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Association Between Increased Carotid Intima Media Thickness and Nonalcoholic Fatty Liver Disease

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Abstract

Objective: To determine the association between increased carotid intima media thickness and nonalcoholic fatty liver disease.

Methodology: This case-control study was carried out in the outpatient department of diagnostic radiology at PAF Hospital Islamabad. It included all patients presenting to the department of radiology. Ultrasound examination was done to detect the presence of NAFLD. CIMT was measured in both the patient groups with and without NAFLD.

Results: The mean age of all subjects was 49.38 ± 0.59 years, while the mean age of cases and controls was 50.04 ± 0.8 and 48.72 ± 0.87. In cases, there were 83(53.55%) male and 72(46.45%) female cases while in controls there were 75(48.39%) male and 80(51.61%) female cases. Among cases and controls there were 29(18.7%) and 16(10.3%) subjects who had raised CIMT, with a significant association, p-value < 0.05, and OR = 2.00 (1.037-3.854).

Conclusion: In our study, CIMT was significantly higher in NAFLD group as compared to control groups. This study will help primary care physicians understand the role of measuring CIMT in preventing future CVD complications and deaths in NAFLD patients.

Keywords: Body mass Index (BMI), Carotid Intima Media Thickness (CIMT), Cardiovascular (CV), Non-Alcoholic Fatty Liver Disease (NAFLD), Ultrasound (US)

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Introduction

Fatty liver, which is a common clinical and histological finding, can be broadly divided into non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD). Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by a varied range of histological abnormalities and clinical outcomes. Among the general population, its prevalence ranges between 14% and 31%.[1] The disease spectrum ranges from simple steatosis to non-alcoholic steato-hepatitis (NASH) to cirrhosis.[2] The most useful and accepted technique to detect fatty liver is ultrasonography, which has a sensitivity and specificity of 84.8% and 93.6%, respectively, for the detection of moderate-severe fatty liver as compared to histology.[3] Carotid intima-media thickness (CIMT) is a known marker for early atherosclerosis, and its progression. CIMT of large peripheral arteries, especially carotid, can be assessed by B-mode ultrasound (US) in a relatively simple way.[4] In several clinical trials, the CIMT measurement is used to determine the harmful effect of various risk factors. Treating the risk factors thus decreases the progression of the IMT, eventually leading to reduction in cardiovascular risks and events.[5, 6]

The existence of an association between NAFLD and high cardiovascular risk has been pointed out in several recent studies. In NHANES III, the authors established that the presence of NAFLD was associated with an increased risk of myocardial infarction, stroke, or both.[7-8] Similarly, in another study, the frequency of increased

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CIMT was 28.9 % in patients with NAFLD as compared to 16.9 % in patients without NAFLD.[9] The rationale of our study was to determine the association between increased carotid intima media thickness and NAFLD on ultrasound examination. This study would help to identify the overt population with CIMT as its early detection and later management may be helpful in limiting the inherent complications of atherosclerosis.

Material and Method

A case control study was conducted in the Radiology Department of PAF Hospital, Islamabad, after approval from the Institutional Review Board (IRB) from 01-07-2020 to 31-01-2021. A total of 310 patients, including 155 in each case and control group, were enrolled in the study using the WHO sample size calculator[25] (level of significance 5% and power of the test 80%) Patients of both genders aged 30 to 65 years were included using consecutive sampling technique in cases (with NAFLD) and controls (without NAFLD). Patients with medical co-morbidities like diabetes mellitus (BSR > 200 mg/dl), hypertension (BP> 160/90 mm Hg) and known dyslipidemias diagnosed on the basis on history were excluded from the study. Patients with history of chronic liver disease (AST and ALT > 40 IU/ml), patients with acute or chronic kidney disease (Serum Creatinine > 1.5 mg/dl), pregnancy or any malignancy were also be excluded from the study. Similarly, cigarette smokers, alcoholics and those taking any medications, like oral contraceptives, were not included in the study. After taking informed consent and detailed history including previous medical history and clinical findings, the patient`s weight was measured in normal clothing to the nearest half kilogram. Similarly, height was measured to the nearest half centimeter. Body mass index (BMI) was calculated. Ultrasound of the liver was done after required fasting. Each subject was examined in both supine and left lateral positions during quiet inspiration after holding breath. Nonalcoholic fatty liver disease (NAFLD) was defined as the presence of ultra-sonographic pattern of parenchymal brightness of the liver (hepatic steatosis) using conventional B mode ultrasonography after the exclusion of secondary causes of fat accumulation in the liver. Hepatic Steatosis was graded as grade 1 to 3.

