Research Article

Evaluation of carotid intima-medial thickness as a marker of atherosclerosis in patients with non-alcoholic fatty liver disease

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Abstract

Aim

To assess the association of non alcoholic fatty liver disease (NAFLD) with carotid intima-medial thickness to predict the risk of atherosclerosis.

Background

Non alcoholic fatty liver disease is the most common cause of abnormal liver function tests in hepatology practice. It's incidence is increasing worldwide. Nonalcoholic fatty liver disease, as it is a part of spectrum of metabolic syndrome, is associated with increased risk of cardiovascular disease. The intima-medial thickness of carotid artery can be measured, which is a marker of atherosclerosis, thereby indicating the risk of cardiovascular disease. In this study, we attempt to evaluate the relation between non alcoholic fatty liver disease and carotid intima medial thickness.

Patients and methods

In the current observational study, 100 subjects were evaluated, who were diagnosed as fatty liver on sonographic examination and on a brief interview, revealed history of either total abstinence from alcohol or consumed <20g/day. High resolution Philips HD 7 ultrasound machine was employed to calculate the intima-medial thickness of right and left carotid arteries.

Results

NAFLD patients had relatively greater carotid IMT value, than the normal value. Notably, carotid IMT measurement was strongly associated with degree of fatty liver, among NAFLD patients (P 0.001 for all). The relative risk of atherosclerosis increased with intima-medial thickness(P<0.001).

Conclusion

Based on our findings, there is a significant association between the presence of NAFLD and atherogenesis. Detection of carotid intima-medial thickness on sonography can be used as a reliable tool to predict the existence of a cardiovascular risk in NAFLD patients.

Keywords : Nonalcoholic fatty liver disease, Atherosclerosis, carotid intima-medial thickness, Ultrasonography.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the causes of fatty liver, occurring when fat is deposited in the hepatocytes due to causes other than excessive alcohol intake . NAFLD is often considered as a part of metabolic syndrome characterized by diabetes, or pre-diabetes (insulin resistance), overweight or obese, elevated blood lipids such as cholesterol and triglycerides, as well as high blood pressure. NAFLD is usually suspected in an overweight or obese person who is found to have elevated levels of liver enzymes._The diagnosis of NAFLD is confirmed by imaging studies, mostly by trans-abdominal ultrasound. NAFLD spectrum includes clinical, laboratory and pathological conditions ranging from mild steatosis to liver diseases such as non- alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and eventually hepatocellular carcinoma [1–3].

Carotid intima-media thickness (CIMT) is a standard method for evaluation of early general atherosclerosis (4). Many studies provide evidence of a strong association between NAFLD and subclinical manifestations of atherosclerosis like increased intima-media thickness, endothelial dysfunction, arterial stiffness, impaired left ventricular function, and coronary calcification. Measurement of carotid intima-media thickness by

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ultrasound is a reliable and widely accepted screening approach to detect the cardiovascular risk. So, in this study, we attempt to evaluate the association of presence and severity of NAFLD with carotid IMT and to assess the role of NAFLD as an independent marker of subclinical atherosclerosis. [5].

Study design and methods

The study was conducted on patients who were referred to department of Radio-diagnosis in Maharajah's Institute of Medical Sciences for trans-abdominal Ultrasonography. A total of 100 patients were studied over a period of 2 years who were apparently diagnosed as NAFLD on Ultrasonography. In all the patients diagnosed with NAFLD, screening for carotid intima-medial thickness was done in both right and left carotid arteries.

Inclusion criteria

Patients who were diagnosed with ultrasonic findings of hyperechoic liver and with negative history of alcohol abuse i.e, either total abstainers or who consumed <20g of alcohol per day[1].

Patients between 30 to 60 years age were considered for the study.

Exclusion criteria

Patients who had clinical evidence of chronic liver or renal disease, cardiovascular events, or recent history of acute illness or consumption of alcohol >20g/day and patients of less than 30 years age were excluded in this study.

Method of evaluating fatty liver -

Patients were evaluated by Philips HD 7 XE ultrasound machine with 3-5 MHz curvilinear probe in supine and right anterior oblique views. Hepatic steatosis was defined as a diffuse increase of fine echoes in the liver parenchyma compared with kidney or spleen. Diffuse steatosis can be graded into mild, moderate and severe depending on the sonographic findings. Definitive diagnosis of steatosis is histopathological finding of liver biopsy.

