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Research Article

Association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness

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ABSTRACT

OBJECTIVES: To determine the association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.

SUBJECT AND METHODS: This case control study was conducted at Department of Medicine, DG Khan Hospital, DG Khan from April 2018 to October 2018 over the period of 6 months. Total 218 patients (109 cases and 109 controls) were selected for this study. All the subjects were undergone abdominal and carotid ultrasound in order to assess nonalcoholic fatty liver disease and carotid IMT measurement. Association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.

RESULTS: Total 170 patients were selected for this study. Age range was 30-45 years with mean age of 37.69 ± 4.792 years. Mean age of cases group was 37.87 ± 4.897 years and mean age of control group was 37.51 ± 4.695 years. In cases, raised CIMT was observed in 80 (59.26%) patients while in control was observed in 54 (40%) patients. Significantly (P = 0.002) higher number of patients found with raised CIMT in cases group as compared to control group.

CONCLUSION: This study concluded that that the frequency of raised carotid intima-media thickness is higher in patients with non-alcoholic fatty liver disease and shows the positive association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.

KEY WORDS: Non-alcoholic fatty liver disease; atherosclerosis; carotid artery; carotid intima-media thickness; meta-analysis

INTRODUCTION:

Non-alcoholic fatty liver disease (NAFLD) is one of the causes of fatty liver, occurring when fat is deposited (steatosis) in the liver due to causes other than excessive alcohol use.[1] Nonalcoholic fatty liver disease (NAFLD) is a term for a broad continuum of liver illnesses extending from the rather benign steatosis to the severe cryptogenic cirrhosis.[2-4] Steatosis, or fatty infiltration of the liver, can progress to nonalcoholic steatohepatitis (NASH). Steatohepatitis, in turn, can progress to permanent liver damage in the form of cirrhosis or malignancy; 3% to 5% of patients with NAFLD

progress to NASH, and 15% of those with NASH develop cirrhosis.[5] Approximately 20-30% of adults in general population of western countries have NAFLD and its prevalence increases to 70-90% among individuals who are obese or have diabetes.[6] The community prevalence of NAFLD in South Asia and South East Asia ranges from 5-30%. Recently a hospital based study in Pakistan have shown a prevalence of NAFLD approximately 14%, however, there is no community based study from Pakistan available.[7]

Ultrasonographic measurement of carotid intima-media thickness (CIMT) is a non-invasive method for demonstrating subclinical atherosclerosis.[1] CIMT is directly proportional to the presence of atherosclerosis in the coronary vessels and the severity of cardiovascular disease.[8] Intima-media thickness is defined as a double-line sign visualized on both walls of the CCAs in a longitudinal echographic image. It is formed by two parallel lines, which represent the leading edges of 2 anatomic boundaries: the lumen-Intima and media-adventitia interfaces. The combined thicknesses of the intimal and medial layers of the arterial wall constitute the Intima-media complex.[9-10] Imaging of arteries to identify and quantify the presence of subclinical vascular disease has been suggested to further refine CVD risk assessment.[11-12]

In recent years, case-control studies have shown a relationship between NAFLD and the presence of early manifestations of atherosclerosis indicated by CIMT measurement.[1] In one study, CIMT was increased in 52.5% of patients with NAFLD compared to 35.8% of controls.[8] However, some degree of variability about the mean carotid IMT values has been observed among all published reports that results in a difficult evaluation of magnitude of the observation. [8] A possible relationship between NAFLD and carotid lesions might have important clinical consequences, considering the frequent incidental finding of hepatic steatosis in subjects undergoing abdominal ultrasound for any reason. In these subjects an ultrasound assessment of carotid arteries might be advisable. [8]

NAFLD is the most common cause of abnormal liver function tests in adults. There is no data available locally regarding the role of carotid atherosclerosis in NAFLD patients. Furthermore, study of this kind was required for establishing if atherosclerosis affects vascular anatomy and physiology in NAFLD patients, independent of other risk factors. Through this study, we would be able to find the relation between nonalcoholic fatty liver disease and carotid intima-media thickness as the main predictor of cardiovascular disease, by comparing CIMT of sonographically diagnosed NAFLD patients with control group having normal liver echogenicity on ultrasound.

