46	<0.0001
CRP	3.531 ± 0.127	3.277 ± 0.1824	0.2575
Uric acid	5.573 ± 0.198	5.253 ± 0.183	0.2405

Table 4: Lipid profile in NAFLD cases and control

Parameters	Case (with NAFLD). N=70	Control (without NAFLD). N=30	P value
Total cholesterol	195.3 ± 2.393	192.1 ± 3.915	0.4829
HDL	39.36 ± 0.698	41.67 ± 0.9164	0.493
Triglyceride	167.9 ± 3.079	137.3 ± 2.613	<0.0001

Table 5: Left ventricular profile in NAFLD cases and control

Cardiac Parameters	*Case (with NAFLD). N=70*	*Control (without NAFLD). N=30*	*P value*
Cardiac geometry			
LVM (gm)	*188.8 ± 6.123*	*152.0 ± 6.01*	*<0.001*

LVMI (gm/m^2)	*108.8 ± 3.68*	*88.43 ± 3.313*	*<0.001*
LVIDD (mm)	*47.09±0.82*	*43.1±0.979*	*0.0027*
PWD (mm)	*10.97±9.1842*	*10.6±0.231*	*0.2155*
IVSD (mm)	*11.01±0.2168*	*11.2±0.3195*	*0.6324*
LVIDS (mm)	*30.06±0.498*	*31.27±0.8656*	*0.2317*
RWT	*0.4746±0.012*	*0.497±0.07*	*0.2797*
Diastolic properties			
E (cm/sec)	*67.8±1.298*	*71.17±1.378*	*0.0793*
E/A	*0.953±0.022*	*1.072±0.255*	*0.0009*
E'(cm/sec)	*9.265±0.239*	*9.6±0.3712*	*0.4566*
E/E'	*8.534±0.424*	*8.361±0.3551*	*0.7565*
Cardiac Function			
LVEF (%)	*63.4±0.70*	*63.53±1.182*	*0.9231*

Table 6: Grade of diastolic dysfunction and LVMI in cases and control

Parameters	**Case (with NAFLD). N=70 % positive**					**Control (without NAFLD) N=30**				**%positive**
USG grade of NAFLD	I	II		III	70/70 = 100%	0				0
	42	19		9						
Diastolic Dysfunction	0	I		II	59/70 = 84.3%	0	I		ii	6/3=20%
	11	53		6		24	6		0	
LVMI grade	0	I	II	III	42/70 = 60%	0	I	Ii	iii	14/30=46.67%
	28	17	11	14		16	10	4	0	

Figure 4: Distribution of E/A ratio in case and control

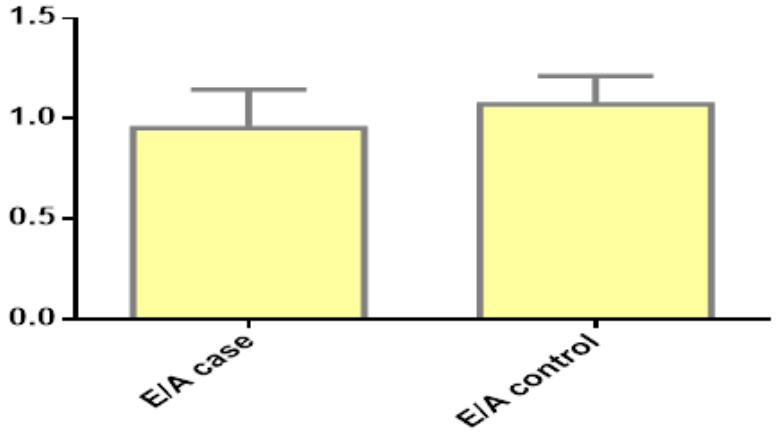

Figure 5: Scatter diagram showing relation between waist circumference and LVMI (r=0.111, P=0.359)

