ORIGINAL ARTICLE

Carotid Artery Stenosis in Non-Alcoholic Fatty Liver Disease: A Tertiary Care Hospital Experience

UMAR FAROOQ DAR[1], WASEEM IQBAL[2], NASIB ULLAH SHAH[3], MUHAMMAD MAJID[4], MUHAMMAD AAMIR USMAN[5], NAVEED IQBAL[6]
[1]Department of Infectious Diseases, Institute of Public Health Lahore, [2]Department of Medicine Unit II, Lahore General Hospital Lahore, [3]Department of Medicine Sandeman Provincial Hospital Bolan Medical College Quetta, [4-6]Department of Medicine, Jinnah Hospital Lahore,
For correspondence: Dr. Umar Farooq Dar, e-mail: umardar84@gmail.com

ABSTRACT
Objective: To determine the frequency of carotid artery stenosis in non-alcoholic fatty liver disease (NAFLD).
Subjects and Methods: This descriptive cross sectional study was carried out on 175 patients with ultrasonic diagnosis of NAFLD. All patients were screened by carotid Doppler scan and in case of a peak systolic velocity greater than 100cm/sec, patient was labeled as having carotid artery stenosis.
Results: The mean age of patients of NAFLD was 42.4±9.3 years. Frequency of carotid artery stenosis (CAS) came out about 12.6% among all patients. Hypercholesterolemia was found significantly associated with CAS in NAFLD patients while age, sex and BMI more than 30 kg/m^2 was not significantly different in patients with and without carotid artery stenosis.
Conclusion: The frequency of CAS is quite high (12.6%) so we should screen all patients of NAFLD for CAS.

Keywords: Carotid artery stenosis, Nonalcoholic fatty liver disease, Atherosclerosis

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) is a clinic-pathological syndrome closely associated with obesity, diabetes, dyslipidemias and atherosclerosis.[1-4] Metabolic syndrome, the collective name used for identification of risk of atherosclerosis is almost always present in patients with NAFLD. Hepatic component of metabolic syndrome is fatty liver. Most important component of metabolic syndrome is insulin resistance which refers to a constellation of features such as overweight/obesity, glucose intolerance, dyslipidaemia and hypertension, all of which are important risk factors for cardiovascular disease (CVD).[2,5,6] According to World Gastroenterology Organization Global Guidelines the prevalence of NAFLD in general population of Pakistan is 18%.[7]

Patients with NAFLD are at a high risk of carotid atherosclerosis regardless of metabolic syndrome and classical cardiovascular risk factors.[8-10] Carotid artery stenosis is a major risk factor for stroke and for the symptomatic cerebrovascular disease.[9] Approximately 20-30% of all ischemic strokes are caused by carotid occlusive disease.[9]Measurement of carotid intima-media thickness (IMT) was used in different studies assessing CAS in NAFLD patients and they showed an increase in frequency of CAS about 13% by carotid intima-media thickness in NAFLD.[10] Asymptomatic CAS prevalence is low in general population about 0.2% for male and 0% in female below age 50 years.[6] Carotid Doppler scan, a simpler and lesser technical procedure can also be used for screening for CAS.

This study was conducted in order to determine that how frequently carotid artery stenosis is prevalent in non-alcoholic fatty liver disease determined by Doppler scan of carotid arteries in Pakistani population, which differs from developed nations in lifestyle and dietary habits.[3] Racial differences are significant in prevalence of NAFLD.[11] Same is the case in carotid artery stenosis as IMT of carotid artery ranged from 0.64±0.10 to 1.24±0.13 for different western countries.[10]

As there is no local study available, ethnic differences can not be verified. Despite several previous studies[11] demonstrated the association between NAFLD and carotid intima-media thickness and/or carotid plaque, there is no systematic screening of carotid atherosclerosis in patients with fatty liver disease.[10] By implementing screening of all NAFLD patients for CAS and vice

versa we can prevent future morbidity by simple non-invasive procedure of carotid Doppler scan. Further local guidelines may be developed in light of result of current study.[11,13]

