ORIGINAL RESEARCH ARTICLE

Association of Intracranial Artery Stenosis and Carotid Artery Disease in Patients with Non-Alcoholic Fatty Liver Disease and Normal Subjects

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ABSTRACT

Introduction: Fatty liver disease(FLD) is frequently detected during ultrasound imaging of abdomen.There are various causes for fatty liver disease among which Non alcoholic fatty liver disease is a major entity. The study was done to evaluate association of intracranial main artery stenosis and carotid artery disease in patients with non alcoholic fatty liver disease(NAFLD) with normal subjects as controls.
Materials and methods: Study consists of a sample population of 200 cases within age group of 18-59 years, stratified into 100 cases with non-alcoholic fatty liver disease and 100 controls without non-alcoholic fatty liver disease. USG was used as a non-invasive investigation done to assess fatty liver disease. Carotid Doppler was done to measure the carotid intima media thickness and to assess presence carotid plaques. MR Angiography brain was done to evaluate any intracranial arterial stenosis.
Results: NAFLD cases have a significantly higher weight (P value = 0.014)and BMI (Body Mass Index) (P value = 0.003) compared to normal controls in anthropometric parameters. The mean $CIMT^{Max}$ was 0.92 ± 0.29mm among NAFLD cases and was 0.72 ± 0.16mm in normal controls. The $CIMT^{Max}$ was significantly higher in the NAFLD cases compared to the normal controls (P value <0.001). ROC analysis was done for $CIMT^{Max}$ and Plaque score in prediction of intracranial arterial stenosis. With a cut-off of 0.85 for $CIMT^{Max}$ and 1.75 for the Plaque Score using ROC curve, $CIMT^{Max}$ had a sensitivity of 75.46%, specificity of 75.68 and a diagnostic accuracy of 75.5%.
Conclusion: Our study inferred that there is an increased risk of adverse cerebrovascular events in the patients with Non-Alcoholic Fatty Liver Disease when compared to the controls without fatty liver as the patients with Non-alcoholic fatty liver disease showed increased carotid intima media thickness/carotid plaque score and intracranial arterial stenosis compared to the controls. Plaque score was relatively better compared to $CIMT^{Max}$ in the prediction of intracranial arterial stenosis.

Keywords: Fatty Liver Disease; Metabolic Syndrome; Intracranial Arterial Stenosis; Carotid Artery Disease

INTRODUCTION

Metabolic syndrome is probably the most commonly encountered however, the most ignored medical condition in the world due to the sheer lack of awareness of its clinical complications. This is also due to inadequacy of studies to prove that it is a sub-clinically prevalent epidemic.[1] Something we most frequently come across during our routine radiological examinations is Fatty liver, especially the non-alcoholic variety. It is actually the hepatic manifestation[2] of a larger clinical entity, the metabolic syndrome. There are various causes of fatty liver disease amongst which Non-alcoholic fatty liver disease (NAFLD)[3] is one of the major entities. The incidences of coronary artery calcification, hypertension, aortic valve sclerosis, diastolic dysfunction, atherosclerotic plaques, and increased carotid intima-media thickness were more common in patients with NAFLD[4] than in those without. A few studies have been done linking FLD (Fatty Liver Disease) as such to the adverse cerebro-vascular events[5] irrespective of the etiology. However, not much of research studies are available linking NAFLD to cerebro-vascular complications.[6] Recent studies also show that presence of NAFLD independently correlates with subclinical inflammation and surrogate markers of atherosclerosis like carotid intima-media thickness (CIMT), impaired flow-mediated vasodilatation in Asian Indians.[7]

The study is aimed at establishing evidence that intracranial (IC) arterial stenosis and carotid arterial disease are linked to the atherosclerotic burden of NAFLD.

MATERIAL AND METHODS

This study was conducted in the Department of Radio-diagnosis in SRM Medical College and Hospital over a period of 18 months from January 2018 to September 2019. A sample population of 200 cases consisting 100 cases with non-alcoholic fatty liver disease and 100 controls without non-alcoholic fatty liver disease were enrolled. The study was approved by the ethical committee. The inclusion criteria were patients between 19 - 59 years of age with fatty liver disease (non-alcoholic) detected during routine ultrasonography for abdomen and incidentally detected non-alcoholic fatty liver cases during CT or MRI of abdomen. The exclusion criteria were history of alcoholism, familial dyslipidemia, drug-induced fatty liver and any other liver pathologies.