Grade 1 or higher was labelled as NAFLD.[10] Carotid Intima Media Thickness (CIMT) was measured by high resolution real-time B mode ultrasonography with a 7.5-MHz linear transducer on the Aloka 3500 Doppler unit in supine position. It was defined as the distance between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (media adventitia interface) of the anterior and posterior arterial walls.[11] The normal value of CIMT was 0.4–0.9 mm.[12]

Data was entered into SPSS (version 21.0) and analyzed. Frequencies and percentages were calculated for the binary variable (gender) and measurement of central tendency (including the mean with SD) was calculated for continuous variables including age, BMI, CIMT and carotid plaque measurement. Odds ratio (OR) for carotid plaque and CIMT in each group was determined. Data was stratified for age, gender and BMI. Post stratification Odds ratio (OR) was calculated. P-value ≤ 0.05 was taken as significant.

Results

The mean age of all subjects was 49.38 ± 0.59 years while the mean age of cases and controls was 50.04 ± 0.8 and 48.72 ± 0.87. In cases, there were 83(53.55%) male and 72(46.45%) female cases, while in controls there were 75(48.39%) male and 80(51.61%) female cases. In cases the mean height, weight, and BMI was 160.60 ± 0.48 cm, 69.50 ± 0.65 and 26.94 ± 0.22 and in controls was 161.42 ± 0.46 cm, 63.39 ± 0.64 kg and 24.32 ± 0.22. The mean CIMT in cases and controls was 0.80 ± 0.02 and 0.67 ± 0.01. Table I

Among cases and controls, there were 29(18.7%) and 16(10.3%) subjects who had raised CIMT, with a

Table I: Descriptive statistics of demographic variables among both study groups.

	Study group		p-value
	Case	Control	
Age (years)	50.04+0.8	48.72+0.87	0.005
Male	75 (48.39%)	83 (53.55%)	0.102
Female	80 (51.61%)	72 (46.45%)	
Height (cm)	160.60+0.48	161.42+42	0.023
Weight	69.50+0.65	63.39+0.64	0.041
BMI	26.94+0.22	24.32+0.2	0.032
CIMT	0.80+0.02	0.67+0.01	0.003

Table II: Comparison of Increased CIMT in both study groups.

		Study group		Total	p-value	Odd Ratio (lower-upper)
		Case	Control			
Increased CIMT	Yes	29(18.7%)	16(10.3%)	45(14.5%)	0.036	2.00 (1.037-3.854)
	No	126(81.3%)	139(89.7%)	265(85.5%)		
Total		155(100%)	155(100%)	310(100%)		

Table III: Comparison of Increased CIMT in both study groups with respect to age groups (years)						
Age groups	**Increased CIMT**	**Study group**			**p-value**	**Odd Ratio (lower-upper)**
		Case	**Control**	Total		
***≤ 50* (years)**	Yes	6(8.5%)	0(0%)	6	0.008*	2.23 (1.86-2.67)
	No	65(91.5%)	82(100%)	147		
	Total	72	81	153		
***> 50* (years)**	Yes	23(27.4%)	16(21.3%)	39	0.376	1.16 (0.84-1.59)
	No	61(72.6%)	59(78.7%)	120		
	Total	84	75	159		

