Association between carotid intima media thickness and retinal arteriovenous ratio in non-alcoholic fatty liver disease

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KEYWORDS

Carotid intima media thickness, diabetes, dyslipidaemia, hypertension, NAFLD, retinal arteriovenous ratio

ABSTRACT:

Background: Nonalcoholic fatty liver disease (NAFLD) is the metabolic syndrome of liver with high risk in developing cardiovascular diseases. Retinal vessels and carotid artery provide early evidence of vascular ill health. In NAFLD by estimating CIMT (carotid intima media thickness) and retinal a-v (arterio venous) ratio the proneness to cardiovascular diseases can be assessed before its development. Objective of the study was to find out an association between CIMT and retinal a-v ratio in NAFLD

Methods: A cross sectional study was done at a tertiary centre in Karnataka. Sample size was 90. Patients with NAFLD of 18-60 yrs were included. After taking consent, clinical examination, liver function test, NAFLD grading, CIMT and retinal a-v ratio calculations were done.

Results: In this study 3/4th had Grade 1 NAFLD and remaining Grade II. Significant associations were found between NAFLD and diabetes, hypertension & their durations. 51.5% with diabetes, 77.8% with HTN and 61.3% with dyslipidemia had increased CIMT. Significant associations were found between a-v ratio and dyslipidemia, hypertension and its duration. Around 91.3% with NAFLD grade 2 had reduced AV ratio compared to 49.3% with NAFLD 1. Patients who had increased CIMT had narrow retinal AV ratio, which was true for both grades.

Conclusion: NAFLD had higher prevalence of increased CIMT and decreased retinal a-v ratio. High CIMT is always associated with small retinal a-v ratio in all grades. Decreased retinal a-v ratio is more prevalent, hence a better predictor of cardiovascular risk in NAFLD

INTRODUCTION

Faulty lifestyle and dietary habits predispose to hyperinsulinemia and metabolic syndrome resulting in premature death and cardiovascular complications[1] .Nonalcoholic fatty liver disease (NAFLD) is the metabolic syndrome in the liver with a higher risk to develop cardiovascular diseases apart from complications in the liver like nonalcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma[2].The global prevalence of NAFLD is

estimated to be 25.24%. It is highest in South America and the Middle East, while lowest in Africa. In India, it is around 9% to 32%[2].

Individuals with non-alcoholic fatty liver disease (NAFLD) are more prone to experience cardiovascular diseases. This condition is independent of the conventional risk factors of CVD and can be detected early enough to prevent it from developing.

When it comes to detecting vascular health issues, the presence of retinal vessels and the thickness of the carotid artery can be useful[3]. In people with non-alcoholic fatty liver disease, the level of intima media thickness (CIMT) is a good indicator of atherosclerosis. This condition is also known to increase the risk of developing cardiovascular disease.

A non-invasive tool that can be used to evaluate the presence of atherosclerosis is the Carotid Ultrasound. This procedure can be performed to check the level of intima media thickness (CIMT) in the artery. It can help to determine the appropriate treatment plan and minimize the risk of developing cardiovascular diseases.

According to epidemiological studies, having a CIMT of more than 1 cm at any age is known to increase the likelihood of suffering from cerebrovascular disease and myocardial infarction. However, in type 2 diabetes mellitus patients, having a lower CIMT of 0.07 cm is associated with a higher incidence of IHD[4].

Individuals with metabolic syndrome and retinal artery lesions are known to have an increased likelihood of experiencing various types of stroke and lacunar infarcts. In several studies, it has been shown that these conditions can be independently predicted. Inflammation and oxidative stress are known to be associated with the development of retinal artery lesions. The link between these conditions and the progression of NAFLD is believed to be due to the increased levels of subclinical inflammation.

In NAFLD patients by doing carotid doppler sonography and snap shot fundal picture analysis for a-v ratio (arterio venous ratio) we can assess the proneness of NAFLD patient to cardiovascular diseases well before their development hence the relevance of the study

MATERIAL AND METHODS

The present study was a cross-sectional study conducted over a period of 18 months at a tertiary hospital in Karnataka. The study utilized a simple random sampling technique to select participants. The sample size was calculated considering a prevalence rate of non-alcoholic fatty liver disease (NAFLD) at 31%, based on the findings of Basavaraju U et al. Using a confidence interval of 95% and a standard error of 10%, the formula applied for determining the sample size was Sample size = $(2 \times S.D \times p \times q) / d^2$, where S.D was 1.96 at a 95% confidence interval, p was 31%, q was 69%, and d was 10. The final sample size was determined to be 82, which was increased to 90 after factoring in a 10% dropout rate.

