ORIGINAL ARTICLE

FREQUENCY AND LOCAL HEMODYNAMIC EFFECTS OF CAROTID LESIONS AMONG PATIENTS WITH DIFFERENT GRADES OF UNCOMPLICATED METABOLIC ASSOCIATED FATTY LIVER DISEASE

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ABSTRACT

OBJECTIVE: To assess the prevalence of local hemodynamic effects of carotid lesions in adult patients with uncomplicated metabolic associated fatty liver disease (MAFLD). **METHODOLOGY:** This descriptive cross-sectional study was conducted in the Radiology Department, Dr. Ruth K.M. Pfau Civil Hospital, Karachi, using a non-probability, consecutive sampling technique from November 2021 to April 2022.This study included 192 patients of either gender between 18-55 years of age with uncomplicated metabolic associated fatty liver disease (MAFLD) according to study criteria. Then duplex ultrasound of carotid arteries was performed to assess the carotid lesions in the term of carotid intimal medial thickness (CIMT), carotid plaque, carotid stenosis and peak systolic velocity (PSV). **RESULTS:** There were 89 (46.4%) males and 103 (53.6%) females with mean age of 42.18 – 10.02 years. Out of 192 patients, 79(41.1%) had mild fatty liver (Grade I), 72 (37.5%) had moderate fatty liver (Grade II) and41(21.4%) had severe fatty liver (Grade III). Carotid lesions were present in 108 (56.2%) patients while 84 (43.8%) had no carotid stenosis. Increased CIMT and frequency of carotid plaque, carotid stenosis and PSV were noted in severe fatty liver. **CONCLUSION:** The carotid lesions are highly prevalent in patients with uncomplicated metabolic associated fatty liver disease. Duplex ultrasound is a reliable and cost effective imaging modality to assess the CIMT which is considered as an independent risk factor of cardiovascular disease.

Keywords: Carotid lesions, Grades of fatty liver, Uncomplicated metabolic fatty liver disease, Urban, Ultrasound

Introduction

Non-Alcohol fatty liver disease (NAFLD) is a chronic disease present worldwide with an estimate of 25% of the population being affected by it.[1,2] Previously it was considered a benign entity but now regarded as a major cause of liver and cardiovascular related morbidity and mortality due to its subtle onset and prolonged course.[3] Non-alcoholic fatty liver disease (NAFLD) is characterized by presence of hepatic steatosis either by biopsy or imaging as well as the lack of secondary causes of hepatic lipid accumulation like excessive alcohol intake, long-term steatogenic pharmaceutical usage, or monogenic genetic illnesses.[2,4] In 2020, NAFLD was renamed as metabolic-associated fatty liver disease (MAFLD) as previous most studies show close relationship and increased prevalence of NAFLD in metabolic disorders particularly in obese and diabetes people.[5] MAFLD is defined as the presence of hepatic steatosis and at least one

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condition such as obesity, Type 2 Diabetes mellitus, or metabolic dysfunction including increased waist circumference, arterial hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL-C), prediabetes, insulin resistance, and subclinical inflammation.[6]

The interlink between MAFLD and cardiovascular dysfunction may be multifactorial but exact pathogenesis is not known. Along with hepatic associated morbidity and mortality, MALFD patients are at high risk of coronary heart disease and stroke.[7] Some recent studies suggest that the fatty and inflamed liver expresses multiple pro-inflammatory and procoagulant factors, as well as certain genes involved in accelerated atherogenesis,[8,9] that lead to development of atherosclerosis particularly in the coronary, carotid and peripheral arteries. In such scenario, MAFLD can be a prognostic and therapeutic target for cardiovascular disorders to decrease intrahepatic inflammation as well as fibrosis and to modify the lifestyle to increase physical activity along with management of associated metabolic disorders to reduce the mortality from cardiovascular disorders.[10]

Previous most studies done for evaluation of association between MAFLD and carotid lesions on different communities have shown controversial results.[3,10,11] This may be either due to different selection criteria, population ethnicity, sample size, different environmental factors or combination of these factors. The incidence of MAFLD is increasing in our population due to a rise in risk factors like hypertension, diabetes and obesity. Concomitantly, the incidence of its associated ailments (particularly carotid lesions) is also expected to rise but the exact local data is not available so this research hopes to evaluate the frequency of incidental finding of carotid lesions in patients with uncomplicated MAFLD on ultrasound. These findings will help to cement the potential of this diagnostic modality to predict development of extrahepatic complications (carotid lesions) of fatty liver disease in primarily asymptomatic patients. It will also guide clinicians to use duplex ultrasound on asymptomatic patients with MAFLD as a screening tool for early detection of carotid lesions thus helping them to plan proper management as well.