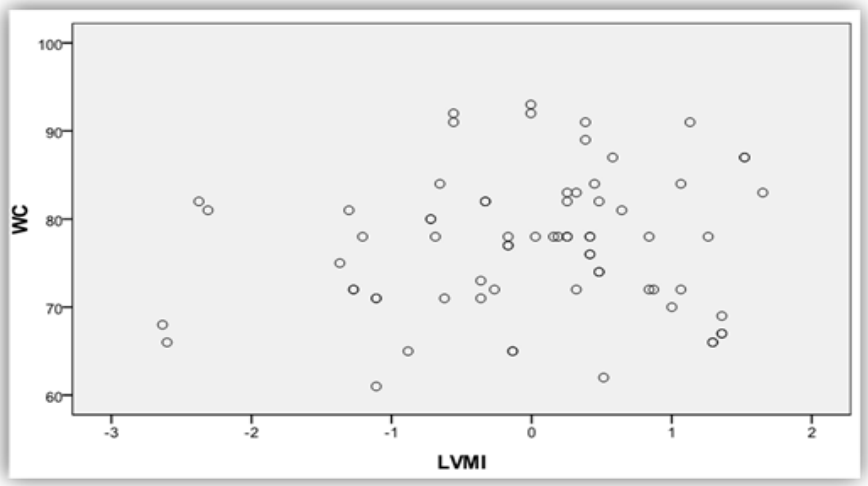

Figure 6: Relationship between waist circumference and LVIDD (r=0.12, P=0.319)

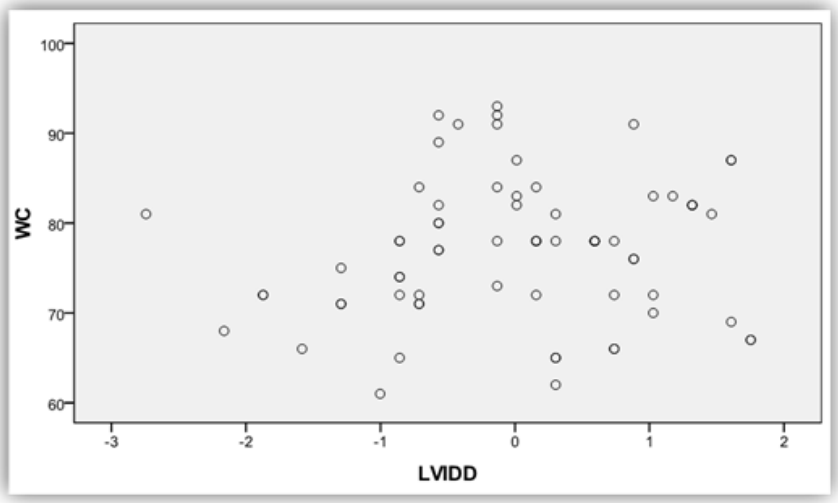

Figure 7: Relationship between Waist circumference and "E" (r=0.01, P= 0.909)

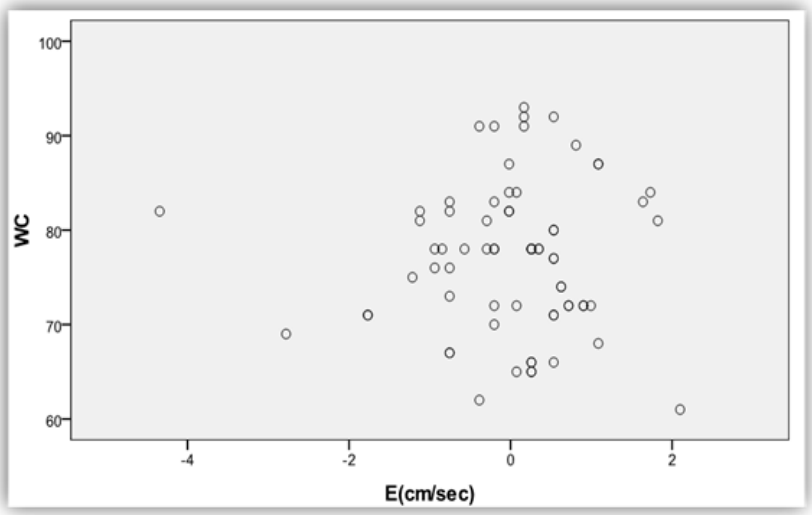

Figure 8: Relationship between LVMI and serum Triglyceride (r=0.174, P=0.149)

