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Evaluating Carotid intima media thickness (CIMT) of patients with Non - Alcoholic fatty liver disease (NAFLD) as a risk factor for atherosclerosis and correlation with metabolic syndrome

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ABSTRACT

This study aimed to evaluate the effect of NAFLD on CIMT as a risk factor for atherosclerosis. The incidence of non-alcoholic fatty liver disease (NAFLD) is escalating worldwide due to mount of obesity and diabetes mellitus (DM) prevalence. Non-invasive appraisal of carotid intima-media thickness (CIMT) by high-resolution carotid B-mode ultrasonography is broadly used for determining atherosclerosis. In this case-control setting, 151 subjects were categorized in three groups: group I counting 49 patients with NAFLD and DM; group II counting 50 non-diabetic NAFLD patients; and the control with 52 normal subjects as group III. The right and left CIMTs and its maximum reading (CIMT max) were deliberated by a skilled sonographist blind to the groups. The sonographic grading of the NAFLD was dogged in groups I and II. Median CIMT max was extensively higher in group I comparing with group II and control group ($p<0.001$). This disparity between group I and group II were not significant after adjusting for age and history of hypertension and hyperlipidemia ($p=0.089$). After scheming the confounders, there was a statistically significant between-group I and group II with the control group ($p<0.05$). There was no significant disparity in median maximal thickness of intima-media in the carotid of group I compare to group II in patients with and without prominent liver enzymes (in both groups, 0.6 mm, $p= 0.402$). Based on our findings, there is a significant relationship between the presence of NAFLD and atherosclerosis. This association was independent to the Diabetes mellitus presence. The grade of NAFLD and elevated liver function tests had no effect on the severity of atherosclerosis.

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INTRODUCTION

Diagnosis of Non – alcoholic fatty liver disease as a source of progress towards the end-stage liver disease is escalating (Nahandi and Khoshbaten, 2014). Today one among every 4 individuals are being diagnosed as having fatty liver. NAFLD is strongly allied with overweight/obesity & insulin resistance. (Setji *et al.*, 2006). The NAFLD – related cirrhosis is about 3-4 times more common than cirrhosis caused by chronic hepatitis C infection. The disease ranges from mild steatosis to liver diseases such as non-alcoholic steato-hepatitis (NASH), cirrhosis & ulti-

mately, Hepatocellular carcinoma (Nahandi and Khoshbaten, 2014). NAFLD is the most common liver disease nowadays. The most common cause of elevated transaminases and cryptogenic cirrhosis is NAFLD (Bellentani *et al.*, 2000). The histological phrase may vary from simple steatosis (HS) to non-alcoholic steatohepatitis (NASH), which occurs due to great input of fatty acids into the liver, which consequently results in increased beta-oxidation that lead to the formation of free radicals, the release of inflammatory cytokines and unreliable degrees of hepatocytic aggression, and fibrosis including perisinusoidal, and pericellular Features of steatohepatitis include hepatocellular injury, inflammation (Farrell and Larter, 2006). The percentage of hepatocytes containing fat droplets is used in estimating the amount of steatosis. The lower threshold is 5% of hepatocytes. The mechanism for hepatocellular injury includes ballooning, apoptosis/necrosis, Mallory's hyaline, giant mitochondria (Hubscher, 2006). Based on the amount of alcohol intake, there are different suggestions that can constantly differentiate between alcoholic fatty liver and NAFLD. By definition of NAFLD, the maximum allowable amount of alcohol consumption is 2 standard drinks per day (140 g of ethanol in a week) for men, and one standard drink per day (70 g of ethanol in a week) for women is accepted in many centres (Paschos and Paletas, 2009).

The metabolic syndrome consists of a cluster of risk factors that increases significantly an individual's odds for budding type 2 diabetes mellitus, chronic kidney disease and atherosclerotic cardiovascular disease (ASCVD) (Kotronen and Yki-Järvinen, 2008) The major fundamental risk factors are abdominal obesity, atherogenic dyslipidaemia, hypertension, raised plasma glucose, a prothrombotic state, and a proinflammatory state. The intima-media thickness (IMT) of the carotid artery is calculated non-invasively by ultrasound techniques. (Lundqvist *et al.*, 1999) An augmented IMT has been shown to be a risk factor for myocardial infarction and stroke. In addition, carotid ultrasound has been a precise diagnostic tool to determine atherosclerotic plaques and to assess the degree of luminal narrowing secondary to atherosclerotic changes of the vessel wall (Chouhan *et al.*, 2017).