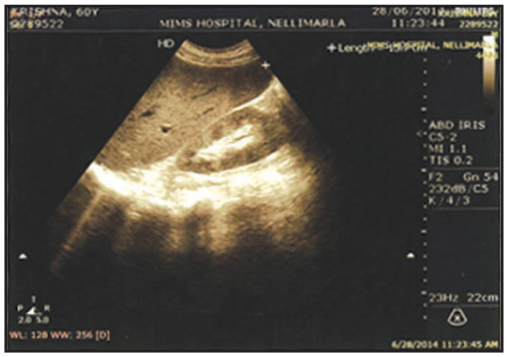
The grading was done accordingly :

Grade I (mild): mild increase in the fine echoes of hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders

Grade II (moderate): moderate diffuse increase in fine echoes with mild impaired visualization of the intrahepatic vessels and diaphragm

Grade III (severe): marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver [6].

Grade - I, fatty Liver



Grade - II, fatty Liver

Method of measurement of carotid IMT -

High frequency linear probe (5-12 MHz) was used for measurement of Carotid IMT bilaterally at one centimeter below the bifurcation of common carotid artery. Thickness of vessel from the edge between intima and the lumen of vessel to media–adventitia was evaluated in a region without plaque. Mean of maximum values of right and left side was calculated. The maximum values of both sides were considered. The basic 2-dimensional mode image was used. The arteries were evaluated along the longitudinal axis. The Ultrasound dual line pattern was identified allowing the definition of the intima-media and media-adventitia interfaces. The distance between the 2 acoustic interfaces was taken as the CIMT measure. Thickness of I-M complex of more than 0.8 mm is considered cut off for the earliest subclinical finding of atherosclerosis, 0.5 to 0.8 mm being normal value [5].

Figure 1: shows intima-medial measurement in common carotid artery.

Study was approved by the ethical committee of our institution. Informed consent was obtained from all the patients who participated in the study. Statistical analysis of this observational study was performed by ANOVA test.

RESULTS

It was an observational study where out of 100 patients, 59 were males and 41 were females with a sex ratio of 1.4:1. Patients of age ranging from 30 to 60 years were studied, where maximum prevalence was noticed among patients of 30- 35 age group. The average of grade – III is significantly greater followed by grade II as per the significant P value.

Fatty Liver Grade	No of P atients
I	**52**
II	**42**
III	**6**
Total	**100**

Table 1:
Grade wise distribution of patients in the study group

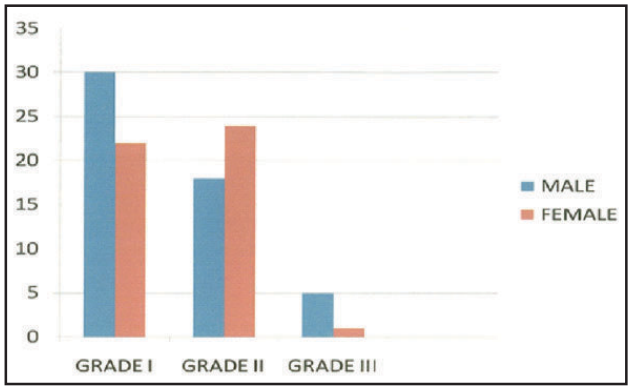


Figure 2:
Grade wise distribution of cases in a bar diagram

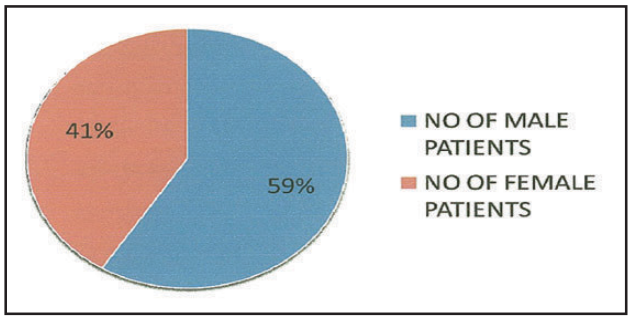


Figure 3: Gender distribution of cases

Age Group	No of Patients
30-35 yrs	**25**
36-40 yrs	**13**
41-45 yrs	**18**
46-50 yrs	**12**
51-55 yrs	**16**
56-60 yrs	**16**
Total	**100**

Table 2: Age distribution of cases

RT CIMT

Fatty Liver	n	Mean	SD	F-Value	P-Value	Decision
I	52	.0629	.00860	46.001	0.000	Significant
II	42	.0792	.01004			
III	6	.0860	.00490			

Table 3: Showing right carotid IMT measurements

The mean of right CIMT is greater in group – III followed by grade – II as per the significant P value (0.000) as per the ANOVA test mentioned above.

