Research Article

Association Between Carotid Intima-Media Thickness and Transaminitis in Patients with Non-alcoholic Fatty Liver Disease

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Abstract

Objectives: Carotid intima-media thickness (CIMT) is one of the subclinical markers for detection of cerebrovascular disease. CIMT can be measured through noninvasive carotid artery Doppler ultrasonography. It has been observed that average CIMT of Non-Alcoholic Fatty Liver Disease (NAFLD) patients are significantly high as compared to non-NAFLD patients which may lead to cerebrovascular complications in these patients. So, this study was conducted to compare CIMT in NAFLD with and without transaminitis.

Methods: This was a comparative cross sectional study, conducted in Mayo Hospital. 236 NAFLD patients were included in the study in accordance with a pre-defined inclusion and exclusion criteria. All the patients underwent abdominal ultrasonography for diagnosis of NAFLD & carotid doppler to measure CIMT. Liver function tests were performed in all the patients and results of carotid intimal media thickness CIMT in NAFLD with and without deranged transaminases were compared.

Results: Mean age of the patients was 46.56 ± 11.60 years with 117(50%) female and 119(50%) male patients. Except Alkaline phosphates (p-value = 0.008), all other parameters of liver function test {ALT (p-value=0.618), AST (p-value=0.551), Albumin (p-value=0.385) & Protein (p-value=0.823)} were statistically similar in patients whose CIMT was >0.8 and <0.8 mm. Among the patients whose CIMT was >0.8, 17(45.9%) patients had deranged liver function test. Similarly among those patients whose CIMT value was <0.8, 95(47.7%) patients had abnormal LFTs. Statistically speaking no significant association was seen between LFTs of patients and CIMT value (> 0.8 & <0.8) p-value= 0.841.

Conclusion: It is concluded that there is no significant correlation between CIMT and transaminitis in NAFLD patients.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is accumulation of >5% liver fat per liver weight while consuming <10 g of daily alcohol, a ecting 10—25% of the populations.[1] NAFLD presents as hyperechoic texture on ultrasonography because of di use fatty infiltration associated with obesity, dyslipidemia, diabetes and atherosclerosis.[2,3]

NAFLD patients are at a high risk (13%) of developing carotid atherosclerosis which can be established

through the measurement of carotid intima-media thickness (CIMT).[4,5] Increased CIMT translates into carotid artery stenosis which is a major risk factor for ischemic stroke. The frequency of carotid stenosis as detected by Doppler USG in ischemic stroke is 56%.[6] Patients with NAFLD have a higher risk of death due to cardio/cerebro vascular complications as compared to complications of liver dysfunction.[7,8] Routine measurement of CIMT, which is a reliable indicator of carotid artery atherosclerosis, may be implemented in cases of NAFLD as a screening procedure to measure the progression of carotid artery atherosclerosis. However, impact of active liver disease on progression of carotid atheroma is still largely unknown while there is a lack of local data on the subject.

Methods

A comparative cross-sectional study was conducted in 236 cases (both male and female), with their age ranging from 18-60 years and no history of alcohol intake. The patients that were included had a high body mass index, known cases of fatty liver disease without any other co-morbidity or history of alcohol intake. All the patients who had history of diabetes, hypertension, chronic viral hepatitis or endarterectomy were excluded from the study. Pregnant and diagnosed patients of alcoholic liver disease were not included. These patients underwent an abdominal ultrasound for diagnosis of NAFLD and carotid doppler was performed using G.E. LOGIC 5 with a linear transducer of 7.5MHz. CIMT was measured (mm) and liver function tests were recorded in all the patients. The data was analysed to see CIMT in patients who had either normal or deranged LFTs and correlation co-e cient was determined for CIMT and liver function test parameters.

Results

Among the patients, there were 119(50%) male and 117(50%) female patients with a mean age of 46.56 ± 11.60 years while minimum and maximum age of patients was 25 and 80 years (Table-1 & 2). Table 3 shows descriptive statistics of liver function tests (ALT, AST, Alkaline phosphatase, Serum protein & albumin). Results of T- test analysis were shown in table 4. It was found that except alkaline phosphatase, all other parameters of liver function tests were statistically similar in patients whose CIMT was >0.8 and <0.8 mm while p-values for di erent parameters are as follows; ALT (0.618), AST (0.551), AP (0.008), Albumin (0.385) & Protein (0.823). In table 5, findings of Chi square analysis showed that among the patients whose CIMT was >0.8, 20(54.1%) patients had normal liver function tests and in the remaining 17(45.9%) patients, liver function tests were deranged. Similarly among the patients whose CIMT value was <0.8, 104(52.3%) patients had normal liver function tests and in the remaining 95(47.7%) patients, liver function tests were deranged. Statistically, no significant association was seen between liver function tests of patients and CIMT value (> 0.8 & <0.8) p-value = 0.841.

Discussion

The idea that NAFLD can be an independent risk factor for cardio/cerebro-vascular disease highlights the importance of NAFLD. Hamaguchi M et al. conducted a prospective study in 2007 on 1221

Table 1: *Descriptive Statistics for Age of Patients*

N	236
Mean	46.56
SD	11.60
Minimum	25
Maximum	80

Table 2: *Gender Distribution Among the Patients*

Gender	N	%
Male	117	50
Female	119	50

Table 3: *Descriptive Statistics For Liver Function Tests*

	Mean	SD	Min.	Max.
ALT	66.62	86.72	10	394
AST	64.82	82.72	11	423
ALK. PHOSPHATASE	352.77	255.63	46	1770
ALBUMIN	4.38	0.61	3.4	5.4
PROTEIN	7.45	0.88	6.0	9.0