NAFLD has clinical, laboratory and pathological circumstances ranged from mild steatosis non-alcoholic steatohepatitis (NASH) to liver diseases such as fibrosis, cirrhosis and eventually hepatocellular carcinoma (Clark *et al.*, 2003). Due to increasing urbanization and behavioural changes such as fat, high energy diet, decreased physical activity and amplified incidence of type II DM, its prevalence has increased in the Asian region. The frequency of the NAFLD is predicted to be 7 and40 per cent in various populations. In Japan, it was 3-20 folds in the past 2 decades (Das *et al.*, 2006). Obesity with diabetes mellitus, hypertension or changes in lipid metabolism has been depicted as a separate disease called "metabolic syndrome", which raises the risk of cardiovascular diseases (Harrison *et al.*, 2002). Because of the major connection between NAFLD and metabolic syndrome and between metabolic syndrome and cardiovascular diseases, various studies were performed concerning the association, which also proved the momentous association between them (Bedogni *et al.*, 2005). Now the query is whether the NAFLD is a risk factor for atherosclerosis and cardiovascular diseases or not? (Adams and Lindor, 2007). The standard method for evaluation of early general atherosclerosis is carotid intima-media thickness (CIMT) (Targher *et al.*, 2004). Studies done in this segment propose a correlation between the carotid intima-media thickness and NAFLD (Targher *et al.*, 2004). In our present study, patients with NAFLD are being evaluated for atherosclerosis by measuring CIMT. By this, we may be able to identify NAFLD as a predisposing factor for atherosclerosis & thereby cardiovascular disease. In our study, we would also like to see the correlation between metabolic syndrome & CIMT as previous studies regarding this were limited.

MATERIALS AND METHODS

The present study is a prospective study carried out between April 2017 to May 2018 and on patients who visited Saveetha Medical College and Hospital, Chennai, a tertiary care referral hospital that caters to the needs of the population of Tamil Nadu and those from neighbouring states such as Andhra Pradesh and Karnataka with a clinical and ultrasound diagnosis of non-alcoholic fatty liver. The study inhabitants based on the existing literature (by allowing alpha error of 5%, beta error of 20% (power 80%) for a relative precision of 20% at 5% significant level the estimated sample size to be studied was calculated to be 55 patients. The inclusion criteria were patients with Age above 18, Either gender, Both In/Outpatients and with a radiological diagnosis of Fatty liver. Exclusion criteria include Alcoholic, Patients with viral hepatitis, Patients who has undergone gastrointestinal & pancreaticobiliary surgery, Pregnancy, Hepatotoxic medications and Inborn errors of metabolism.

Permission was taken from the Institutional Ethics Committee of Saveetha Medical College

and Hospital prior to the initiation of the study (006/05/2015/IEC/SU) for Study Site Department of General Medicine at Saveetha Medical College and Hospital. Basic demographic details are collected - name, age, sex and discipline of study. Patients diagnosed to have fatty liver by a radiologist were eligible for the study. By applying exclusion criteria, all other causes of fatty liver were excluded. Thereby non-alcoholic fatty liver disease (NAFLD) persons were obtained. Around 55 NAFLD persons were included for whom right and left CIMT are measured. The people with NAFLD were divided into those with increased CIMT group & those with normal CIMT group. These groups were evaluated further by doing liver function test, Fasting & post-prandial blood sugar, HbA1c, fasting lipid profile, renal function test, urine routine & complete blood counts were done. Physical examination for height, weight & waist circumference, BMI, Blood pressure will be measured. The metabolic syndrome will be identified based on the National cholesterol education program, Adult treatment plan-III criteria. Patients with NAFLD with metabolic syndrome are corelated with patients with NAFLD without metabolic syndrome in terms of mean CIMT Diabetics with NAFLD are compared with Non-Diabetics with NAFLD in terms of mean CIMT.

The present study was undertaken for "Evaluating carotid intima media thickness of persons with non-alcoholic fatty liver disease". As a risk factor for atherosclerosis & correlation with metabolic syndrome. The data was collected and analysed. All the statistical analysis was done with Statistical Package for Social Science (SSPS, version 22) from Microsoft windows. The data were expressed as Mean and Standard deviation (S.D.). A two-sided p-value of 0.05 is taken to be statistically significant.