USG Abdomen and Carotid Doppler were done in the machines GE LOGIQ P9 (Curvi-Linear probe 3-5 MHz; Linear probe 7-12 MHz). MRI Brain and MR Angiogram were done in 1.5 Tesla Siemens MAGNETOM ESSENZA with 3D Time of flight – MR Angiogram sequences.

Standardized protocol for the measurement of the Carotid Intima Media Thickness (CIMT) and Plaque score based on the Updated Consensus of Mannheim CIMT and Plaque (2004–2006–2011)[8] was used

CIMT Measurement[9]: Intima media thickness was measured on the far wall of the CCA (Common Carotid Artery) at least 5 mm below its bifurcation.

CIMT^{Max} is the maximum measurement of the 3 mean Carotid Intima Media Thickness measurements observed in the bilateral carotid arteries.

Sites of plaque measurement[10] are as depicted in the figure. Plaque was designated as focal intima-media thickening greater than or equal to 1.0 mm. The Plaque score was calculated by summing up all plaque thicknesses at 4 sites (S1 to S4) as described in Figures 1(b),(c),(d) and (e).[11]

STATISTICAL ANALYSIS

Descriptive analysis of the study group was performed by using "Chi square test/Fisher's Exact test". The utility of the Plaque score and the CIMT^{Max} were individually assessed using the "Receiver Operative Curve (ROC) analysis". The "AUC (Area under the ROC curve)", their corresponding "95% confidence interval and p values" are tabulated. Based on the ROC analytics, we arrived at a cut-off for plaque score and CIMT^{Max}. With these cut-off values, the "sensitivity, specificity, predictive values and the diagnostic accuracy" of these tests,their corresponding "95% confidence interval and p values" were tabulated. "P value < 0.05"was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

The mean weight in NAFLD cases was 67.85 ± 11.76 kg, it was 63.89 ± 10.86 in Normal controls. The difference in weight between two groups was statistically significant. (P value 0.014). The mean height in NAFLD cases was 1.65 ± 0.11, it was 1.64 ± 0.1 in Normal controls. The difference in height between two groups was statistically not significant. (P value 0.780). The mean BMI in NAFLD cases was 25.03 ± 3.5 and was 23.62 ± 2.99 in Normal controls. The difference in BMI between two groups was statistically significant. (P value 0.003). [Table 1(a)]

Among NAFLD cases, the mean CIMT of Right CCA in NAFLD cases was 0.83 ± 0.27, it was 0.65 ± 0.14 in Normal controls. Among NAFLD cases the mean CIMT Left CCA in NAFLD cases was 0.85 ± 0.27, it was 0.69 ± 0.16 in Normal controls. Among NAFLD cases, the mean CIMT^{Max} was 0.92 ± 0.29 and was 0.72 ± 0.16 in Normal controls. The difference in CIMT Right CCA, CIMT Left CCA and the CIMT^{Max} between two groups was statistically significant. (P value <0.001) {Table 1(b)}. Among NAFLD cases 78 (78%) had fatty liver grade I, 20 (20%) had grade II and 2 (2%) had grade III.

Among NAFLD cases, 66 (66%) had insignificant IC artery stenosis and 34 (34%) had significant artery stenosis (Figure

1(a): Comparison of mean of anthropometric parameters.			
Parameter	Study group (Mean± SD)		P value
	NAFLD cases (N=100)	Normal controls (N=100)	
Weight	67.85 ± 11.76	63.89 ± 10.86	0.014
Height	1.65 ± 0.11	1.64 ± 0.1	0.780
BMI	25.03 ± 3.5	23.62 ± 2.99	0.003
1(b): Comparison of mean CIMT^{max} between the study groups (N=200)			
CIMT Rt CCA	0.83 ± 0.27	0.65 ± 0.14	<0.001
CIMT Lt CCA	0.85 ± 0.27	0.69 ± 0.16	<0.001
CIMT Max	0.92± 0.29	0.72 ± 0.16	<0.001

Table-1: Anthopometry and Mean CIMT comparison between study groups:

IC Artery Stenosis	Study Group		Fisher exact P value
	NAFLD cases (N=100)	Normal controls (N=100)	
Insignificant	66 (66%)	97 (97%)	<0.001
Significant	34 (34%)	3 (3%)	

Table-2: Comparison of IC artery stenosis between the study groups (N=200)

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2). Among Normal controls 97 (97%) had insignificant IC artery stenosis, 3 (3%) had significant artery stenosis. The difference in the proportion of IC artery stenosis between two groups was statistically significant (P value <0.001) {Table 2}. Majority of population that is 9 (24.32%) had stenosis of Right IC ICA, 9(24.32%) had RT MCA, 8(21.62%) had LT IC ICA and 7(18.92%) had LT MCA.