LT CIMT

Fatty Liver	n	Mean	SD	F-Value	P-Value	Decision
I	52	.0654	.01012	37.494	0.000	Significant
II	42	.0799	.00893			
III	6	.0900	.00580			

Table 4: Showing left carotid IMT measurements

Regarding left CIMT, group III(0.09) has a significantly higher value than the rest of two as per significant P value of ANOVA test.

Type of CIMT Vs grade	Correlation value	P-value	Decision
Right	0.683	0.000	Significant
Left	0.657	0.000	Significant

Table 5: Showing type of CIMT Vs grade.

From the above statistics, it clearly states that grade of fatty liver increases with a greater value of intimal thickness as per significant P values.

DISCUSSION

NAFLD is a highly prevalent condition characterized by fatty infiltration of more than 5% hepatocytes in presence of <20g (2.5U) of alcohol consumption per day, without any evidence of chronic liver disease. NAFLD is the most common cause of chronic liver disease in general population accounting for about 14- 23%, and it's prevalence is highly increased in obese and insulin resistant patients to approximately 70-90%. NAFLD has emerged as a growing public health problem worldwide and there are studies which proved that there is increased cardiovascular mortality in patients with NAFLD. Likewise, there is growing evidence, which suggests that NAFLD is associated with an increased risk of subclinical atherosclerosis [8].

Clinical and metabolic changes often associated with the more severe NAFLD forms are obesity, age around 40-50 years, diabetes and arterial hypertension.

The biological mechanisms by which NAFLD could contribute to accelerated atherosclerosis are still poorly understood. According to some recent studies, NAFLD in more advanced form might act as a stimulus for further increased whole-body insulin resistance and dyslipidemia, leading to accelerated atherosclerosis. A possible atherogenic mechanism linking NAFLD and carotid IMT could be represented by increased oxidative stress and subclinical inûammation, which could represent causal factors in the progression from simple steatosis to more advanced forms of NAFLD [1]. Reactive oxygen species derived from steatosis-stimulated fatty acid oxidation, attendant hepatocyte injury, and cytokine release and the ensuing proinûammatory milieu may precipitate the liver damage of NAFLD and can act as further atherogenic stimuli to the already high oxidative/proinûammatory status closely related to the metabolic syndrome.

Sookoian et al evaluated the relationship between CIMT and non- alcoholic fatty liver by summarizing several studies done as a case control study on 1427 patients and 2070 healthy individuals. They concluded that there was strong correlation between NAFLD and atherosclerosis (increased CIMT) [7]. The comparison of the carotid arteries examination between NAFLD patients showed a higher proportion of atheromatous plaque in the NAFLD group, which is more severe with increasing degree of NAFLD. In our study too, the severity of CIMT is increasing with degree of NAFLD. Hence we could infer that risk is directly proportional with severity of fatty liver.

In another study done by Targher et al showed CIMT is higher in patients with NAFLD compared with healthy subjects [8]. The severity of histological features of NAFLD (steatosis, necrosis,inûammation,and ûbrosis) were strongly related with increased carotid IMT and a greater prevalence of metabolic syndrome. The marked differences in carotid IMT observed among were little affected by age, sex, and BMI. Additional history of smoking, LDL cholesterol concentration and the presence of metabolic syndrome did not alter the results.

Fracanzani et al evaluated CIMT values in 125 patients with NAFLD and 250 healthy individuals. In this study, the mean CIMT was significantly higher among NAFLD patients [9]. Though our study is not a case control study, the results were similar implying CIMT was higher in NAFLD patients.

The current study results are compatible with the results of mentioned studies; This emphasizes the importance of NAFLD in developing atherogenesis. Previous studies demonstrated obviously increased risk of cardiovascular-related mortality in patients with non-alcoholic fatty liver [10,11]. Our findings are compatible with the results of these studies. Therefore, prompt treatment and preventive interventions can considerably reduce the risk of atherosclerosis [12].

Manco et al didn't report significant association between CIMT and severity of NAFLD [13] which is not compatible with our study. Due to such controversies, further investigations in this field with larger sample size and with control groups can achieve better results.

O'Leary et al. [14] have previously reported that a carotid IMT value <0.86 mm carries a low risk of developing CVD, whereas an IMT value >1.10 mm carries a high risk of developing CVD. We could compare this with our study because in patients with grade III fatty liver , CIMT was > 1mm which shows a higher association of increased CIMT with severity of fatty liver.

Variability in measurement of intima-medial thickness might have affected our results. The strong correlations between replicate readings of the intima-medial thickness are similar to those already published. Any increase in precision of the measurements as a result of technological improvements might increase their predictive power for cardiovascular events.