The data is depicted as Tables and Figures

RESULTS AND DISCUSSION

The study involves a sum of 55 patients. In this study population, 43.6% (n=24) were males and 56.4% (n=31) were females with a nominal age of 25 years and ceiling age of 85 years.

Table 1 shows the age distribution of the study population. According to age distribution, 55 NAFLD patients are age from 25 years to 85 years. Out of which 9(16.38%)patients are among 25-34 years with a mean CIMT of 0.68mm, 14(25.48%) patients are in between 35-44years with a mean CIMT of 0.77mm, 17(30.94%) patients are in between 45-54 years with mean CIMT of 0.83mm, 9(16.38%) patients are in between 55-64 years with mean CIMT of 0.83mm, 5(9.1%) patients are in between

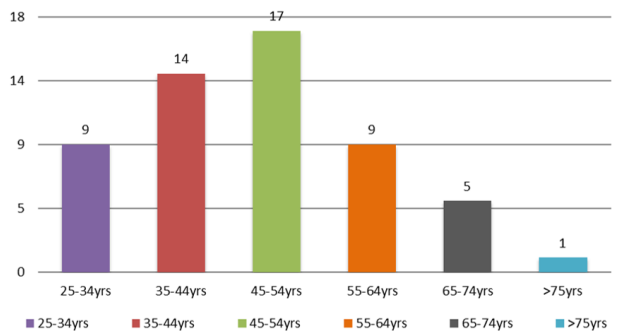

Figure 1: Age distribution in NAFLD patients

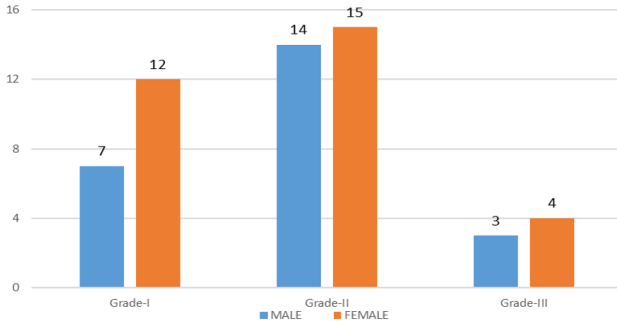

Figure 2: Gender distribution in various grades of fatty liver

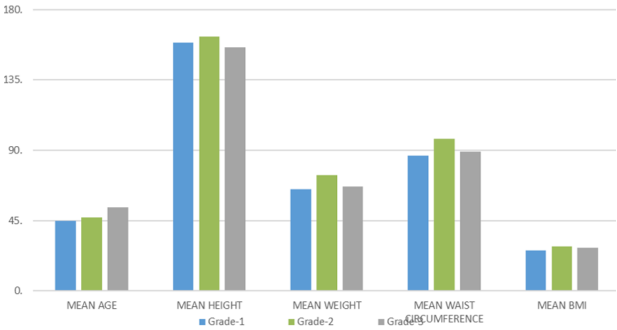

Figure 3: Demographic parameters in various grades of NAFLD patients

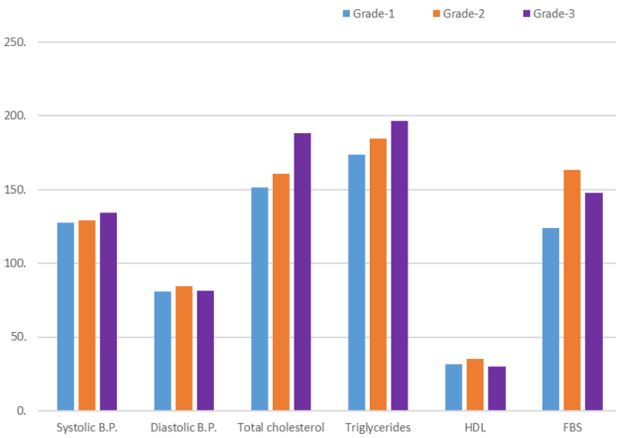

Figure 4: Comparison of physical and laboratory parameters in various grades of fatty liver in NAFLD patients

