

# TO DETERMINE FREQUENCY OF INCIDENTAL FINDING OF CAROTID INTIMA MEDIA THICKNESS > 1MM IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND COMPARE SEVERITY OF HEPATIC STEATOSIS WITH INCREASED CAROTID INTIMA MEDIA THICKNESS > 1MM

Ayesha Hanif,<sup>1</sup> Atique Ur Rehman Slehra,<sup>1</sup> Mobeen Shafique,<sup>1</sup> Muhammad Usman Khan,<sup>2</sup> Muhammad Omer Amir,<sup>1</sup> Umar Kaleem,<sup>3</sup> Awon Raza Shah Bukhari,<sup>4</sup> Mehwish Razzaq<sup>5</sup>

<sup>1</sup> Department of Radiology, Armed Forces institute of Radiology and Imaging, Rawalpindi, Pakistan.

<sup>2</sup> Department of Radiology, Bahria University Medical and Dental College, Rawalpindi, Pakistan.

<sup>3</sup> Department of Radiology, Rawalpindi Medical University, Rawalpindi, Pakistan.

<sup>4</sup> Department of Radiology, National Institute of Heart Diseases, AFIC, Rawalpindi, Pakistan.

<sup>5</sup> Department of Radiology, Army Medical College Rawalpindi, Pakistan.

PJR April - June 2020; 30(2): 104-109

## ABSTRACT

**INTRODUCTION:** Ultrasonography has become widespread diagnostic tool and presently it is the preferable method for diagnosing patients with nonalcoholic fatty liver disease as it is noninvasive, in expensive and widely available. **OBJECTIVES:** To determine frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease and compare severity of hepatic steatosis with increased carotid intima media thickness >1mm. **MATERIALS & METHODS:** This descriptive, cross-sectional study was conducted from 26<sup>th</sup> December 2017 to 25<sup>th</sup> June 2018 in the department of radiology, Armed Forces Institute of Radiology and Imaging, military hospital, Rawalpindi. A total of 96 patients having fatty liver on ultrasound scan, 18 to 70 years of age were included. Patients with history of alcohol ingestion, renal disease or stigmata of chronic liver disease and previous diagnosis of stroke or transient ischemic attack were excluded. After taking informed consent and relevant history, patient was guided to take ultrasound scan of the abdomen and duplex ultrasound scan of carotids in order to assess the hepatic steatosis and carotid intima media thickness measurement. **RESULTS:** Mean age was 50.80 – 9.64 years. Out of the 96 patients, 48 (50.0%) were male and 48 (50.0%) were females with male to female ratio of 1:1. Majority of patients were with grade I i.e. 44 (45.83%). Frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease was found in 55 (57.29%) patients. **CONCLUSION:** This study concluded that frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease is very high. **Keywords:** Non-Alcoholic Fatty liver disease, common carotid artery, intima media thickness.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common condition seen in patients with

obesity, type 2 diabetes, atherogenic dyslipidemia and arterial hypertension. The leading cause of death

**Correspondence :** Dr. Ayesha Hanif  
Department of Radiology,  
Armed Forces institute of Radiology and Imaging,  
Rawalpindi, Pakistan.  
Email: momeramir@gmail.com

Submitted 10 May 2020, Accepted 30 May 2020

in patients with NAFLD is cardiovascular mortality, which is not surprising given the high prevalence of the above mentioned cardio metabolic risk factors. However, a large body of data indicates that the fatty and inflamed liver expresses several pro-inflammatory and procoagulant factors, as well as genes involved in accelerated atherogenesis.<sup>1</sup> This raises the possibility that the link between NAFLD and cardiovascular mortality might not simply be mediated by shared, underlying, common risk factors but rather that NAFLD independently contributes to increasing this risk. While an increased prevalence of cardiovascular disease in NAFLD is largely accepted, existing data also show an increased incidence.<sup>2</sup> This suggests that steatosis predates clinical cardiovascular disease, and that it may trigger or accelerate its occurrence.

Patients with NAFLD die primarily of cardiovascular disease, and the extent to which the liver disease rather than associated co-morbidities is responsible for excess cardiovascular death is still under debate. On the other hand, it should also be remembered that NAFLD is independently associated with an increased risk of diabetes mellitus (T2DM) (two fold increase) and cardiovascular disease (CVD) (1.4- to 2-fold increase).<sup>3</sup> Furthermore, CVD is the most common cause of death among NAFLD patients.<sup>4</sup> Although the association of cardiovascular mortality with NAFLD has been shown, the nature and strength of this association remain controversial.<sup>5,6</sup> Adams et al<sup>7</sup> have shown that CVD accounts for about 25% of deaths in NAFLD patients versus 13% death from liver disease.