Table 4: *Comparison of Live Function Test Parameters In Relation to Cimt*

LFT Parameters	CIMT	N	Mean	SD	p-value
ALT	>0.8 mm	37	60.08	81.67	.618
	<0.8 mm	199	67.84	87.76	
AST	>0.8 mm	37	57.35	72.17	.551
	<0.8 mm	199	66.21	84.63	
AP	>0.8 mm	37	250.51	212.02	.008
	<0.8 mm	199	371.78	258.98	
ALBUMIN	>0.8 mm	37	4.303	0.57	.385
	<0.8 mm	199	4.398	0.61	
PROTEIN	>0.8 mm	37	7.422	0.92	.823
	<0.8 mm	199	7.457	0.88	

patients and found out that the incidence of cardiovascular disease was higher in 231 NAFLD patients (5 coronary heart disease, 6 ischemic stroke, and 1 cerebral hemorrhage) as compared to the 990 patients who did not have NAFLD (3 coronary heart disease,6 ischemic stroke, and 1 cerebral hemorrhage). This was proved through multivariate analyses that NAFLD was a predictor of cardiovascular disease independent of conventional risk factors (p-value = 0.004).[8] This was further supported by El Azeem who proved through Logistic regression analysis that NAFLD was the best predictor for cardiovascular and renal impairment.[9] Moreover, the hypothesis that NAFLD may also be involved in the pathogenesis of cardio/cerebro-vascular disease in addition to being a marker of the disease has gained further evidence. Silvia Fargion conducted a meta-analysis and reviewed many retrospective and prospective studies. The meta-analysis provided further evidence that a strong association exists between NAFLD and subclinical manifestation of atherosclerosis (increased intima-media thickness, endothelial dysfunction, arterial sti ness, impaired left ventricular function and coronary calcification).[10] This is in accordance with the latest guidelines for diagnosis and management of NALFD patients that greatly stress on the early diagnosis of this condition to estimate and track the progression of disease from fatty changes with or without inflammation leading to NASH, cirrhosis, and end-stage liver disease.[11,12,13] Various mechanisms that are supposed to influence the progression to di erent stages include: endothelial dysfunction seen in the vessels, progression of inflammation, gradual rise in oxidative stress and deranged metabolism of lipoproteins.[14]

The relationship between NAFLD and CIMT has been evaluated in several studies and the resultant data supports the idea of independent associations between NAFLD and AS.[5,11] In 2008, Sookoian et al. (2008) published a meta-analysis by analysing studies that included 1427 patients and 2070 healthy subjects. They studied the relationship between NAFLD and CIMT. They concluded that an increase in CIMT can be strongly correlated with NAFLD while an increase in CIMT is directly proportional to AS.[5] Yun Huang evaluated the association between NAFLD and AS in his study. According to his findings, those patients who had NAFLD were found to be carrying a higher degree of CIMT while comparing these findings in patients who did not have NAFLD (0.594±0.105 mm versus 0.578±0.109 mm, P<0.0001).[15] In 2007, Targher et al. were able to prove through their study that CIMT is higher in patients with NAFLD in comparison with the healthy subjects.[16] In 2008, after inducting 250 healthy subjects and 125 NAFLD patients into his study, Fracanzani et al. reported that among the patients who had NAFLD, they were found to have a high CIMT. This finding of a high mean CIMT carried statistical significance. Nahandi studied patients who were either diabetic or normoglycemic and compared their CIMT values. All the patients that were included in the study carried fatty liver disease with normal or increased liver enzymes. The two sets of patients were found to be statistically similar. Additionally, they established that di erent grades of fatty liver based on the grading by ultrasonography do not have any significant association with CIMT.[17]

The previous research suggests that cardiovascular risk factors like an increase in intima media thickness are more prevalent among NAFLD patients in comparison with the healthy individuals without any degree of fatty liver disease. Although NAFLD patients with transaminitis were the group of patients to be included into these studies, most of these studies proved that increase in CIMT is associated with NAFLD irrespective of the fact that whether or not liver enzymes are elevated. [18,19]

In 2016, Hafsa Riaz studied the association between CIMT and abnormal LFTs and found out that the frequency of raised carotid intima-media thickness was higher in patients with non-alcoholic fatty liver disease and showed the positive association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.[20] This relationship between fatty liver disease and carotid intima media thickness was later studied by Chohan in 2017. After enrolling 88 patients of fatty liver disease and 80 controls, he concluded that CIMT was high in patients with NAFLD or AFLD with an increase in risk of atherosclerosis.[21] However, In this study it was observed that except Alkaline phosphates all other parameters of liver function test i.e. ALT, AST, Albumin and Protein were statistically similar in patients whose CIMT was >0.8 and <0.8 mm. Furthermore, among the patients whose CIMT was > 0.8, 20(54.1%) patients had normal liver function test and the remaining 17(45.9%) patients had deranged LFTs. Similarly, among the patients whose CIMT value was <0.8, 104(52.3%) patients had normals

LFTs while LFTs were deranged in the remaining 95(47.7%) patients. No significant association was seen between liver function test of patients and CIMT value (> 0.8 & <0.8) in statistical terms.

However, this was a cross-sectional study and there was no follow-up of the patients included in the study hence the progression in CIMT with or without transaminitis in NAFLD patients was not studied. Whether the relation between the progression in CIMT and transaminitis in NAFLD patients carries any significance can only be proved via a thoroughly designed study incorporating patient cohorts with or without elevated liver enzymes with a pre-exisiting non-alcoholic fatty liver disease.

Conclusion

Hence it is concluded that in NAFLD patients, there is no significant association between CIMT and transaminitis. However, a prospective cohort study with an extended follow-up may help prove that the progression in CIMT in NAFLD patients is related with transaminitis which in turn can help in prediction of cerebrovascular complications in NAFLD patients.

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Conflict of Interest: None
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