

# Determination of association between nonalcoholic fatty liver disease and carotid artery atherosclerosis among nondiabetic individuals

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## ABSTRACT

**Background:** Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by the infiltration of fat in the liver cells. High levels of fat in the liver associated with increased risk of diseases like diabetes, high blood pressure and kidney disease, high cholesterol, metabolic syndrome. **Aim and Objective:** To determine the association between NAFLD and carotid intima media thickness (CIMT) among nondiabetic individuals. **Materials and Methods:** A total of 90 in-patients and outpatients (45 NAFL subjects and 45 patients with the normal liver as controls) with NAFL on abdomen ultrasound scan from Bangalore Baptist Hospital were included in our study. All the participants were subjected to a doppler study for carotid intima thickness and a blood sample (4 ml) was collected from all the subjects. **Results:** In this study, there is an elevated level of BMI, weight, dyslipidemia in NAFLD compared with controls. The present study suggests that cardiovascular risk factors such as increased carotid intima-media thickness occur more frequently among NAFLD patients compared to healthy individuals. **Conclusion:** We can conclude that NAFL has a significant association with higher cardiovascular risk in terms of carotid intima-media thickness, dyslipidemia, and hypoalphalipidemia. Lifestyle changes include weight loss, dietary changes, reduction of sedentary habits and physical exercise are recommended in the NAFL disease subjects with higher BMI and weight.

**Keywords:** Cardiovascular disorders, carotid intima media thickness, diabetes, dyslipidemia, nonalcoholic fatty liver

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by the infiltration of fat in the liver cells. Mainly seen in people who are overweight or obese. NAFLD is seen in the people who are not abused by alcohol. NAFLD initially harmless but leads to liver damage and cirrhosis if the condition gets worse.

High levels of fat in the liver associated with increased risk of diseases like diabetes, high blood pressure and kidney disease,

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high cholesterol, and metabolic syndrome (MetS).<sup>[1]</sup> NAFLD leads to elevated levels of liver enzymes. In western countries, the prevalence rate of NAFLD is 30% whereas in Asia-pacific nations; it is up to 5-30% rises to 80-90% in obese adults, 30-50% in diabetic patients, and 90% in hyperlipidemia. It affects 3-10% of children and 40-70% of obese children.<sup>[2]</sup>

Atherosclerosis is a condition characterized by the hardening and narrowing of arteries. It leads to heart attacks, strokes and peripheral vascular diseases together called cardiovascular disease.

Many studies have shown that there is an association between NAFLD and cardiovascular diseases. So, it is important to predict whether NAFLD is an independent predictor of

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cardiovascular morbidity and mortality.<sup>[3-8]</sup> Increased carotid intima media thickness (CIMT) is an early indicator of cardiovascular diseases.<sup>[9-11]</sup> In some studies, mean CIMT ranges from  $0.64 \pm 0.10$  mm to  $1.24 \pm 0.13$  mm in NAFLD patients<sup>[12]</sup> carotid atherosclerosis screening should be recommended in all NAFLD patients. Currently available epidemiological data indicate that a value of CIMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction or cerebrovascular disease.<sup>[11]</sup>

In our study, we selected a random group of consecutive outpatients and in-patients undergoing abdominal USG. In addition, we evaluated whether any association is independent of classical risk factors and mass features.

## Materials and Methods

A total of 90 in-patients and out-patients (45 NAFL subjects and 45 patients with the normal liver as controls) on the abdomen ultrasound scan (USG scan) from the Department of Radiology, Bangalore Baptist Hospital were included in our study. The study was done after obtaining informed consent from the patients and institutional ethical committee clearance.

A detailed history regarding smoking, alcohol consumption, calorie intake, etc., were collected from the patients by administering a questionnaire.

Patients under the age of 65 with normal liver and who do not consume alcohol were included in our study.

## Exclusion criteria for both the study and control group

Patients with any clinical evidence of cirrhosis or other causes of chronic liver disease, History of alcohol consumption, Smoking, Viral hepatitis, Autoimmune hepatitis, Dyslipidemia, Hemochromatosis, Use of hepatotoxic medications (ATT, antiepileptics, and steroids), Type 2 diabetes mellitus.

All the participants were subjected to the doppler study for carotid intima media thickness. An experienced radiologist to prevent variance did the carotid doppler. BMI, height, weight, pulse rate, systolic blood pressure, and diastolic blood pressure were recorded. Blood samples (4 ml) were drawn from all the subjects following a fast of 12 hours and analyzed for Serum Triglycerides (TG), Total cholesterol (TC) and High-density lipoprotein cholesterol (HDL) by enzymatic methods with the help of Glaxo kits on ERBA Chem- 5 semi auto analyzer. Serum Low-density lipoprotein cholesterol (LDL) was calculated by Frederickson-Friedwald's formula according to which LDL cholesterol = Total cholesterol - (HDL cholesterol + VLDL cholesterol).