SUBJECTS AND METHODS

This descriptive cross sectional survey was carried out in Jinnah Hospital and Lahore General Hospital, Lahore from 1st May 2013 to 30th December 2013. One hundred and seventy five patients of either sex with diagnosis of non-alcoholic fatty liver disease were included in study using non probability consecutive sampling. Informed consent was taken from patients. Non-alcoholic fatty liver disease was defined as fatty infiltration on ultrasonography,[12] not resulting from excessive alcohol consumption (>20 grams/day), drugs e.g. isoniazid, rifampicin, amiodrone, methotrexate , toxins e.g. afla toxin, CCL_4, infectious diseases like hepatitis B, hepatitis C, EBV, pyogenic liver abscess, or any other identifiable exogenous causes like iron and copper intoxication determined by history, laboratory investigation and ultrasonography. Demographic data including age (in years) and sex (male or female) was recorded on a structured proforma. All the patients who were labeled as NAFLD were investigated with Doppler ultrasonography. Doppler study was performed using Toshiba Nemio 20 with a linear transducer of 7.5MHz. The patients were labeled with CAS (yes/no) if peak systolic velocity comes out greater than 100cm/sec as per operational definition. Obesity (body mass index >30) and hypercholesterolemia (serum cholesterol levels >200 mg/dl) was treated as effect modifiers as they have non-proportionate effect on both NAFLD and CAS.

All the information was collected on a specially designed proforma (attached). All the collected data was entered into SPSS version 17 and analyzed. The qualitative data like demographics (male or female), obesity, and hypercholesterolemia, presence of NAFLD (yes or no) and presence of CAS (yes or no) was presented as frequency and percentage. Quantitative data like age (in years) was presented as means and standard deviations. Data was stratified and cross-tabulated to determine the effect of obesity and cholesterol level on CAS. To determine the post stratification association, chi square or Fischer exact test was applied. A p value <0.05 was considered as significant.

RESULTS

In the study one hundred and seventy five patients were included with mean age 42.45±9.2 years ranging from 28 to 60 years. Seventy four patients (52.6%) were male with 103 patients with age more than 40 years. Carotid artery stenosis was detected in 22 patients (12.6%). 28 patients (16%) had BMI more than 30 kg/m^2 and 37 patients (21.2%) had hypercholesterolemia. When gender was cross tabulated against frequency of carotid artery stenosis, results were non-significant (p value=0.796) while using chi square test.

Table 1: Descriptive characteristics of patients with non alcoholic fatty liver disease (n=175)

Variable	No.	%
Gender		
Male	92	52.6
Female	83	47.6
CAS (Present)	22	12.6
Hypercholesterolemia (Present)	37	21.2
BMI >30kg/m^2 (Present)	28	16.0
Age (years)		
28 - 40	72	41.1
41 - 60	103	58.9
Mean±SD	42.4±4.9	

Table 2: Cross tabulation of different risk factors with non alcoholic fatty liver disease (n=175)

Variable	No. of patients with CAS	P value
Gender		
Male	11	0.796
Female	11	
Hypercholesterolemia		
Present	14	<0.001
Absent	8	
Body mass index >30kg/m^2		
Yes	6	0.123
No	16	
Age (years)		
<40	7	0.324
>40	15	

To determine the effect of age on frequency of Carotid artery stenosis, data was stratified and grouped. 41% patients were below 40 years while rest were above 40 years. When age groups were cross tabulated against frequency of Carotid artery stenosis, results were non-significant (p value=0.324) while using chi square test similar to gender effect. Patients with BMI more and less than 30 kg/m^2 were cross tabulated against frequency of CAS, results were similarly non-

significant (p value=0.123) showing no effect of obesity on frequency of carotid artery stenosis at this sample size. But hypercholesterolemia has shown significant association with Carotid artery stenosis showing increased duration in hypercholesterolemic group [P<0.001] (Tables 1-2).