Comparision of CIMT^{max} and plaque score in the prediction of significant intracranial stenosis CIMT^{max} had a good predictive validity in predicting intracranial artery stenosis, as indicated by area under the curve of 0.802 (95% CI 0.731 to 0.872, P value <0.001). The sensitivity of CIMT^{max} in predicting IC artery stenosis was 75.46%, Specificity was 75.68 and the total diagnostic accuracy was 75.50% {Table 3}.

Plaque score had good predictive validity in predicting intracranial artery stenosis, as indicated by area under the

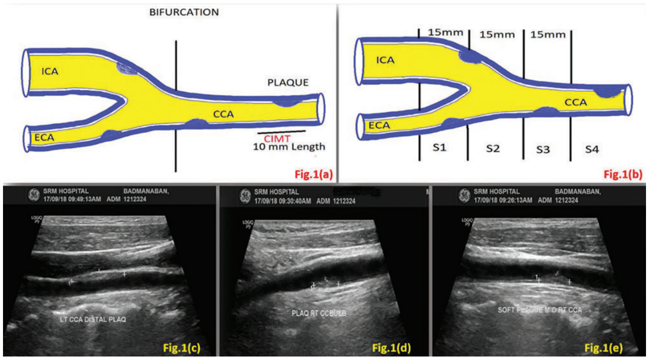


Figure-1: Measurement of carotid intima media thickness (CIMT) and plaque score[8]

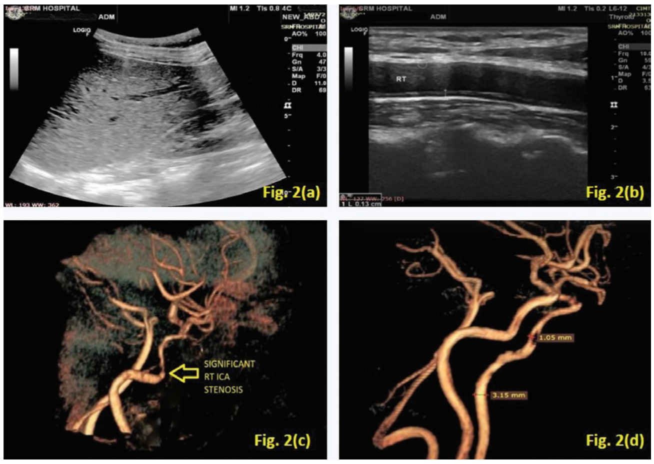
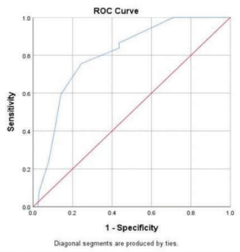


Figure-2: 45 year old male patient having grade II fatty liver with obscured portal vessel [Fig. 2(a)] had raised right CIMT [Fig. 2(b)]. On MRA, representative MIP image shows significant right ICA stenosis [Fig 2(c)]. Percentage stenosis was calculated as depicted in Fig 2(d): [(1-0.33) x 100] = 67%.



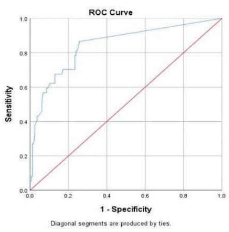
Test Result Variable(s): CIMT ^{max}

Area Under the Curve	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.802	0.036	0.731	0.872	<0.001

CIMT ^{max}	IC Artery Stenosis		Chi square	P value
	Insignificant (N=163)	Significant (N=37)		
Low (<0.85)	123 (75.46%)	9 (24.32%)	35.139	<0.001
High (>=0.85)	40 (24.54%)	28 (75.68%)		

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	75.46%	68.12%	81.85%
Specificity	75.68%	58.80%	88.23%
False positive rate	24.32%	11.77%	41.20%
False negative rate	24.54%	18.15%	31.88%
Positive predictive value	93.18%	87.45%	96.84%
Negative predictive value	41.18%	29.37%	53.77%
Diagnostic accuracy	75.50%	68.94%	81.29%

Figure-3: Predictive validity of CIMT^{max} in predicting IC artery stenosis (N=200)



Test Result Variable(s): Plaque score

Area Under the Curve	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.845	0.039	0.769	0.920	<0.001

Plaque Score Category	IC Artery Stenosis		Chi square	P value
	Insignificant (N=163)	Significant (N=37)		
Low (<1.75)	125 (76.69%)	8 (21.62%)	41.044	<0.001
High (>=1.75)	38 (23.31%)	29 (78.38%)		

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	76.69%	69.43%	82.94%
Specificity	78.38%	61.79%	90.17%
False positive rate	21.62%	9.83%	38.21%
False negative rate	23.31%	17.06%	30.57%
Positive predictive value	93.98%	88.49%	97.37%
Negative predictive value	43.28%	31.22%	55.96%
Diagnostic accuracy	77.00%	70.54%	82.64%

Figure-4: Predictive validity of plaque score in predicting IC artery stenosis (N=200)

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curve of 0.845 (95% CI 0.769 to 0.920, P value <0.001). Plaque score had sensitivity of 76.69% in predicting IC artery stenosis, Specificity was 78.38% and the total diagnostic accuracy was 77 .00% {Table 4}.