Ultrasonography has become widespread diagnostic tool and presently it is the preferable method for diagnosing patients with nonalcoholic fatty liver disease as it is noninvasive, in expensive and widely available.<sup>8</sup> It may yield information beyond the specific question asked. One example of great impact is chance finding of carotid atherosclerosis seen in duplex Ultrasonography. In this context, a strong correlation between hepatic steatosis diagnosed by ultrasound and increased intima media thickness has been documented.<sup>9</sup> Mean intima media thickness is found to be raised significantly in patients with nonalcoholic fatty liver disease and has shown positive correlation between ultrasonographic hepatic steatosis grade and intima media thickness as well.<sup>10,11</sup>

In a study conducted in 2012 it was noticed that

carotid intima thickness >1mm was found in 52.55 % of NAFLD patients as compared to 35.8% in patients not having NAFLD.<sup>12</sup> The incidence of nonalcoholic fatty liver disease is increasing in our population (due to a rise in risk factors like hypertension, diabetes and obesity). The purpose of this study was that evaluating the frequency of incidental finding of increased intima media thickness in patients with nonalcoholic fatty liver disease using duplex ultrasonography will add to its potential to predict development of complications of fatty liver disease in primarily healthy patients in outpatient departments, which in turn will provide us with the burden of the disease in local population and will generate local data for further research purpose in this field. It will also guide clinicians in routine use of duplex ultrasonography on asymptomatic patients thus helping them plan proper management as well.

## Objectives

To determine frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease and compare severity of hepatic steatosis with increased carotid intima media thickness >1mm.

## Materials & Methods

This descriptive, cross-sectional study was conducted from 26<sup>th</sup> December 2017 to 25<sup>th</sup> June 2018 at Department of radiology Armed Forces Institute of Radiology and Imaging, military hospital, Rawalpindi. After approval from ethical review committee, a total of 96 having fatty liver on ultrasound scan, 18 to 70 years were included. Patients with history of alcohol ingestion, renal disease or stigmata of CLD and previous diag-nosis of stroke or Transient ischemic attack were excluded. After taking informed consent and relevant history patient was guided to take ultrasound scan of the abdomen and duplex ultrasound scan of carotids in order to assess the hepatic steatosis and carotid intima media thickness measurement. According to sample size, patients admitted in other departments of Military Hospital Rawalpindi and were referred by clinician to the radiology department (Armed Forces

Institute of Radiology & Imaging) fulfilling the inclusion/exclusion criteria were included in the study. After taking informed consent and relevant history patient was guided to take ultrasound scan of the abdomen and duplex ultrasound scan of carotids in order to assess the hepatic steatosis and carotid intima media thickness measurement.

Thickness of common, internal and external carotids were seen and mean reading was taken. All the data was entered in specially designed Performa. Confounders were excluded by history and physical examination. This all data was recorded on a specially designed Performa which included the patient's bio-data and study variables. All the data was entered and analyzed on SPSS (Statistical package for social sciences) Version 21.0. Descriptive statistics were calculated. For qualitative variables i.e. gender, carotid intima media thickness >1mm and grade of hepatic steatosis frequency and percentages were calculated. For quantitative variables, i.e. age mean and standard deviation were calculated.

Stratification of age, gender and grade of hepatic steatosis was done. Post stratification chi square test was applied. P-value of  $\leq 0.05$  was considered significant.

## Results

Age range in this study was from 18 to 70 years with mean age of 50.80 – 9.64 years. Majority of the patients 82 (85.42%) were between 41 to 70 years of age.

Out of the 96 patients, 48 (50.0%) were male and 48 (50.0%) were females with male to female ratio of 1:1. Distribution of patients according to grade of hepatic steatosis showed that majority of patients were with grade I i.e. 44 (45.83%).

Frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease was found in 55 (57.29%) patients, whereas there was no carotid intima media thickness >1mm in 41 (42.71%) patients.

When stratification of incidental finding of carotid intima media thickness >1mm was done on age groups, it was found that there was no significant difference between different age groups while the stratification of incidental finding of carotid intima media thickness >1mm with respect to gender is also

done which also showed no significant difference between male and female. (Tab. 1) has shown the stratification of incidental finding of carotid intima media thickness >1mm with respect to grade of hepatic steatosis. Although it showed that percentage increases with grade but the difference was not statistically significant.

Grade of hepatic steatosis	Incidental finding of carotid intima media thickness >1mm		p-value
	Yes	No	
I	22 (50.0%)	22 (50.0%)	0.412
II	23 (63.89%)	13 (36.11%)	
III	10 (62.50%)	06 (37.50%)	

**Table 1:** Stratification of incidental finding of carotid intima media thickness >1mm with respect to grade of hepatic steatosis.