The study was hospital-based, and participants included NAFLD patients between the ages of 18 and 60 years. Each participant provided written informed consent before inclusion in the study. A comprehensive medical history was recorded, followed by a detailed clinical examination with a specific focus on soft hepatomegaly. Additional history regarding comorbidities, alcohol consumption, viral hepatitis, Wilson's disease, hemochromatosis, and autoimmune hepatitis was collected. Under aseptic conditions, blood samples were drawn to assess liver function tests. The study utilized a Philips IU22 ultrasound machine equipped with a curved array transducer (3-5 MHz) for abdominal ultrasound and a linear array transducer (7.5-12 MHz) for carotid ultrasonography. Furthermore, a detailed fundus examination was conducted using a 90D lens following pupillary dilation with Phenylephrine + Tropicamide 0.8% (Tropicacyl Plus eye drops). Digital fundus photography was performed using a ZEISS VISUCAM NM/FA 450 retinal camera, obtaining two retinal images per eye, one centered on the optic disc and another on the fovea. Quantitative parameters were measured using VAMPHIRE software.

The study population comprised 90 NAFLD patients recruited from the outpatient and inpatient departments of General Medicine. The inclusion criteria encompassed non-alcoholic patients or those without significant alcohol intake who presented with soft hepatomegaly on physical examination. Patients with a history of coronary artery disease (CAD) or cerebrovascular accidents (CVA) were excluded. Additionally, known cases of viral hepatitis, autoimmune hepatitis, hemochromatosis, and Wilson's disease were not included in the study. The study strictly adhered to the ethical guidelines outlined by the Indian Council of Medical Research (ICMR) for biomedical and health research on human participants. Data collected during the study were analyzed using SPSS version 23. Demographic information was summarized using standard deviations and percentages, and findings were frequently represented in pie and bar diagrams. Statistical comparisons were performed using the Fisher's exact test after confirming data normality. The results revealed significant associations between various demographic characteristics and the study outcomes, with statistical significance confirmed through the Chi-square test.

RESULTS

The mean age among the study participants was 49.2(11.1- standard deviation) years of age.

The mean(sd) carotid intima media thickness was 0.08(0.1). The mean retinal AV ratio was 0.5(0.08).

Table 1: Profile of subjects with NAFLD

		Count	%
Age	20-39 years	21	
	40-59 years	45	
	>60 years	24	
Gender	Male	52	58%
	Female	38	42%
CIMT	<0.07	57	63%
	≥0.07	33	37%
NAFLD	Grade 1	67	
	Grade 2	23	
Retinal AV ratio	AV ratio <2/3	36	40%
	AV ratio >2/3	54	60%

This study analyzed the profile and associations of subjects with Non-Alcoholic Fatty Liver Disease (NAFLD). **Table 1** presents the demographics and baseline characteristics of the participants. Among the 90 subjects, 58% were male and 42% female. The majority (50%) were between 40-59 years old. Carotid Intima-Media Thickness (CIMT) was <0.07 in 63% of participants, while 37% had CIMT ≥0.07. NAFLD Grade 1 was more prevalent (67 cases) than Grade 2 (23 cases). The retinal Arterio-Venous (AV) ratio was <2/3 in 40% and >2/3 in 60% of participants.

Table 2: Comparison Between NAFLD and Baseline Characteristics of Study Participants (N=90)