DISCUSSION

Our study was to determine the association of cerebro-vascular disease in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) by measuring CIMT and quantifying intracranial main artery stenosis with normal patients as control subjects. The prevalence of NAFLD in a study conducted by Mohan et al[12] (2009) was 32% in the urban Chennai population. The sample size was calculated for our study based on this study and was estimated to be around 200. Our study therefore consisted of a total sample size of 200 including 100 cases of NAFLD and 100 normal controls.

Michael R. Skilton[13] (2019) and associates had published a study in which they had mentioned that lipid depositions in the carotid arteries start as early as 16 years and are clinically inapparent at this age. Citing this reason, our study group included patients above the age of 18 years. William Insull[14] (2009) and Katja Ritz[15] (2014) assessed the atherosclerotic pathologies in various age groups. Their study revealed that in the patients aged beyond 55 years, age related advanced atherosclerotic changes set in. Hence, our study includes an age group of 19-59 years which is comparable to most of the studies done in this aspect.

Comparison of various clinical parameters between the cases and controls

Mean BMI levels between cases and controls: Hyemin Jang[16] (2019) and associates gathered NAFLD and normal controls in the Korean population whose mean BMI levels were 25.6 and 23.0 respectively (P value < 0.01). Asakawa et al[1] (2012) calculated a BMI of 25.8 in the NAFLD cases and 24.8 in the controls. (P value < 0. 0127). In our study, the mean BMI of the NAFLD cases were found to be significantly higher as compared to that of our normal control group. This difference was in agreement with few of the studies in the literature as described above.

Fatty liver grading: Mohammadzadeh[17] (2019) et al studied the presence of NAFLD. Their study had 78.7% grade I, 18.7% Grade II and 2.7% Grade III fatty liver patients which were compatible with our study. In our study, similar results were observed consisting of 78 patients with Grade I fatty liver, 20 patients with Grade II fatty liver and 2 patients with Grade III fatty liver were observed.

Relationship between CIMT and fatty liver grading: Mohammedzadeh et al (2019)[17] did a study in Tehran, Iran on the relationship between NAFLD, increased CIMT and other cardiovascular risks. The study concluded that Among NAFLD patients, 38 [25.3%] had increased IMT while this frequency was 8 [5.3%] among normal subjects [P < 0.001]. In our study, there was increase in $CIMT^{Max}$ of cases (0.92 +/- 0.29) with Non-alcoholic fatty liver disease compared to the controls without fatty liver which is statistically significant which was similar to the study described above.

Relationship between significant intracranial stenosis and non-alcoholic fatty liver disease: Asakawa[1] et al sub-divided their primary study group into fatty liver disease (FLD) and Non-FLD sub-groups. The FLD subgroup had a higher incidence of ICAS (25%) compared to the Non-FLD sub-group (5.7%). The authors also sub-divided their primary study group into ICAS and Non-ICAS groups. In the ICAS group there was increased incidence of fatty liver (66.7%) compared to that of the Non- ICAS group. Moshayedi[18] (2014) and associates studied the relationship between NAFLD and Ischemic stroke. NAFLD was found in 47% of ischemic stroke patients and 22.7% of the controls.

In our study, there was statistically significant (P value = < 0.001) increase in the presence of intracranial main arterial stenosis in patients with NAFLD (34%) compared to the normal control subjects (3%). Hence, our study is in agreement with other studies proving there is higher incidence of the cerebral ischemia in patients with NAFLD.

Mean $CIMT^{Max}$ comparison between cases and controls

The $CIMT^{Max}$ was the maximum measurement of the two mean CIMTs measured on both sides of the neck. Natsumi Morito[19] et al, obtained a $CIMT^{Max}$ of 1.0 ± 0.43 in the normal subjects and 1.65 ± 1.09 in the cases with triple vessel cardiac disease. The $CIMT^{Max}$ in the normal controls was significantly higher than that of the cases (P value= 0.001). In our study, the mean $CIMT^{max}$ found to be significantly higher in the NAFLD cases than in the normal controls. (P value < 0.001) which is similar to the study mentioned above.