## Discussion

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver function tests in adults and almost one third of the population in the Korean has hepatic steatosis.<sup>13,14</sup> NAFLD is commonly associated with visceral obesity, dyslipidemia, insulin resistance, and type 2 diabetes and may represent another component of the metabolic syndrome (MetS),<sup>15-17</sup> a condition associated with a high cardiovascular risk and, in particular, an increased prevalence of carotid lesions.<sup>18</sup> It is important to determine whether NAFLD is an independent predictor of cardiovascular morbidity and mortality and several studies have suggested that there is an association between NAFLD and cardiovascular disease.<sup>19-24</sup> Noninvasively detected increased carotid intima media thickness (IMT) is generally accepted as an early indicator of generalized atherosclerosis and has been related to cardiovascular risk factors, and cardiovascular disease including incidence of myocardial infarction and stroke.<sup>25</sup>

Some case-controlled and cross-sectional studies<sup>18-20</sup> showed a relationship between NAFLD and carotid IMT.<sup>21</sup> Indeed, it is hypothesized that NAFLD is not merely a marker of cardiovascular disease but may also be involved in its pathogenesis.<sup>22</sup> A possible relationship between NAFLD and carotid lesions might have important practical consequences, considering the frequent incidental finding of hepatic

steatosis in subjects undergoing abdominal ultrasound (US) for any reason. In these subjects, an US assessment of carotid arteries might also be advisable. However, some degree of variability about the mean carotid IMT values has been observed among all the published reports that result in a difficult evaluation of the magnitude of the observation. For instance, among the different studies, mean carotid IMT values in NAFLD patients range from 0.64 – 0.10 mm to 1.24 – 0.13 mm.<sup>21</sup>

Age range in this study was from 18 to 70 years with mean age of 50.80 – 9.64 years. Majority of the patients 82 (85.42%) were between 41 to 70 years of age. Out of the 96 patients, 48 (50.0%) were male and 48 (50.0%) were females with male to female ratio of 1:1. Frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease was found in 55 (57.29%) patients, whereas there was no carotid intima media thickness >1mm in 41 (42.71%) patients. Since this was a hospital based study so there were few limitation which included non inclusion of diabetic and hypertensive patients in the inclusion criteria. This study focused more on fatty liver with intima media thickness without particularly considering diabetic and hypertensive patients. Another study can be conducted in this regard to see the degree of fatty infiltration of liver in these patients. In a study conducted in 2012 it was noticed that NAFLD patients had a significantly increased mean carotid IMT (0.79 – 0.18 vs. 0.73 – 0.13 mm;  $p < 0.001$ ) than those without the condition. The prevalence of increased IMT, defined as  $IMT \geq 1$  mm, and carotid plaque were 52.5% and 34.1% in the patients with NAFLD vs. 35.8% and 18.8% in the patients without this condition ( $p < 0.001$ ).<sup>12</sup>

In another study, two hundred and ninety individuals were found to have fatty change on abdominal ultrasonography, and were labeled NAFLD. Compared to normal individuals, NAFLD patients had significantly higher prevalence of increased CIMT (OR, 1.66;  $p < 0.001$ ). Those with hypertension (HTN), diabetes mellitus (DM), higher waist circumference (WC) and older ages had significantly higher prevalence of thick CIMT. Through adjusting the effects of different variables, the author indicated that NAFLD could be an independent risk factor for thick common carotid intima-media (OR, 1.90; 95% CI, 1.17-3.09;  $p = 0.009$ ).

It was also shown that age could be another independent risk factor for thick CIMT.

In a local study, 54 patients with NAFLD (33 males, 21 females) and 50 controls (28 males, 22 females) were assessed. The mean patient age in NAFLD group was 47.5 years while it 46.7 years in the control group. The mean CIMT in NAFLD group in our study was 0.80 – 0.12 while it was 0.58 – 0.15 in the control group ( $p = 0.0001$ ). These values clearly show a strong relationship between hepatic steatosis and increased thickness of carotid intima media. In another study, the prevalence rate of hepatic steatosis was 29.9%. Among subjects aged  $> \text{or} = 45$  years, an association between hepatic steatosis and IMT of the carotid arteries was found in bivariate analysis, but not after adjustment for atherosclerotic risk factors. Individuals with fatty liver had more often carotid plaques than persons without fatty liver (plaque prevalence rate 76.8% vs 66.6%;  $P < 0.001$ ). This association persisted after adjustment for confounding factors and was predominantly present in subjects with no to mild alcohol consumption.

Recently, it was seen in a large observational study that patients with biopsy-proven NAFLD had a significant increase in carotid IMT in comparison with age, sex, and BMI-matched healthy controls; carotid IMT was significantly higher for individuals with NASH than for those with simple steatosis, and, more importantly, the histological severity of NAFLD (i.e., steatosis, necroinflammation and fibrosis) predicted carotid IMT independently of classical risk factors, HOMA-estimated insulin resistance, and components of the Mets. Previously, O Leary et al. reported that a carotid IMT value = 0.86mm carries a low risk of CVD, whereas an IMT value = 1.10 carries a high risk of CVD. It is worth emphasizing that the mean carotid IMT values we found among healthy controls and NAFLD patients were of 0.82 and 1.14 mm, respectively.