Table 1: Age distribution of the study population

S. No.	Range of Age (Years)	No. of patients (%)	Mean CIMT (in mm)
1.	25-34	9(16.38%)	0.68
2.	35-44	14(25.48%)	0.77
3.	45-54	17(30.94%)	0.83
4.	55-64	9(16.38%)	0.83
5.	65-74	5(9.1%)	0.96
6.	>75Years	1(1.82%)	1.2

Table 2: Distribution of study population according to USG grade of fatty liver

S. No.	Grading of Fatty liver	Frequency	Percent
1.	GRADE I	19	34.5
2.	GRADE II	29	52.7
3.	GRADE III	7	12.7
4.	Total	55	100.0

Table 3: Sex distribution in various grades of fatty liver

Sex		Grade of fatty liver			Total
		Grade I	Grade II	Grade III	
Male	Count	7	14	3	24
	% within Sex	29.2%	58.3%	12.5%	100.0%
Female	Count	12	15	4	31
	% within Sex	38.7%	48.4%	12.9%	100.0%
Total	Count	19	29	7	55
	% within Sex	34.5%	52.7%	12.7%	100.0%

Table 4: Mean right and left CIMT distribution according to fatty liver grading in NAFLD patients

		No. of patients (N)	Mean CMT	Standard deviation	Level of significance
Right CIMT	Grade I	19	0.70	0.137	0.053
	Grade II	29	0.85	0.341	
	Grade III	7	0.92	0.197	
	Total	55	0.82	0.279	
Left CIMT	Grade I	19	0.70	0.156	0.044
	Grade II	29	1.01	0.256	
	Grade III	7	1.03	0.305	
	Total	55	0.91	0.242	
Mean CIMT	Grade I	19	0.7	0.1354	0.050
	Grade II	29	0.93	0.2912	
	Grade III	7	0.97	0.2375	
	Total	55	0.86		

Table 5: Comparison of demographic, physical parameters in various grades of fatty liver in NAFLD patients

		No. of patients (N)	Mean Age In years	Standard Deviation	Level of Significance
Age	Grade I	19	44.74	9.474	0.276
	Grade II	29	47.10	12.356	
	Grade III	7	53.71	19.242	
	Total	55	47.13	12.564	
Height	Grade I	19	158.79	6.795	0.146
	Grade II	29	162.83	10.351	
	Grade III	7	155.86	12.240	
	Total	55	160.55	9.712	
Weight	Grade I	19	64.95	12.241	0.051
	Grade II	29	74.17	12.765	
	Grade III	7	66.86	15.507	
	Total	55	70.05	13.445	
Waist Circumference	Grade I	19	86.42	10.663	0.009
	Grade II	29	97.28	11.326	
	Grade III	7	89.29	16.740	
	Total	55	92.51	12.734	
BMI	Grade I	19	25.832	4.6719	0.194
	Grade II	29	28.606	4.8261	
	Grade III	7	27.814	7.2912	
	Total	55	27.547	5.1871	

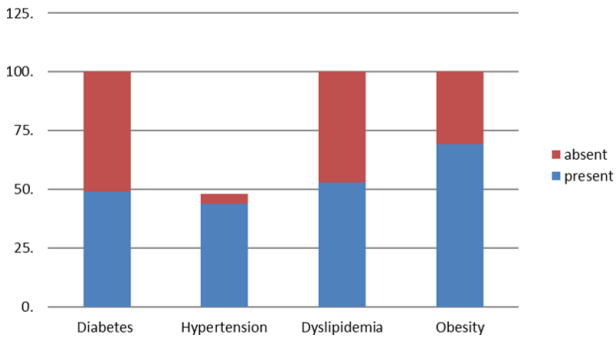

Figure 5: Prevalence of various risk factors in NAFLD patients

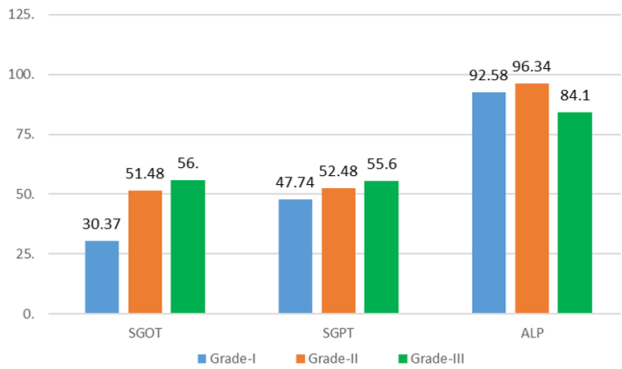

Figure 6: Comparison of liver enzymes in various grades of fatty liver in NAFLD patients