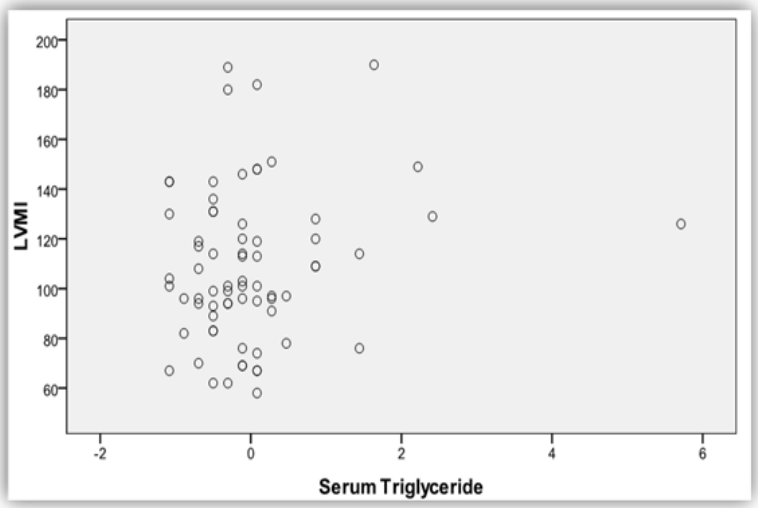

Figure 9: Relationship between Insulin Resistance and LVMI (r=0.135, P= 0.333)

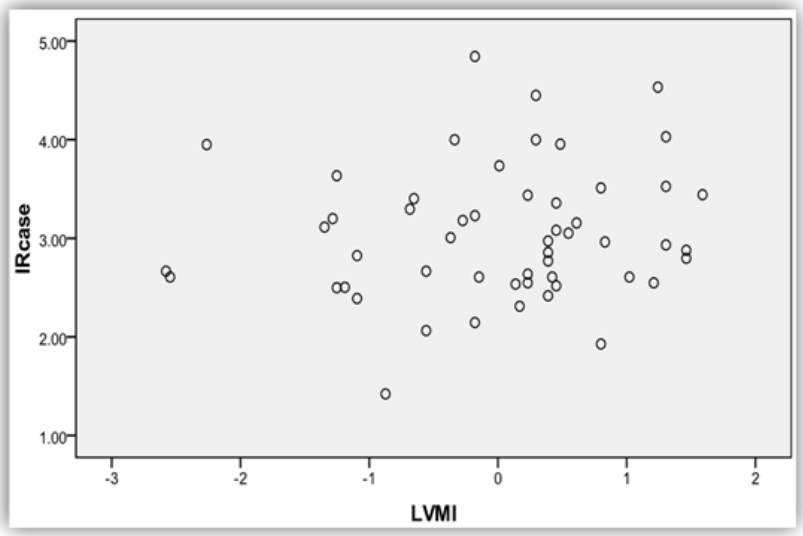

Figure 10: Relationship between Insulin Resistance and "E" (r=0.74, P=0.599)