## Statistical analysis

All values expressed as Mean  $\pm$  standard deviation (SD). An independent *t*-test was used to test the significance of the

difference in means between the study group and controls. A Chi-square test for independence is used to determine the relationship between two variables of a sample. A  $P < 0.05$  considered statistically significant. The statistical software namely SPSS 16.0 were used for the analysis of the data and Microsoft word and excel have been used to generate tables.

## Results

The present study was conducted with 45 NAFL subjects and 45 patients with the normal liver as controls in the department of radiology. The average age of NAFL subjects was  $44.87 \pm 10.58$  years. The oldest subject was 65 years and the youngest being 21 years. Among the study group, 26 were males and 19 were females in NAFLD patients whereas 28 were males and 17 were females in the control group. Height (cm), weight (kg), Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) and waist circumferences (cm) were compared between NAFLD and control group. Pulse rate (bpm), systolic blood pressure (mmHg), diastole blood pressure (mmHg) were compared with the control group [Table 1].

Table 1 depicts mean height in the control group was  $166 \pm 8.4$  cm and the study group was  $167 \pm 6.9$  cm. The mean waist circumference in the control group was  $87 \pm 6.5$  cm and the study group was  $86 \pm 7.8$  cm. In terms of height and waist circumference in relation to NAFLD, there was no statistical significance noted.

The mean BMI in the control group was  $25 \pm 2.6$   $\text{kg}/\text{m}^2$ , wherein the study group was  $27 \pm 2.3$   $\text{kg}/\text{m}^2$ . There was a significant association between NAFLD and higher BMI in the study group, which was lacking in the control group, with a significant  $P = 0.01$ .

The mean weight in the control group was  $69 \pm 12$  kg wherein the study group was  $77 \pm 9.18$  kg. The study and the control group were statistically comparable in terms of higher weight associated with NAFLD with a significant  $P = 0.01$ .

**Table 1: Association between NAFLD and the control group**

Variable	Group	Mean $\pm$ SD	t	P
Height (cm)	Normal	166 $\pm$ 8.4	0.873	0.385
	Fatty liver	167 $\pm$ 6.9		
Weight (kg)	Normal	69 $\pm$ 12	3.569	0.001*
	Fatty liver	77 $\pm$ 9.18		
BMI	Normal	25 $\pm$ 2.6	3.496	0.001*
	Fatty liver	27 $\pm$ 2.3		
Waist circumference (cm)	Normal	87 $\pm$ 6.5	0.958	0.341
	Fatty liver	86 $\pm$ 7.8		
Pulse rate (bpm)	Normal	82 $\pm$ 9.1	0.853	0.396
	Fatty liver	80 $\pm$ 9.1		
Systolic BP (mmHg)	Normal	128 $\pm$ 15	0.054	0.95
	Fatty liver	128 $\pm$ 22		
Diastolic BP (mmHg)	Normal	75 $\pm$ 9.3	0.172	0.864
	Fatty liver	76 $\pm$ 10		

\*Statistically significant. NAFLD=Nonalcoholic fatty liver disease, SD=Standard deviation, BMI=Body mass index, bpm=Beats per minute, BP=Blood pressure

The mean systolic blood pressure (in mm of Hg) in the control group was 128 ± 15 and the study group was 128 ± 22 and diastolic blood pressure (in mm of hg) in the control group was 75 ± 9.3 and study group was 76 ± 10. In terms of systolic and diastolic blood pressures in relation to NAFLD, there was no statistical significance noted.

Table 2 depicts the control group mean right CIMT (in mm) was 0.54 ± 0.109 whereas in the study group it was 0.62 ± 0.150 and mean left CIMT (in mm) of the control group was 0.53 ± 0.108 whereas in the study group it was 0.65 ± 0.205. The study and the control group were statistically comparable in terms of CIMT in relation to NAFLD with a significant *P* value of 0.05 and 0.01 respectively.

Table 3 depicts the control group mean total cholesterol, HDL, LDL and triglycerides (in mg/dl) was 109 ± 32, 23 ± 8.4, 77 ± 24 and 197 ± 152 and in study group, it was 139 ± 57, 31 ± 13, 98 ± 42 and 169 ± 72 respectively. The study and the control group were statistically comparable in terms of dyslipidemia i.e. higher total cholesterol, HDL, LDL in relation to NAFLD with a significant *P* value of 0.04, 0.01 and 0.01 respectively.

Table 4 depicts the prevalence of significant CIMT changes is higher in fatty liver subjects (13%) as compared to normal liver subjects (2%), which was statistically significant (*P* = 0.04). The prevalence of fatty liver is more in males (58%) as compared to females (42%).