65-74 years with mean CIMT of 0.96mm and 1 (1.82%) patient in age group >75 years with mean CIMT of 1.2mm. There is an age-wise increase in mean CIMT in NAFLD patients. Figure 1 depicts the age distribution in NAFLD patients. Table 2 depicts the distribution of the study population according to the USG grade of fatty liver. Table 3 shows the sex distribution in various grades of fatty liver. According to ultrasound grading of fatty liver 19(34.5%) are having Grade-I fatty liver, out of which 7(29.2%) are males and 12(38.7%) are females (Figure 4). Out of 29(52.7%) are having Grade-II fatty liver out of which 14(58.3%) are males and 15 (48.4%) are females. 7(12.7%) are having Grade-III fatty liver out of which 3(12.5%) are males and 4(12.9%) are females. More than half of patients are having Grade-II fatty liver.

Table 6: Comparison of physical and laboratory parameters in various grades of fatty liver in NAFLD patients

		No. of patients (N)	Mean	Standard Deviation	Sig.
Systolic B.P. (mmHg)	Grade I	19	127.37	19.676	0.730
	Grade II	29	129.31	19.444	
	Grade III	7	134.29	20.702	
	Total	55	129.27	19.423	
Diastolic B.P. (mmHg)	Grade I	19	81.05	11.496	0.541
	Grade II	29	84.48	10.885	
	Grade III	7	81.43	10.690	
	Total	55	82.91	11.000	
Total Cholesterol (mg/dl)	Grade I	19	151.63	44.233	0.156
	Grade II	29	160.52	31.004	
	Grade III	7	188.00	70.102	
	Total	55	160.95	42.687	
Triglycerides	Grade I	19	173.68	86.918	0.492
	Grade II	29	184.59	96.763	
	Grade III	7	196.43	71.749	
	Total	55	182.33	89.443	
HDL	Grade I	19	31.79	8.430	0.250
	Grade II	29	35.17	8.426	
	Grade III	7	30.29	9.447	
	Total	55	33.38	8.618	
FBS (mg/dl)	Grade I	19	124.00	36.857	0.261
	Grade II	29	163.55	81.067	
	Grade III	7	147.86	44.570	
	Total	55	147.89	66.436	

Figure 2 shows the gender distribution in different grades of fatty liver.Figure 3 shows the demographic parameters in various grades of NAFLD patients.

Table 4 shows the mean right and left CIMT distribution according to fatty liver grading. Out of 55 NAFLD patients 14 (25.48%) have mean CIMT >0.9mm, 12(21.84%) patients have mean CIMT between 0.8-0.89mm and 29(52.78%) patients have mean CIMT <0.8mm. The mean of right CIMT in Grade-I, Grade-II and Grade – III fatty liver are 0.7mm, 0.85mm and 0.92mm, whose P-value is 0.05 which is statistically significant (Table 8).

The mean of left CIMT in Grade-I, Grade-II and Grade – III fatty liver are 0.7mm, 1.01mm and 1.03mm, whose P-value is 0.04 which shows significance. The mean CIMT of Grade-I fatty liver is 0.7mm, mean CIMT of Grade-II fatty liver is 0.93mm and mean CIMT of Grade-III fatty liver is 0.97mm, whose P-value is 0.05, which is statistically significant.

Table 5 shows the comparison of demographic, physical parameters in various grades of fatty liver in NAFLD patients.

Table 6 shows a comparison of physical and laboratory parameters in various grades of fatty liver in NAFLD patients.

Out of 55 NAFLD patients, 19 patients having Grade-I fatty liver have mean systolic blood pressure (SBP) is 127.37mmHg, 29 patients having Grade-II fatty liver have a mean SBP of 129.31mmHg, and 7 patients having Grade-III fatty liver have a mean SBP of 134.29mmHg. The mean SBP for three Grades of fatty liver is 129.27mmHg. P-value is 0.73.