OPERATIONAL DEFINITION

1. **Nonalcoholic Fatty Liver Disease (NAFLD):**
   NAFLD will be defined by the presence of at least 2 of 3 abnormal findings on abdominal ultrasound: diffusely increased echogenicity (bright) liver with liver echogenicity greater than kidney or spleen, vascular blurring and deep attenuation of ultrasound signal, after exclusion of significant alcohol intake (more than 140g weekly in men and 70g weekly in women).
2. **Carotid intima-media thickness (CIMT):**
   Maximal IMT will be measured bilaterally at posterior wall of common carotid artery, 2cm before the bifurcation as the distance between first (lumen-intima interface) and second (media-adventitia interface) echogenic lines of anterior and posterior arterial walls. Three measurements will be taken at each site and average measurement used. The cut-off value for CIMT will be set at 0.8 mm (CIMT $\geq$ 0.8mm will be considered raised).

Body Mass Index (BMI):

It is calculated as "weight in kilogram divided by height in square **meter".**

MATERIAL AND METHODS

This case control study was conducted at Department of Medicine, DG Khan Hospital, DG Khan from April 2018 to October 2018 over the period of 6 months. Total 218 patients (109 cases and 109 controls) were selected for this study.

Inclusion Criteria:

For cases:

- Patients age range from 30 to 45 years.
- Both male or female patients.
- Patients having nonalcoholic fatty liver disease on ultrasound
- Patients with HbsAg –ve, AntiHCV –ve

For controls:

- Age range from : 30-45 years
- Both male or female
- Having normal liver on ultrasound
- HbsAg –ve, AntiHCV –ve

Exclusion Criteria:

- Patients with diabetes mellitus (having fasting serum glucose ≥ 126mg/dl or on treatment for diabetes)
- Patients with hypertension (having BP ≥ 140/90 mmHg or on treatment for hypertension)
- Patients with history of ischemic heart disease.
- Patients with history of chronic liver disease.
- Alcohol consumption (more than 140g weekly in men and 70g weekly in women)
- Cigarette smoking (smoking ≥ 20 cigarettes/day for last 6 months)
- History of pregnancy in previous year or history of delivery within past six months
- Positive viral markers.

DATA COLLECTION PROCEDURE

Total 109 patients fulfilling the inclusion criteria, presenting medical OPD of DG Khan Hospital were included in the study. Total 109 controls, preferably from relatives of these patients, having normal liver echogenicity on abdominal ultrasound, were matched for age, gender and body mass index. Approval of the ethical committee of the institution was sought. Written informed consent of the patients was taken.

Weight and height of all the subjects was noted by using weighting machine and measuring tape to calculate the BMI.

All the subjects were undergone abdominal and carotid ultrasound in order to assess nonalcoholic fatty liver disease and carotid IMT measurement. Hospital had beard the cost of these scans. All investigations were performed by two consultant sonologists (one performing abdominal ultrasound and the other doing carotid ultrasound) at radiology department, using standardized ultrasound equipment and blinded to each other regarding respective ultrasound measurements and unaware of patients' clinical data. Nonalcoholic fatty liver disease was defined according to operational definition.

For carotid ultrasound, patients were examined in a supine position, neck extended and chin facing contralateral side. Maximum CIMT was measured bilaterally at posterior wall of common carotid artery, 2cm before the bifurcation. Thickness of intima media was measured vertical to arterial wall. Three readings will be recorded at each site and average measurement was used. The cut-off value for CIMT will be set at 0.8 mm (CIMT ≥ 0.8mm was considered raised). All the findings along with demographic profile of the subjects was entered in pre-designed proforma.

DATA ANALYSIS PROCEDURE

All the collected data was entered and analyzed using SPSS-18. Mean and SD was calculated for age and BMI. Frequencies and precentages were calculated for gender, raised CIMT and NAFLD. Chi-square test was used to determine the association between NAFLD and raised CIMT. P-value ≤0.05 was considered as significant and odds ratio was also calculated.