		NAFLD 1 (N=67)	**NAFLD 2 (N=23)**	**p value**
		n (%)	n (%)	
Diabetes	Present	20(60.6)	13(39.4)	**0.02*#**
	Absent	47(82.5)	10(17.5)	
Hypertension	Present	9(50)	9(50)	**0.01*#**
	Absent	58(80.6)	14(19.4)	
Dyslipidemia	Present	21(67.7)	10(32.3)	0.31
	Absent	46(78)	13(22)	
Duration of diabetes [Mean ± SD]		2.2(4.1)	5.8(6.8)	**0.003***
Duration of HTN [Mean ± SD]		1.1(2.7)	4.4(7.5)	**0.002***
BMI^ (>23kg/cm^2) [Mean ± SD]		26.7(3.9)	29.5(4.2)	**0.004***
Total bilirubin [Mean ± SD]		1.1(1.6)	1.3(2.4)	0.76
Direct bilirubin [Mean ± SD]		0.7(1.5)	0.7(2.2)	0.98
AST [Mean ± SD]		44.9(52.6)	50.4(51.6)	0.67
ALT [Mean ± SD]		32.4(29.7)	33.1(30.1)	0.93
Total protein [Mean ± SD]		6.6(0.8)	6.8(0.4)	0.34
Albumin [Mean ± SD]		3.6(0.7)	4.1(0.3)	**0.02***
Albumin Globulin ratio[Mean ± SD]		1.2(0.3)	1.4(0.2)	**0.01***

#Fishers exact test, Unpaired t test

Table 2 compares NAFLD grades with baseline characteristics. A significant association was found between NAFLD severity and diabetes (p=0.02), hypertension (p=0.01), and BMI (p=0.004), with higher BMI observed in NAFLD Grade 2. The duration of diabetes (p=0.003) and hypertension (p=0.002) was longer in those with severe NAFLD. Furthermore, albumin levels (p=0.02) and albumin-globulin ratio (p=0.01) were significantly higher in NAFLD Grade 2.

Table 3: Association Between CIMT and Baseline Characteristics of Study Participants (N=90)

		CIMT <0.07 (N=57)	CIMT ≥0.07 (N=33)	p value
		n(%)	n(%)	
Diabetes	Present	16(48.5)	17(51.5)	**0.04*#**
	Absent	41(71.9)	16(28.1)	
Hypertension	Present	14(22.2)	14(77.8)	**<0.001*#**
	Absent	53(73.6)	19(26.4)	
Dyslipidemia	Present	12(38.7)	19(61.3)	**0.001*#**
	Absent	45(76.3)	14(23.7)	
Duration of diabetes [Mean ± SD]		2.1(3.9)	5.1(6.4)	**0.006***
Duration of HTN [Mean ± SD]		0.5(1.5)	4.3(6.6)	**<0.001***
BMI^ (>23kg/cm^2) [Mean ± SD]		26.5(3.7)	29.2(4.3)	**0.002***
Total bilirubin [Mean ± SD]		1.2(1.8)	1.1(2.1)	0.64
Direct bilirubin [Mean ± SD]		0.8(1.7)	0.6(1.8)	0.53
AST [Mean ± SD]		50.9(57.9)	38.4(39.8)	0.28
ALT [Mean ± SD]		36.2(33.8)	26.4(19.4)	0.13
Total protein [Mean ± SD]		6.5(0.8)	6.9(0.6)	**0.003***
Albumin [Mean ± SD]		3.5(0.7)	4.1(0.4)	**<0.001***
Albumin Globulin ratio [Mean ± SD]		1.2(0.3)	1.3(0.2)	**0.08***

#Fishers exact test, Unpaired t test

Table 3 shows the association between CIMT and baseline characteristics. CIMT ≥0.07 was significantly associated with diabetes (p=0.04), hypertension (p<0.001), and dyslipidemia (p=0.001). Subjects with higher CIMT had a longer duration of diabetes (p=0.006) and hypertension (p<0.001), as well as a higher BMI (p=0.002). Additionally, albumin levels (p<0.001) and total protein (p=0.003) were significantly elevated in individuals with increased CIMT.

Table 4: Association Between Retinal Av Ratio and Baseline Characteristics of Study Participants (N=90)

		CIMT <0.07 (N=57)	CIMT ≥0.07 (N=33)	p value
		n (%)	n (%)	
Diabetes	Present	22(66.7)	11(33.3)	0.37#
	Absent	32(56.1)	25(43.9)	
Hypertension	Present	15(83.3)	3(16.7)	**0.03*#**
	Absent	39(54.2)	33(45.8)	
Dyslipidemia	Present	24(77.4)	7(22.6)	**0.02*#**
	Absent	30(50.9)	29(49.1)	
Duration of diabetes [Mean ± SD]		4.1(5.8)	1.9(3.6)	0.05*
Duration of HTN [Mean ± SD]		2.7(5.6)	0.6(2.2)	**0.03***
BMI^ (>23kg/cm^2) [Mean ± SD]		28.3(4.5)	26.2(3.1)	**0.02***
Total bilirubin [Mean ± SD]		1.1(1.8)	1.2(1.9)	0.77
Direct bilirubin [Mean ± SD]		0.5(1.4)	1.1(2.1)	0.15
AST [Mean ± SD]		41.1(40.6)	54.1(65.7)	0.25