Table IV: Comparison of Increased CIMT in both study groups with respect to BMI (obese/non-obese)						
BMI	**Increased CIMT**	**Study group**			**p-value**	**OR (lower-upper)**
		Case	**Control**	**Total**		
Obese >25	Yes	21(20.6%)	14(26.4%)	35	0.410	0.722 (0.332-1.570)
	No	81(79.4%)	39(73.6%)	120		
	Total	102	53	155		
Non-obese ≤ 25	Yes	8(15.1%)	2(2%)	10	0.022*	8.889 (1.815-43.542)
	No	45(84.9%)	100(98%)	145		
	Total	53	102	155		

significant association, p-value < 0.05, and OR = 2.00 (1.037-3.854). Table II

Data was stratified with respect to age, gender and BMI, significant association was found in ≤ 50 years of age groups and non-obese (BMI ≤ 25) subjects, i.e., p-value = 0.008 and 2.23(1.86-2.67) and p-value = 0.022 and 8.889(1.81-43.54) respectively. Table III and Table IV

Discussion

This study was conducted to determine the association between increased carotid intima media thickness and NAFLD on ultrasound examination. It was observed that patients with fatty liver with or without other features of the metabolic syndrome had significant CIMT. These findings support the view of NAFLD as a hepatic manifestation of metabolic syndrome. It was pointed out by some studies that NAFLD is an independent risk factor for cardiovascular disease.[13] NAFLD was also hypothesized to be involved in the pathogenesis of cardiovascular diseases.[14] A possible atherogenic mechanism linking NAFLD and carotid IMT could be represented by increased oxidative stress and subclinical inflammation, which are thought to be causal factors in the progression from simple steatosis to more advanced forms of NAFLD.[15-17] A number of studies have been performed to evaluate CIMT in these patients, but different findings have been found. Targhee et al.[18] found a significant increase in carotid IMT in NAFLD subjects whereas in another study, there is an association between NAFLD and carotid IMT concerned only the patients with Metabolic Syndrome.[19]

In a meta-analysis, Sookoian et al. described the association between CIMT and non- alcoholic fatty liver by summarizing 7 studies, including 1427 patients and 2070 healthy individuals. And it was concluded that there existed a strong correlation between NAFLD and atherosclerosis (increased CIMT).[20] In another study, CIMT values in 125 patients with NAFLD and 250 healthy individuals was evaluated by Fracanzani et al. In this study, the mean CIMT was significantly higher among NAFLD patients.[21] Our findings are consistent with the findings of the previous studies, which found that the median CIMT in patients with fatty liver was significantly higher than in patients with normal liver.Previous prospective studies[22-25] have found a strong association between NAFLD and the incidence of CID in both diabetic and nondiabetic people.

This study has some limitations. Firstly, because our study was cross-sectional, the causative nature of the associations cannot be established. To sort out the time sequence of events, further prospective studies will be required. Another of the limitations of this study was that, among the control subjects, the exclusion of NAFLD was based on medical history, blood testing, and ultrasound imaging but was not confirmed by liver biopsy. Liver biopsy remains the gold standard for identifying steatosis, however, being an invasive procedure, it is not feasible in a population-level study. On the other hand, liver ultrasound is the most widely used non-invasive technique to detect fatty infiltration of the liver, with good sensitivity and specificity for detecting moderate and severe steatosis. Thus, our results are probable conservative estimates, depicting the relationship between NAFLD and carotid IMT. The presence of NAFLD on ultrasound examination should alert clinicians to the coexistence of multiple underlying CVD risk factors necessitating evaluation and treatment as early as possible to reduce the risk of advancing liver disease.

Conclusion

CIMT was significantly higher in the NAFLD group than in the control group in our study. Upon stratification, a significant association with raised CIMT was found in young and non-obese subjects. Our research will help primary care physicians better understand the importance of CIMT measurement. The early detection of raised

CIMT will help in its management, preventing the inherent complications of CV risks and deaths.

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