Effect modifiers like age, gender and BMI was controlled by stratification. Post stratification chi-square test was also applied and odds ratio was also calculated.

RESULTS

Total 170 patients were selected for this study. Age range was 30-45 years with mean age of 37.69 ± 4.792 years. Mean age of cases group was 37.87 ± 4.897 years and mean age of control group was 37.51 ± 4.695 years. Table 1

In cases, raised CIMT was observed in 80 (59.26%) patients while in control was observed in 54 (40%) patients. Significantly (P = 0.002) higher number of patients found with raised CIMT in cases group as compared to control group and OR was 2.18. (Table 2)

Patients were divided into three age groups i.e. age group 30-35 years, age group 36-40 years and age group 41-45 years. In age group 30-35 years, there were 48 (35.56%) cases and 57 (42.22%) were control and raised CIMT was noted in 29 (60.42%) patients and 21 (36.84%) patients respectively in cases and control. Raised CIMT rate was significantly higher in cases as compared to control with p value 0.019 and OR 2.62. In age group 36-40 years, out of 37 (27.41%) cases, raised CIMT was noted in 22 (59.46%) patients. Out 33 (24.44%) controls, raised CIMT was noted in 16 (48.48%) but the difference was not statistically significant with p value 0.472 and OR 1.56. Total 50 (37.04%) cases and 45 (33.33%) were belonged to age group 41-45 years and raised CIMT was noted in 29 (58%) and 17 (37.78%) respectively in cases and controls but the difference was significant with p value 0.065 and OR 2.28. (Table 3)

Out of 87 (64.44%) male cases, raised CIMT was observed in 56 (64.37%) patients. Out of 87 (64.44%) male controls, raised CIMT was seen in 38 (43.68%) patients. Significantly (P = 0.010) higher proportion of raised CIMT was noted in male cases as compared to male controls and OR was 2.32. In 48(35.56%) female cases, raised CIMT was found in 24 (50%) patients. In 48 (35.56%) female controls, raised CIMT was seen in 16 (33.33%) patients. But the difference was not significant with p value 0.147 and OR was 2.00. (Table 4). There were obese and non-obese were equal in cases and control group. In obese group, total 32 (50.79%) cases and 31 (49.21%) controls were found with raised CIMT and the difference was not significant with p value 1.00 and OR was 1.07. Total 48 (66.67%) non-obese cases and 23 (31.94%) non-obese controls were found with raised CIMT and the difference was statistically significant with p value 0.000 and OR was 4.26. (Table 5)

Table 1: Mean and SD of cases and controls

Group	Mean	N	Std. Deviation
Case	37.87	135	4.897
Control	37.51	135	4.695
Total	37.69	270	4.792

Table 2: Comparison of frequency of raised CIMT between cases and control

Group	Raised CIMT		Total	P value OR
	Yes (%)	No (%)		
Case	80 (59.26)	55 (40.74)	135	0.002 2.18
Control	54 (40)	81(60)	135	

Table 3: Comparison of frequency of raised CIMT between cases and control for age

Group	Raised CIMT		Total (%)	P value OR
	Yes (%)	No (%)		
Age group 30-35				
Case	29 (60.42)	19 (39.58)	48 (35.56)	0.019

Control	21 (36.84)	36 (63.16)	57 (42.22)	2.62
Age group 36-40				
Case	22 (59.46)	15 (40.54)	37 (27.41)	0.472 1.56
Control	16 (48.48)	17 (51.52)	33 (24.44)	
Age group 41-45				
Case	29 (58)	21 (42)	50 (37.04)	0.065 2.28
Control	17 (37.78)	28 (62.22)	45 (33.33)	

Table 4: Comparison of frequency of raised CIMT between cases and control for gender