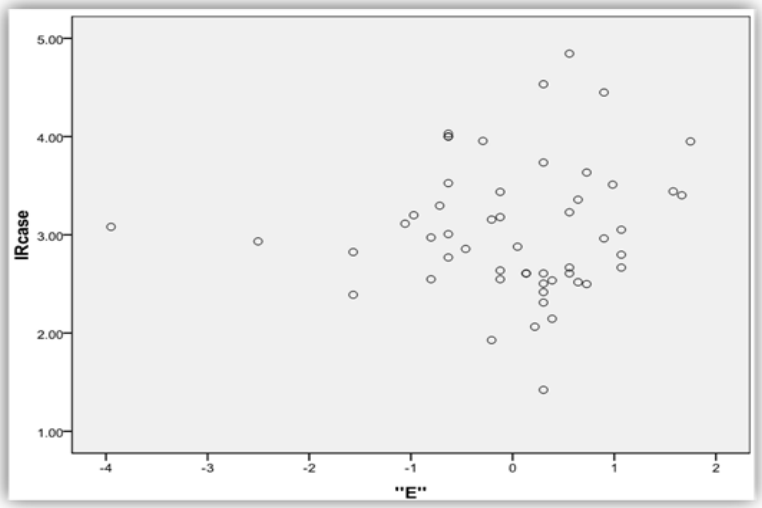

Figure 11: ROC curve of LVMI

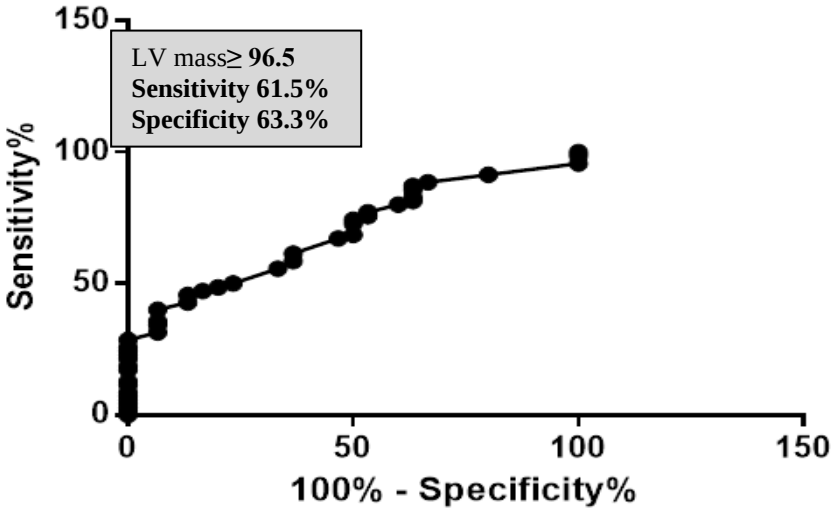

Table 7: ROC curve table of LVMI

Area under the ROC curve (AUC)	**0.695**
Standard Error	0.0531
95% Confidence Interval	0.59 to 0.79
Significance level P (Area=0.5)	0.002

DISCUSSION

NAFLD is a very common disease and is strongly linked to the metabolic syndrome and its components of insulin resistance, obesity, hypertension, diabetes mellitus and hypertriglyceridemia [1,2,3]. Despite the fact that hypertension and diabetes (central components of the metabolic syndrome) were exclusion criteria for our study, 20out of 70 patients (28.57 %) had IDF criteria consistent with the diagnosis of the metabolic syndrome because of higher Waist circumference and significant trigly ceridemia.

In previous studies [13,14,15,16] which included patients with marked obesity; changes in LV geometry and function, were well correlated with waist circumference and BMI. Recently, a cohort of young obese [16] women has been found to have decreased systolic and early diastolic velocities on Tissue Doppler Imaging, and BMI was the only predictor of these changes. In another study that evaluated patients with severe obesity, BMI was positively correlated with LVM and only borderline associated with early diastolic mitral annular velocity (E') [15, 16]. In our study, patients with NAFLD had greater waist circumference than the control group, but did not have higher BMI or obesity (BMI >30 gm/m^2). We did not find a strong correlation between the indices of LV structure (LVM index, LVIDD), diastolic function (E, E/A, E') and waist circumference or serum triglyceride in NAFLD patients. This finding can be explained by the fact that, alteration of LV geometry and diastolic dysfunction in this population may not a sole function of the increased waist circumference or triglyceride level.

There is paucity of data concerning the in fluence of the metabolic syndrome on LV function, especially inpatients without hypertension, diabetes, and morbid obesity. A slight increase in plasma glucose levels was shown to be associated with abnormal diastolic function, independent of LV hypertrophy, in non-diabetic patients with treated hypertension [22]. In our study, NAFLD patients had higher blood glucose level than of control, but the difference did not achieve statistical significance. The effect of the metabolic syndrome on LV diastolic function was also shown in the Strong Heart Study, where, lower mitral E/A ratio values with comparable Deceleration time (DT) were found in patients with metabolic syndrome; but only the increased blood pressure, even in the high normal range, was strongly associated with changes in LV geometry and function. But in our study population blood pressure were within normal limit and equal to that of control.