**Table 2: Association between NAFLD and CIMT**

Variable	Group	Mean±SD	t	P
Average right CIMT (mm)	Normal	0.54±0.109	2.863	0.005*
	Fatty liver	0.62±0.150		
Average left CIMT (mm)	Normal	0.53±0.108	3.356	0.001*
	Fatty liver	0.65±0.205		

\*Statistically significant. NAFLD=Nonalcoholic fatty liver disease, CIMT=Carotid intima media thickness, SD=Standard deviation

**Table 3: Association between lipid profile of NAFLD and the control group**

Variable	Group	Mean±SD	t	P
Total cholesterol	Normal	109±32	2.968	0.004*
	Fatty liver	139±57		
HDL	Normal	23±8.4	3.467	0.001*
	Fatty liver	31±13		
LDL	Normal	77±24	3.467	0.001*
	Fatty liver	98±42		
Triglycerides	Normal	197±152	1.115	0.268
	Fatty liver	169±72		

\*Statistically significant. NAFLD=Nonalcoholic fatty liver disease, SD=Standard deviation, HDL=High density lipoprotein cholesterol, LDL=Low density lipoprotein cholesterol

**Table 4: Prevalence of significant CIMT in NAFLD**

CIMT	Fatty (n=45)	Normal (n=45)	Chi-square	P
<0.9 mm	39 (87%)	44 (98%)	3.873	0.049*
>0.9 mm	06 (13%)	01 (2%)		

\*Statistically significant. CIMT=Carotid intima media thickness, NAFLD=Nonalcoholic fatty liver disease

## Discussion

The present study includes nondiabetic outpatients and in-patients undergoing abdominal USG assessment for health screening. It was observed that people with fatty liver with or without other features of the metabolic syndrome had significant CIMT. These findings not only support the view of NAFLD as a hepatic manifestation of MetS but also suggest that the hepatic fat accumulation is atherogenic saying that NAFLD has associated carotid artery atherosclerosis and increased cardiovascular morbidity and the risk of strokes. Some studies show that NAFLD is an independent risk factor for cardiovascular disease.<sup>[13]</sup> Some hypothetical studies say that NAFLD is not only a marker of cardiovascular disease but may also be involved in its pathogenesis.<sup>[14]</sup>

In previous studies, the association between NAFLD and CIMT has currently had already been reported. Targhee *et al.*<sup>[3]</sup> found a significant increase in carotid IMT in NAFLD nonobese healthy volunteers whereas in another study, there is an association between NAFLD and carotid IMT concerned only the patients with MetS.<sup>[8]</sup>

The following table gives information about 1947 patients Data analysis showed the subject with NAFLD is 35% of pathological CIMT whereas patients without NAFLD, subclinical atherosclerosis was detected as 21.8%, *P* < 0.0001. Three of the four studies found a relationship between NAFLD and pathological CIMT [Table 5].

In our study, there is an elevated level of BMI, weight, dyslipidemia in NAFLD compared with controls [*P* = 0.01] [Table 1] which is similar to the study of Ji. Hoon Kang *et al.* as he says there is a significantly higher BMI, BP, and liver enzymes C-reactive protein.

In our study, we found NAFLD was independently associated with CIMT [Table 2]. Those with NAFLD had a higher prevalence of increased CIMT in comparison with controls. These results are supported by previous perspective studies reporting a strong association between NAFLD<sup>[18-21]</sup> and incidence of CID in both diabetic and nondiabetic individuals.<sup>[22-24]</sup>

In our study, we found the incidence of Metabolic Syndrome was higher in males when compared with females. The relation between NAFLD and MetS has not shown statistically significant.

Our study suggests that cardiovascular risk factors such as increased CIMT occur more frequently among NAFLD patients compared to healthy individuals.

Primary care physicians and specialists have a great role in the management of NAFLD patients with proper care can avoid CVD with the help of measurement of CIM thickness. According to the current scenario, the most common death in NAFLD is CVD<sup>23</sup>. Hence, this study finding would help the primary care

**Table 5: Studies included in meta-analysis, according to subclinical atherosclerosis**

International studies	Year (of publishing)	Number of patients	NAFLD evaluation	Carotid phenotype	OR score (95% CI)	Country
Kim <i>et al.</i> <sup>[8]</sup>	2009	1021	Ultrasound	CIMT	2.15 (1.56-2.96)	South Korea
Wang <i>et al.</i> <sup>[15]</sup>	2009	169	Ultrasound	CIMT	1.45 (0.67-3.15)	Taiwan
Kang <i>et al.</i> <sup>[16]</sup>	2012	663	Ultrasound	CIMT	1.98 (1.14-2.73)	South Korea
Agarwal <i>et al.</i> <sup>[17]</sup>	2011	179	Ultrasound	CIMT	2.48 (1.07-5.06)	India

NAFL=Nonalcoholic fatty liver, OR=Odds ratio, CI=Confidence interval, CIMT=Carotid intima media thickness

physicians to better understanding the role of measurement CIMT can avoid CVD deaths in NAFLD patients. Primary care Physicians and specialists should consider measurement CIMT should consider the best diagnostic method.<sup>[21]</sup>

## Conclusion

We can conclude that NAFLD has a significant association with higher cardiovascular risk in terms of CIMT, Dyslipidemia and Hypoalphalipidemia. We recommend screening of all NAFLD patients for the above risk factors and advise accordingly. Lifestyle changes include weight loss, dietary changes, reduction of sedentary habits and physical exercise are recommended in the NAFLD subjects with higher BMI and weight.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflict of interest

There is no conflict of interest.

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