Group	Raised CIMT		Total	P value OR
	Yes (%)	No (%)		
Male				
Case	56 (64.37)	31 (35.63)	87 (64.44)	0.010 2.32
Control	38 (43.68)	49 (56.32)	87 (64.44)	
Female				
Case	24 (50)	24 (50)	48(35.56)	0.147 2.00
Control	16 (33.33)	32 (66.67)	48 (35.56)	

Table 5: Comparison of frequency of raised CIMT between cases and control for obesity

Group	Raised CIMT		Total	P value OR
	Yes (%)	No (%)		
Obese				
Case	32 (50.79)	31 (49.21)	63 (46.67)	1.00 1.07
Control	31 (49.21)	32 (50.79)	63 (46.67)	
Non-obese				
Case	48 (66.67)	24 (33.33)	72 (53.33)	0.000 4.26
Control	23 (31.94)	49 (68.06)	72 (53.33)	

DISCUSSION

Objective of present study was to assess association between non-alcoholic fatty liver disease and raised carotid intima-media thickness. Total 170 patients were selected for this study. Age range was 30-45 years with mean age of 37.69 ± 4.792 years. Mean age of cases group was 37.87 ± 4.897 years and mean age of control group was 37.51 ± 4.695 years. In one study by Guleria A et al[13], mean age of the patients was 37 years which is comparable with our study. In another study by Zayed BE et al[14] mean age of the patients was 39 which is also comparable with our study. Some other studies reported mean age of the patient >50 years which higher than our study. [15-16]

In cases, raised CIMT was observed in 80 (59.26%) patients while in control was observed in 54 (40%) patients. Significantly (P = 0.002) higher number of patients found with raised CIMT in cases group as compared to control group. A case control study have shown a relationship between NAFLD and the presence of early manifestations of atherosclerosis indicated by CIMT measurement. [1]

In one case control study, raised CIMT was found in 52.5% cases and in 35.8% controls. [17]

Out of 87 (64.44%) male cases, raised CIMT was observed in 56 (64.37%) patients. Out of 87 (64.44%) male controls, raised CIMT was seen in 38 (43.68%) patients. Significantly (P = 0.010) higher proportion of raised CIMT was noted in male cases as compared to male controls. In 48(35.56%) female cases, raised CIMT was found in 24 (50%) patients. In 48 (35.56%) female controls, raised CIMT was seen in 16 (33.33%) patients. But the difference was not significant with p value 0.147. Higher proportion of male cases was found as compared to female patients. This male predominance is also found in many previous studies.[13,16]

Some studies reported a link between NAFLD and increased carotid intima-media thickness (IMT). In one case control study by Fracanzaniet al[18] independent risk predictors of increased intima-media thickness were the presence of hepatic steatosis (odds ratio (OR) = 6.9), age (OR 6.0), and increased systolic blood pressure (OR 2.3).

Algarem NH et al[19] also found a significant increase in carotid IMT in patients with NAFLD (0.73±0.1mm) than normal control persons (0.50±0.08mm) which was highly significant (*p* value <0.001). Similarly, Guleria A et al[13] had found the mean CIMT of both the right and left side significantly higher (0.70±0.11 mm vs. 0.61±0.08 mm) (p=0.007) and FMD% significantly lower in patients with NAFLD (9.79±3.81%) in comparison to controls (17.02±3.39%) (p<0.0001). In a recent study from India, Thakur ML et al[19] examined the association of subclinical atherosclerosis and endothelial dysfunction in patients with NAFLD. They recruited 40 nondiabetic subjects with NAFLD and 40 apparently healthy controls without NAFLD with similar age, gender and BMI and measured the anthropometric parameters, oral GTT, fasting and 2-hour insulin, lipid profile, C-reactive protein, CIMT and brachial artery FMD. They showed that patients with NAFLD had a higher average and maximum CIMT (0.6±0.12 and 0.684±0.16 mm, respectively, vs. 0.489±0.1 and 0.523±0.1 mm, respectively; p<0.05), and higher prevalence of atherosclerotic plaques (20% vs. 5%,p<0.05) than controls.

CONCLUSION

This studyconcluded that that the frequency of raised carotid intima-media thickness is higher in patients with non-alcoholic fatty liver disease and shows the positive association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.