We found significant differences in LV diastolic function between the nondiabetic, normotensive patients with NAFLD and the control group. In the current study, patients with NAFLD had a lower early diastolic velocity (E) and lower early to late diastolic velocity ratio (E/A). 59 out of 70 patients i.e., 84.28% patients had diastolic dysfunction in our study. TDI has proven to be very useful for the evaluation of load-independent myocardial velocities which correlate better [23,24] with LV function and prognosis than those observed using trans-mitral pulsed-wave Doppler velocities. This technique has been shown to be highly sensitive in detecting early features of LV dys function [24]. We suggest that, low early diastolic velocities, in TDI, in our patients, may represent very early pre-clinical cardiac manifestation of NAFLD.

It is well established that, metabolic syndrome and insulin resistance have effects on the heart, both on LV geometry and function [25-30]. A study in rats demon started that, insulin resistance altered cardiac structure and contractile function at the level of the myocyte [30]. These results have been confirmed in human studies that showed an association between insulin resistance and LV re modelling in nondiabetic subjects. Whether insulin resistance seems to be

independently associated with cardiac remodelling is still unclear [14]. The influence of insulin resistance on LVM was seen in normotensive diabetic patients; where, fasting plasma insulin was found to be the strongest independent predictor of LVM [30]. Another recent study has shown that insulin resistance in uncomplicated obesity in the absence of diabetes is associated with an increased LV Mand precocious changes of LV geometry [29]. However, not all studies in the nondiabetic population support these results [31]. When adequate account was taken of BMI and blood pressure, insulin resistance was not found to be an independent determinant of LVM [32]. Sorel Goland et al in Journal of Clinical Gastroenterology, Volume 40, Number10, November/ December 2006, suggested that the presence of insulin resistance may have a negative impact on LV diastolic function in NAFLD patients or subjects with metabolic syndrome without hypertension and diabetes. They also showed that E' (early diastolic velocity of mitral annulus) on TDI was the only independent index able to characterize patients with NAFLD [33,34]. In our study, we did not find a strong correlation between the indices of LV structure (LVM index, LVIDD, and RWT), diastolic function (E, E/A, E'), and Insulin resistance (HOMA-IR) or serum Fasting Insulin level in NAFLD patients. This finding can be explained by the fact that alteration of LV geometry and diastolic dysfunction in this population may not be a sole function of Insulin resistance, that is, it may be multifactorial or, it may be due to demographic variation, or further studies are needed to establish such a correlation.

It is important to remember, that, for this study, we chose young and middle-aged asymptomatic patients who were otherwise healthy a part from having either elevated liver enzymes or a fatty liver on ultrasound. Thus, we have shown that, NAFLD patients without conventional cardiovascular risk factors as hypertension, obesity and diabetes, have significant alteration of LV structural geometry and early features of LV diastolic dys function. Recently, endothelial dysfunction and increased risk of cardiovascular events have been found inpatients with NAFLD as described by Garther et al. Though our study could not pinpoint the etiological parameter(s) associating NAFLD and cardiovascular remodelling, we propose that, it may be multifactorial and further Indian studies may be needed to establish this relationship and relevance of early recognition and scope for effective prevention of development and progression of this cardiological alteration in a very early stage in this novel population, well before conventional risk factors appear.

CONCLUSION

NAFLD is an integral part of the metabolic syndrome, a cluster of risk factors for cardiovascular disease. In this study, we have shown that patients with NAFLD without hypertension, diabetes, and obesity have early manifestations of LV diastolic dysfunction in the form of lower early diastolic velocity- 'E' and lower early to late diastolic flow velocity-E/A ratio and alteration of LV geometry in the form of increased left ventricular mass index (LVMI) and increased left ventricular end diastolic diameter- LVIDD. The cutoff value for LVMI as derived from our study, can be used suitably for Indian population. Further studies are needed especially in Indian subcontinent to evaluate the prognostic implication of these findings and the importance of early recognition, prevention and treatment.

Declaration by Authors

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