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized clinic-pathological entity that may progress to end-stage liver disease and is similar to chronic hepatitis.[1-5] The symptoms range from simple fatigue to severe myalgia. It is proposed to be an additive to accelerating atherosclerosis. The pathological picture resembles alcohol-induced liver injury, but occurs in patients who deny alcohol abuse.[4] Non-alcoholic fatty liver disease comprises a wide spectrum of liver damage ranging from simple, uncomplicated steatosis to steato-hepatitis to advanced fibrosis and cirrhosis.[2,4,6]

Carotid artery stenosis is a risk factor for stroke and cerebrovascular events and patient become prone to increased disabilities as age progress.[8-11] ultrasonic screening may find out patients at risk of developing thrombo-emboli. Ultrasonic detection of Carotid artery stenosis is possible by simple non-invasive duplex scan. Early intervention may save many chronic disabilities. Non-alcoholic fatty liver disease has been shown to be atherogenic in different studies previously but there is ethnic differences found both in prevalence of NAFLD and carotid artery stenosis.[3,7,11,13]

Frequency of carotid artery stenosis came out 12.6% which is quite high. As previously shown that there is more prevalence in female patients but in our study there is almost equal distribution in both sexes. Obesity is known risk factor for CAS in NAFLD but at current sample size the difference was non-significant. Hypercholesterolemia was found associated with increased frequency of carotid artery stenosis.

The results shown in this study imply that every patient coming with NAFLD should be screened for carotid artery stenosis by non-invasive duplex scan of carotid artery. We may intervene early and prevent many debilitating cerebrovascular diseases. Because our study was cross-sectional, the causative nature of the associations cannot be established. Prospective studies will be required to sort out the time sequence of events.

CONCLUSION

It was concluded that the frequency of carotid artery stenosis in non-alcoholic fatty liver disease is. quite high. Carotid Doppler scan is a non-invasive procedure which can help screen many patients and prevent stroke and early onset dementia. Limitations of this study includes small sample size, not taking into account the life style factors, proxy measurement of fatty liver by ultrasonography as gold standard is biopsy.

REFERENCES

1. Bhala N, Angulo P, van der Poorten D. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: An international collaborative study. Hepatology 2011;54:1208.
2. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. Semin Liver Dis 2001;21:3-9.
3. Musso G, Gambino R, De Michieli F. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 2003;37:909-16.
4. Nonomura A, Mizukami Y, Unoura M. Clinicopathologic study of alcohol-like liver disease in non-alcoholics; non-alcoholic steatohepatitis and fibrosis. Gastroenterol Jpn 1992;27:521-27.
5. Choi SY, Kim D, Kang JH, Park MJ, Kim YS, Lim SH, et al. 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.
6. Matteoni CA, Younossi ZM, Gramlich T. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413-22.
7. Poanta LI, Albu A, Fodor D. Association between fatty liver disease and carotid atherosclerosis in patients with uncomplicated type 2 diabetes mellitus. Med Ultrasound 2011;13(3):215-9.
8. Shaikh NA, Bhatty S, Irfan M, Khatri G, Vaswani AS. Jakhrani N. Frequency, characteristics and risk factors of Carotid Artery Stenosis in ischaemic stroke patients at Civil Hospital Karachi. J Pak Med Assoc 2010;60: 8-12.
9. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol 2008;49(4): 600-5.
10. Chitturi S, Farrell GC, Hashimoto E. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. J Gastroenterol Hepatol 2007;22:778-4.
11. Perseghin G. The role of non-alcoholic fatty liver disease in cardiovascular disease. Dig Dis 2010; 28(1):210-3.
12. Williams CD, Stengel J, Asike MI. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124-30.
13. Amarapurkar DN, Hashimoto E, Lesmana LA. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol 2007;22:788-99.