REFERENCES:

1. Mohammadi A, Bazazi A, Ghasemi-rad M. Evaluation of atherosclerotic findings in patients with nonalcoholic fatty liver disease. Int J Gen Med. 2011;4:717-22.
2. Bayard M, Holt J, Boroughs E. Nonalcoholic fatty liver disease. Am Fam Physician. 2006;73(11):1961–1968.
3. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–1231.
4. Clark JM, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis JAMA. 2003;289:3000–3004.
5. Law K, Brunt EM. Nonalcoholic fatty liver disease. Clin Liver Dis. 2010;14:591–604.
6. Lankarani KB, Mahmoodi M, Lofti M, Zamiri N, Heydari ST, Ghaffarpasand F, et al. Common carotid intima-media thickness in patients with nonalcoholic fatty liver disease: a population-based case-control study. Korean J Gastroenterol. 2013;62:344-51
7. Parkash O, Hamid S. Are we ready for a new epidemic of under recognized liver disease in south asia especially in Pakistan? Nonalcoholic fatty liver disease. J Pak Med Assoc. 2013;63(1):95-99.
8. Kang JH, Cho KI, Kim SM, Lee JY, Kim JJ, Goo JJ, et al. Relationship between nonalcoholic fatty liver disease and carotid artery atherosclerosis beyond metabolic

disorders in non-diabetic patients. J Cardiovasc Ultrasound. 2012;20(3):126-33.
9. Sharma P, Lohani B, Chataut SP. Ultrasonographic evaluation of carotid intima-media thickness in hypertensive and normotensive individuals. Nepal Med Coll J. 2009;11(2):133-5.
10. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER et al. Use of carotid ultrasound to identify sub clinical vascular disease and evaluate cardiovascular disease risk. J Am SocEchocardiogr. 2008;21(2):98-100.
11. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention conference V: beyond secondary prevention, identifying the high-risk patient for primary prevention, noninvasive tests of atherosclerotic burden, writing group III. Circulation. 2000;101:16-22.
12. Taylor AJ, Merz CN, Udelson JE. 34th Bethesda conference: executive summary–can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? J Am CollCardiol. 2003;41:1860-2.
13. Guleria A, Duseja A, Kalra N, Das A, Dhiman R, Chawla Y, et al. Patients with non-alcoholic fatty liver disease (NAFLD) have an increased risk of atherosclerosis and cardiovascular disease. Tropical Gastroenterol. 2013;34(2):74–82.
14. Zayed BE, El-Din SS, El-Mooatism E. Association between Non Alcoholic Fatty Liver Disease and Early Carotid Atherosclerosis. Med J Cairo Univ. 2012;80(1):143-49.
15. Algarem NH, Amin MA, Fawzi MM, Aiad AH. Carotid Intima Media Thickness (CIMT) in Nondiabetic Patients with non Alcoholic Fatty Liver Disease (NAFLD). Med J Cairo Univ. 2011;79(1):491-96.
16. Kim D, Choi SY, Park EH, Lee W, Kang JH, Kim W, et al. Nonalcoholic Fatty Liver Disease Is Associated With Coronary Artery Calcification. Hepatol. 2012;56(2):605-13.
17. Kang JH, Cho KI, Kim SM, Lee JY, Kim JJ, Goo JJ, et al. Relationship between nonalcoholic fatty liver disease and carotid artery atherosclerosis beyond metabolic disorders in non-diabetic patients. J Cardiovasc Ultrasound. 2012;20(3):126-33.
18. Fracanzani AL, Burdick L, Raselli S. Carotid artery intima-media thickness in nonalcoholic fatty liver disease. Am J Med. 2008;121(1):72–8.
19. Thakur ML, Sharma S, Kumar A, Bhatt SP, Luthra K, Guleria R, et al. Nonalcoholic fatty liver disease is associated with subclinical atherosclerosis independent of obesity and metabolic syndrome in Asian Indians. Atherosclerosis. 2012;223:507–11.