Table 7: Prevalence of various parameters in NAFLD patients

Parameter	No. of patients	Percentage
Diabetes Mellitus	28	50.96%
Dyslipidemia	29	52.78%
Hypertension	24	43.68%
Obesity	38	69.16%

Table 8: Summary of demographic, physical and laboratory parameters in various grades of fatty liver in NAFLD patients

	Grade-I	Grade-II	Grade-III	Total Mean	P-value
Age	44.74	47.10	53.71	47.13	0.276
Height	158.79	162.83	155.86	160.55	0.146
Weight	64.95	74.17	66.86	70.05	0.05
Waist Circumference	86.42	97.28	89.29	92.51	0.009
BMI	25.83	28.606	27.814	27.547	0.194
SBP	127.37	129.31	134.29	129.27	0.730
DBP	81.05	84.48	81.43	82.91	0.541
Total Cholesterol	151.63	160.52	188	160.95	0.156
Triglycerides	173.68	184.59	196.43	182.33	0.492
HDL	31.79	35.17	30.29	33.38	0.250
FBS	124	163.55	147.86	147.89	0.261
SGOT	30.37	51.48	56	44.76	0.593
SGPT	47.74	52.48	55.57	51.24	0.976
ALP	92.58	96.34	84.14	93.49	0.672
Right CIMT	0.70	0.85	0.92	0.82	0.053
Left CIMT	0.70	1.01	1.03	0.91	0.044
Mean CIMT	0.7	0.93	0.97	0.86	0.048

Figure 4 shows a comparison between physical and laboratory parameters in various grades of NAFLD patients. Table 7 shows the prevalence of various parameters in NAFLD patients. Figure 5 depicts the incidence of risk factors in NAFLD patients. Figure 6 shows the comparison of liver enzymes in various grades of fatty liver.

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease occurring commonly these days and it is also the most common cause of prominent transaminases. 70% of cases of cryptogenic cirrhosis are due to NASH. NAFLD patients demonstrate a higher mortality rate than the general population (Lidofsky, 2008). The most common causes of death in NAFLD patients are liver-related diseases, malignant neoplasms and cardiovascular disease (113). This study involves 55 patients who are found to have fatty liver by ultrasonogram and met the criteria for the non- alcoholic.

In this study, out of 55 NAFLD patients, 43.6% are males and 56.4% are females, i.e. female predominance, which is similar to the evidence described from Yatsuji et al. a series of 193 Japanese patients with NASH confirmed by histopathology primarily in women aged more than 55 years. Mean CIMT in males is 0.82mm and females is 0.8mm where there is no considerable difference between two groups our results are similar to Chouhan et al. study in which NAFLD patients mean CIMT of the left common carotid artery in males was 0.71±0.18 mm and in females was 0.70±0.19 mm. Similarly, the mean CIMT of the right common carotid artery in males was 0.72±0.17mm and in females was 0.70±0.18 mm. This study showed that there is no major disparity in mean CIMT between males and females of NAFLD group.

In our study, according to ultrasound grading of fatty liver, 19(34.5%) are having Grade-I fatty liver, 29(52.7%) are having Grade-II fatty liver, and 7(12.7%) are having Grade-III fatty liver, which is similar to Rasool et al. Grade 1 fatty liver was seen in 36% patients while Grade 2 fatty liver was found in 39% and Grade 3 fatty liver in 25%(114). Our study is in contrast to Agarwal et al. proved that

48.1%, 40.3% and 11.3% had grade I, II and III fatty liver respectively and Chouhan et al., NAFLD group 25 (54.34%) patients had grade I fatty liver, 19 (41.30%) had grade II fatty liver and 2 (4.34%) had grade III fatty liver.

CONCLUSION

Though non-alcoholic fatty liver disease is associated with obesity and type-II diabetes, it is an independent risk factor for cardiovascular disease, which is evidenced by a significant increase in carotid intima media thickness in our study. Non-alcoholic fatty liver disease also has a significant correlation with metabolic syndrome in our study, but not all non-alcoholic fatty liver disease patients in the study have metabolic syndrome. In our study, mean carotid intima media thickness in diabetics patients with non-alcoholic fatty liver disease is significantly increased compared to non-diabetics with non-alcoholic fatty liver disease which indicates the role of insulin resistance in causing atherosclerosis. In our study, we found a noteworthy raise in carotid intima media thickness in patients with non -alcoholic fatty liver disease with metabolic syndrome than compared to non-alcoholic liver disease patients without metabolic syndrome. Identification of subgroups of individuals diagnosed to have non-alcoholic fatty liver disease and metabolic syndrome will get particular benefit with lifestyle modification and management with drugs to reduce cardiovascular risk.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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