Plaque score comparison between cases and controls

Nobutaka Ikeda[11] (2012) and colleagues conducted a study to establish the diagnostic accuracy of CIMT and Plaque scores in the prediction of coronary artery disease by using the SYNTAX angiographic score. The mean plaque score in their total study population was 1.31 with a 95% CI ranging from 1.23 – 1.39 (P value < 0.001) which was comparable to our study results. A study by Natsumi Morito[19], et al (2007) showed that the patients with cardiovascular disease had a significantly higher mean plaque score (1.3) compared to the normal controls (7.9) with a significant P value of < 0.001. The area under the ROC curve for Plaque score in predicting the coronary artery disease was 0.7851 and the cut-off was determine to be 1.9 giving a sensitivity of 79.7%, Specificity of 63.4% and accuracy of 73.9%. Sakaguchi et al[20] (2003) calculated the Plaque score in evaluating the risk of coronary artery disease. The mean plaque score in the patients with coronary lesions was 14.1 ± 9.5, which was significantly higher than patients without coronary lesions which amounted to 4.6 ± 5.9 . (P value of < 0.001) . These findings were compatible with the results obtained in our study.

In our study, the plaque score was significantly higher in the NAFLD cases compared to the normal controls.

CIMT and plaque score in ICAS prediction: Though both the parameters appear to predict intracranial arterial stenosis rather well with good sensitivity and specificity, Plaque score appears to be a slightly better parameter in the detection of subclinical carotid atherosclerosis with an accuracy of compared 77% to the accuracy of $CIMT^{Max}$ which was 75.5%. A study done by Nobutaka Ikeda[11], et al compared the

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diagnostic accuracy of Carotid IMT and Carotid Plaque score in prediction of coronary artery disease as part of the Metabolic syndrome. ROC curve analysis was done for both CIMT and Carotid plaque score in predicting the Risk of coronary artery disease using the SYNTAX angiographic score. The authors concluded that both CIMT and Plaque score were good predictors of coronary artery disease, however, the Plaque score was a slightly better predictor of the same.

Natsumi Morito[19] (2008) and associates did a study to compare the efficacy of carotid USG and severity of coronary artery disease. The area under the ROC curve for Plaque score in predicting the coronary artery disease was 0.781 and the cut-off was determine to be 1.9 giving a sensitivity of 79.7%, Specificity of 63.4% and accuracy of 73.9% which was comparable to that of our study. Their study concluded that plaque score was a better predictor of coronary artery stenosis detected by angiographic techniques.

Sakaguchi, et al[20] compared the efficacy of Plaque score and CIMT in predicting severe coronary artery disease with ROC curves. The study concluded that Plaque score more directly reflects the plaque burden of carotid arteries than CIMT, likely because the focal plaques are more frequent in the carotid bulb and ICA compared to the CCA alone.

In our study, we had done a comparative analysis between $CIMT^{Max}$ and Plaque score in predicting Intra-cranial main artery stenosis with ROC curve analysis. With a cut-off of 0.85 for $CIMT^{Max}$ and 1.75 for the Plaque Score using ROC curve, we have obtained an area of 0.845 under the curve, sensitivity of 76.69% and specificity of 78.38% in predicting intracranial stenosis. The diagnostic accuracy for Plaque score was 77%, which is relatively better compared to $CIMT^{Max}$. These findings were compatible with the previous studies described above.

CONCLUSION

Our study inferred that there is an increased risk of adverse cerebrovascular events in the patients with Non-Alcoholic Fatty Liver Disease. Higher incidence of increased weight and Body Mass index was noted in the patients with NAFLD compared to the normal controls. Patients with higher $CIMT^{Max}$ had a higher incidence of intracranial arterial stenosis. Carotid Intima Media Thickness ($CIMT^{Max}$) and Coronary Plaque score had good accuracy in predicting intracranial main arterial stenosis. However, Plaque score had a slightly better sensitivity, specificity and diagnostic accuracy compared to the Carotid Intima Media Thickness in predicting intra-cranial arterial stenosis.

Limitations: A larger sample size is required for the solid reinforcement of the results inferred in our study. Although the MR Angiogram modality used in our study doesn't involve ionizing radiation / invasive contrast injections, it has a very poor resolution when compared to Digital Subtraction Angiography or CT Angiography. Also, all our patients were not subjected to confirmation of intracranial arterial stenosis with catheter angiography. The patients were not followed up prospectively into the future to evaluate for the development of cerebrovascular accidents.

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