## Conclusion

This study concluded that frequency of incidental finding of carotid intima media thickness >1mm in patients with non-alcoholic fatty liver disease is very high. So, we recommend that duplex Ultrasonography should be done routinely to predict development of complications of fatty liver disease in primarily healthy patients in outpatient departments.

**Conflict of Interest:** Declared none by authors.

## References

1. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; **61**: 1547-54.
2. Pais R, Giral P, Khan JF, Rosenbaum D, Housset C, Poynard T, Ratzu V . Fatty liver is an independent predictor of early carotid atherosclerosis. LIDO Study Group . *J Hepatol*. 2016; **65**: 95-102.
3. Musso G, Gambino R, Cassader M. Need for a three-focused approach to nonalcoholic fatty liver disease. *Hepatology* 2004; **53(5)**: 1773; author reply 1774.
4. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin. Gastroenterol. Hepatol*. 2012; **10(6)**: 646-50.
5. Rafiq N, Bai C, Fang Y et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin. Gastroenterol. Hepatol*. 2009; **7(2)**: 234-8.
6. Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. *Gut* 2010; **59(10)**: 1410-5.
7. Adams LA, Lymp JF, St Sauver J et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129(1)**: 113-21.
8. AlShalan R, Aljiffry M, Al-Busafi S, Metrakos P, Hassanain M. Nonalcoholic Fatty Liver Disease: Noninvasive Methods of Diagnosing Hepatic Steatosis. *Saudi J Gastroenterol* . 2015; **21(2)**: 64-70.
9. Guth S, Windler E, Leise U, Bamberger CM. Ultrasound Diagnosis of Hepatic Steatosis as a Surrogate for Atherosclerosis. *Ultrasound Int Open*. 2016; **2(1)**: E27-E31.
10. Metin kukukazman, Naim Ata. Evaluation of early Atherosclerosis markers in patients with non alcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. 2013;
11. Emel, Torn, Sinem Ayden, Selim Gokce, Ikler Tolga Ozgen, Tugrul Donmez. Carotid intima-media thickness and flow-mediated dilation in obese children with non-alcoholic fatty liver disease *Turk J Gastroenterol*. 2014; **25**: 92
12. Kang JH, Cho KI, Kim SM. 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.
13. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, Sung IK, Sohn CI, Keum DK, Kim BI. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *J Gastroenterol Hepatol*. 2006; **21(1-1)**: 138-43.
14. Choi SY, Kim D, Kang JH, Park MJ, Kim YS, Lim SH, Kim CH, Lee HS. [Nonalcoholic fatty liver disease as a risk factor of cardiovascular disease: relation of non-alcoholic fatty liver disease to carotid atherosclerosis] *Korean J Hepatol*. 2008; **14**: 77-88.
15. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002; **346**: 1221-31.
16. Adams LA, Angulo P. Recent concepts in non-alcoholic fatty liver disease. *Diabet Med*. 2005; **22**: 1129-33.
17. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis*. 2004; **8**: 521-33.
18. Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic

- hepatic steatosis to early carotid atherosclerosis in healthy men: role of visceral fat accumulation. *Diabetes Care*. 2004; **27**: 2498-500.
19. Aygun C, Kocaman O, Sahin T, Uraz S, Eminler AT, Celebi A, Senturk O, Hulagu S. Evaluation of metabolic syndrome frequency and carotid artery intima-media thickness as risk factors for atherosclerosis in patients with nonalcoholic fatty liver disease. *Dig Dis Sci*. 2008; **53**: 1352-7.
  20. Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care*. 2007; **30**: 2119-21.
  21. Musso G, Gambino R, Bo S, Uberti B, Biroli G, Pagano G, Cassader M. Should nonalcoholic fatty liver disease be included in the definition of metabolic syndrome? A cross-sectional comparison with Adult Treatment Panel III criteria in nonobese nondiabetic subjects. *Diabetes Care*. 2008; **31**: 562-8.
  22. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001; **50**: 1844-50.
  23. Kim HC, Kim DJ, Huh KB. Association between nonalcoholic fatty liver disease and carotid intima-media thickness according to the presence of metabolic syndrome. *Atherosclerosis*. 2009; **204**: 521-5.
  24. Jeong JW. Intima-media thickness of the carotid artery: non-invasive marker of atherosclerosis. *J Korean Soc Echocardiogr*. 2002; **10**: 8-12.
  25. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999; **340**: 14-22.