ALT [Mean ± SD]	30.1(26.6)	36.4(33.7)	0.33
Total protein [Mean ± SD]	6.8(0.6)	6.4(0.8)	**0.006***
Albumin [Mean ± SD]	3.9(0.6)	3.5(0.7)	**0.003***
Albumin Globulin ratio [Mean ± SD]	1.3(0.3)	1.2(0.3)	**0.04***

#Fishers exact test, Unpaired t test

Table 4 examines the relationship between retinal AV ratio and baseline characteristics. Hypertension (p=0.03) and dyslipidemia (p=0.02) were significantly associated with AV ratio >2/3. Subjects with AV ratio >2/3 had a shorter duration of diabetes (p=0.05) and hypertension (p=0.03) but exhibited a lower total protein (p=0.006) and albumin (p=0.003) compared to those with an AV ratio ≤2/3.

Table 5: Association Between NAFLD And Carotid Intima-Media Thickness(N=90)

	CIT <0.07 (N=57)	CIT ≥0.07 (N=33)	P value
NAFLD 1	54 (80.6)	13 (19.4)	<0.001*
NAFLD 2	3 (13)	20 (87)	

Fishers exact test

Table 5 evaluates the relationship between NAFLD and CIMT. A significant proportion (80.6%) of NAFLD Grade 1 cases had CIMT <0.07, whereas NAFLD Grade 2 was predominantly associated with CIMT ≥0.07 (87%, p<0.001).

Table 6: Association Between NAFLD and Retinal Av Ratio (N=90)

	AV RATIO ≤2/3 (N=54)	AV RATIO >2/3 (N=36)	p value*
NAFLD 1	33(49.3)	34(50.7)	<0.001*
NAFLD 2	21(91.3)	2(8.7)	

Fishers exact test

Table 6 assesses the association between NAFLD and retinal AV ratio. NAFLD Grade 2 was significantly associated with an AV ratio ≤2/3 (91.3%, p<0.001), whereas NAFLD Grade 1 showed a more balanced distribution between AV ratio categories.

Table 7: Association Between Carotid Intima Media Thickness and Retinal AV Ratio With respect to NAFLD Grade

	NAFLD 1		p value*	**NAFLD 2**		P value*
	AV RATIO ≤2/3 (N=33)	AV RATIO >2/3 (N=34)		AV RATIO ≤2/3 (N=21)	AV RATIO >2/3 (N=2)	
CIMT <0.07 (N=57)	20 (37)	34 (63)	<0.001	1(33.3)	2(66.7)	0.012*
CIMT ≥0.07 (N=33)	13(100)	0		20(100)	0	

Fishers exact test

Finally, **Table 7** examines the relationship between CIMT, retinal AV ratio, and NAFLD severity. In NAFLD Grade 1, CIMT <0.07 was more common in those with AV ratio >2/3 (63%, p<0.001), whereas CIMT ≥0.07 was observed exclusively in individuals with AV ratio ≤2/3. Similarly, in NAFLD Grade 2, CIMT ≥0.07 was significantly associated with an AV ratio ≤2/3 (p=0.012).

These findings suggest a strong association between NAFLD severity, metabolic risk factors (diabetes, hypertension, and dyslipidemia), CIMT, and retinal AV ratio, indicating potential shared vascular pathology in NAFLD progression.

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent liver pathology, encompassing a spectrum that ranges from simple hepatic steatosis to hepatocellular carcinoma. The global rise in NAFLD incidence is largely attributed to the increasing prevalence of obesity and Type II Diabetes Mellitus. The pathophysiology of NAFLD involves oxidative stress markers, insulin resistance, and endothelial cell dysfunction. While cardiovascular manifestations are common in metabolic syndrome, NAFLD is increasingly recognized as its hepatic counterpart. Studies suggest that NAFLD is a significant risk factor for cardiovascular disease (CVD). Recent guidelines emphasize early intervention to prevent progression to end-stage liver disease.