Other such studies stated that B mode ultrasound enables noninvasive, direct visualization of arterial wall, by which carotid intima-medial thickness can be measured, which is a reliable predictor of atherogenic burden. High resolution ultrasonography of carotid artery intima medial thickness measurements, at the level of carotid artery bifurcation are now recognized as a surrogate measure of atherosclerosis to predict the risk of future stroke or myocardial infarction.

NAFLD is characterized by early onset of typical metabolic and vascular pathogenic alterations in atherosclerosis. In our study, which assessed whether noninvasive measurements have any predictive power with respect to subsequent atherosclerosis, we were aware that carotid artery intima-medial thickness is strongly associated with cardio-vascular risk factors. Increased intima-medial thickness, an indicator of subclinical disease, may reflect the consequences of past exposure to

risk factors. The addition of measurements of intima-medial thickness to cardiovascular risk equations may help to identify asymptomatic persons who would benefit from aggressive preventive measures.

Measurement of carotid intima-media medial thickness and plaque burden by ultrasound is a well validated and widely accepted screening approach to the predilection of CVD in asymptomatic subjects. Importantly, the severity of the histological features of NAFLD appear to be independently correlated with increased C-IMT.

The advantage of this method is that Ultrasonography is a non-invasive, cheap method which can be used to assess both liver changes of NAFLD and also the carotid IMT.

Limitations of study are small sample size and lack of control group. Furthermore the findings of NAFLD were not correlated with laboratory parameters or any other variables.

Conclusion

NAFLD can be considered as an independent risk factor to predict atherosclerosis and thereby to predict the risk of cardiovascular events. This study has shown that the patients with NAFLD have a marked increase in carotid IMT and the measurement of carotid IMT is higher for higher degree of NAFLD. So the patients diagnosed with NAFLD should be evaluated for other markers of atherosclerosis and prompt intervention can be done to prevent the progression of disease and to prevent potential cardio-vascular complications.

Reference

1. Angulo P. Nonalcoholic Fatty Liver Disease. New England J Med. 2002;16:1221–31. [PubMed]
2. Moller DE, Berger JP, Hui JM. Hepatic steatosis and insulin resistance. PharmacolTher. 2005;22:64–70.
3. El-Serag HB, Manson AC, Marrero JA. Stenosis, the metabolic syndrome and cancer. Aliment Pharmacol Ther. 2005;22:40–43.
4. Targher G, Zenari L, Bertolini L. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men. Diabetes Care. 2004;27:2498–500. [PubMed]
5. Lorenz M. W., Markus H. S., Bots M. L., Rosvall M. & Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 115, 459–67, (2007).10.1161 / circulationaha. 106.628875 [PubMed] [Cross Ref]
6. McGahan JP, Goldberg BB, Editors. 1st ed. USA: Lippincott Williams & Wilkins; 1998. Diagnostic ultrasound: a logical approach; pp. 655–56.
7. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol. 2008;49:600–607. [PubMed]
8. argher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007; 191: 235-40
9. Fracanzani AL, Burdick L, Raselli S, Pedotti P, Grigore L, Santorelli G, et al. Carotid artery intimamedia thickness in nonalcoholic fatty liver disease. Am J Med 2008; 121:72-78.
10. Jepsen P, Vilstrup H, Mellemkjaer L. Prognosis of patients with a diagnosis of fatty liver: a registry-based cohort study. Hepatogastroenterology 2003; 50: 2101104.
11. Sanyal A, Banas C, Sargeant C. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology 2006; 43: 682-89.
12. Schindhelm RK, Diamant M, Heine RJ. Nonalcoholic fatty liver disease and cardiovascular disease risk. CurrDiab Rep 2007; 7: 181-87
13. Manco M, Bedogni G, Monti L, Morino G, Natali G, Nobili V. Intima-media thickness and liver histology in obese children and adolescents with non-alcoholic fatty liver disease. Atherosclerosis 2010; 209:463-68
14. O'Leary DH, Polak JF, Kronmal RA, KittnerSJ, Bond MG, Wolfson SKjr, Bommer W, Price TR, Gardin JM, Savage PJ: Distribution and correlates of sonographically detected carotidartery disease in the Cardiovascular Health Study: the CHS Collaborative Research Group. Stroke 23: 1752–1760, 1992.

Abbreviations – NAFLD – nonalcoholic fatty liver disease, NASH – nonalcoholic steato-hepatitis,

IMT – intima medial thickness, CVD- cardiovascular disease, CIMT –Carotid intima medial thickness, USG:Ultrasonography.