Liver biopsy remains the gold standard for diagnosing NAFLD; however, its invasive nature limits its widespread use. Ultrasonography (USG), on the other hand, can detect hepatic steatosis when it comprises up to 33% of liver texture, making it a preferred diagnostic tool. USG's sensitivity increases when combined with liver enzyme assessments.

In this study, 90 NAFLD patients were recruited, with 67 (74%) classified as having grade 1 NAFLD. No significant differences were observed in age and gender among various NAFLD grades, contradicting findings from previous studies by Xu C et al. (7) and Bhamba K et al. (8), which reported a higher prevalence of NAFLD with increasing age. The discrepancy in findings is likely due to the predominance of grade 1 NAFLD cases in our cohort. Additionally, while men are generally at higher risk for NAFLD, no gender-specific associations were found in this study, possibly because our analysis focused solely on patients with NAFLD, whereas prior studies examined gender associations with NAFLD prevalence.

A significant proportion (more than three-fourths) of participants with grade 2 NAFLD exhibited increased carotid intima-media thickness (CIMT). This finding aligns with prior research, including studies by Lei Zhang and Kaifeng Guo et al. (9), which demonstrated a higher CIMT among NAFLD patients compared to healthy individuals. In our study, the mean CIMT was 0.08, with values of 0.07 (0.1) in NAFLD grade 1 and 0.13 (0.14) in grade 2. Compared to prior studies, our study reported lower CIMT values, likely due to the predominance of grade 1 NAFLD cases. Higher CIMT values correlated with more severe NAFLD, supporting findings from Bhatia et al., who reported CIMT regression upon NAFLD treatment (10). Similarly, Lankarani et al. (11) demonstrated an increased prevalence of CIMT in NAFLD patients compared to controls, reinforcing the hypothesis that NAFLD can serve as an independent predictor of carotid arteriosclerosis.

The prevalence of high CIMT was more pronounced among NAFLD patients with comorbidities such as diabetes, hypertension, and dyslipidemia. These results are consistent with findings by Sayed et al. (12), who reported a higher prevalence of increased CIMT among NAFLD patients with metabolic risk factors.

Additionally, this study found that more than three-fourths of NAFLD patients with hypertension and dyslipidemia had a reduced Retinal Arteriovenous (AV) ratio, indicating arteriole narrowing relative to venules. This finding corroborates prior studies by Wong et al. (13), Kawasaki et al. (14), and Josef et al. (15). Notably, all participants with abnormal CIMT also exhibited a narrow retinal AV ratio, and this association was statistically significant for both NAFLD grades 1 and 2. To our knowledge, this association has not been previously documented in the literature.

Mortality in NAFLD patients is primarily driven by cardiovascular complications rather than liver-related dysfunction. Given this, patients with incidental NAFLD diagnoses should undergo cardiovascular risk assessments. The prognosis of NAFLD patients is more influenced by cardiovascular risk factors than by liver dysfunction itself. The correlation between CIMT and the retinal AV ratio underscores the microvascular pathophysiology underlying NAFLD rather than macrovascular changes.

CONCLUSION

The severity of NAFLD is strongly linked to obesity and other lifestyle-related conditions such as diabetes, systemic hypertension, dyslipidemia, and the duration of these conditions, in addition to lower serum albumin levels and albumin-globulin ratios. No significant association between age or gender and NAFLD severity was observed. The condition is characterized by a higher prevalence of increased carotid intima-media thickness and decreased retinal arteriovenous ratio, with an elevated CIMT consistently correlating with a reduced retinal AV ratio across all NAFLD grades. Furthermore, a decreased retinal AV ratio appears more common than increased CIMT, suggesting that it may serve as a superior predictor of cardiovascular risk in NAFLD patients.

LIMITATION OF THE STUDY

The study's generalizability is limited due to the absence of a control group. Additionally, the use of ultrasonography for NAFLD grading introduces the possibility of inter- or intra-observer variations, leading to information bias. Furthermore, the hospital-based selection of NAFLD cases may not accurately represent the broader general population.

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Conflicts of Interest: Nil

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