Methodology

This descriptive cross-sectional study was conducted from November 2021 to April 2022 in the Department of Radiology, Dr. Ruth KM Pfau Civil Hospital, DUHS, Karachi, using a non-probability, consecutive sampling technique. The study was duly approved by the ethical review committee. A total of 192 patients with uncomplicated metabolic associated fatty liver disease (MAFLD), with an age between 18 and 55 years of either gender, were included in the study, whereas patients with stigmata of chronic liver disease, portal hypertension, hepatic mass, a history of myocardial infarction, and / or stroke, were excluded from the study.

Sample size was calculated by using frequency of carotid lesions as 57.8%,[12] margin of error 7% and confidence interval 95%. Total calculated sample size was 192. After taking informed consent, relevant history and demographic data including age, gender, height, weight, body mass index (BMI), Diabetes mellitus, hypertension and smoking status was collected. Patients with BMI ≥ 18.5to 22.9 Kg/m^2 was labelled as normal weight, BMI between 23 and 24.9 Kg/m^2 as overweight and those with BMI > 25 Kg/m^2 as obese.[13] Gray scale ultrasound of abdomen was performed to grade the severity of the fatty liver, then Duplex ultrasound of carotid arteries was performed toevaluate for intima media thickness and atherosclerotic plaque along with severity of carotid stenosis. Carotid intima media thickness (CIMT) of <1mm was labelled as normal while <1mm was defined as thickened.[14,15] Carotid plaque was defined when focal carotid IMT was ≥1.5cm or focal wall thickening ≥50% than that of surrounding vessel wall.[15,16] The severity of stenosis was classified as normal (no stenosis) and carotid stenosis (<50% stenosis; ≥50% stenosis or occlusion).17 According to the criteria of Society of Radiologist in Ultrasound Consensus Conference,[17,18] normal (no stenosis) was defined as peak systolic velocity (PSV) of internal carotid artery (ICA) <125cm/s without carotid plaque or intima media thickness, < 50% stenosis as ICA-PSV< 125cm/s with carotid plaque or intima media thickness; and ≥50% stenosis or occlusion as ICA-PSV > 125cm/s withcarotid plaque, or no detectable patent lumen/flow on ultrasound. On grey-scale ultrasound, fatty liver is labelled as Grade1when there is mild increase in

liver parenchymal echogenicity with normal echogenicity of portal vein wall and diaphragmwhile Grade 2 when there is moderate increase in liver parenchymal echogenicity with reduced echogenicity of portal vein wall and diaphragm and Grade 3 fatty liver is labelled when there is severe increase in liver parenchymal echogenicity almost no visualization of the portal vein wall and diaphragm.[19]

Data collected was analyzed using SPSS Version 26.0. Demographic details such as age, weight, height and BMI of the patients were expressed as means and standard deviations. Frequencies and percentages were calculated for gender, hypertension, diabetes, smoking status, grades of fatty liver, and carotid lesion. A Chi square was applied to determine the association between demographics, and the grading of fatty liver and carotid lesions. A p-value of < 0.05 was reflected as statistically significant.

Results

A total of 192 patients with MAFLD were enrolled in the study to assess the prevalence of local hemodynamic effects of carotid lesions. There were 89 (46.4%) males and 103 (53.6%) females in the range of 18-55years with mean age of 42.18 –10.02 years. The mean weight of the patients was76.97 –11.28 kg and had a height of 1.68 – 0.08 meters, resulting in a mean body mass index (BMI) of 27.26 – 4.28 kg/m^2. Out of 192 patients, 51 (26.6%) patients had Diabetes mellitus and 79 (41.1%) had hypertension while 69 (35.9%) patients were smokers, as shown in (Tab.1).

Majority of patients were categorized as having mild fatty liver (41.1%) on the basis of ultrasound findings, while 72 patients (37.5%) were categorized with moderate fatty liver and 41 patients (37.5%) with severe fatty liver. Frequencyof carotid lesions was noted in 108 (56.3%) patients, while the remaining 84 (43.8%) did not exhibit such lesions, as shown in (Tab.2). The association among patients with and without carotid lesions with respect to age group, gender, BMI, smoking status, and comorbidities such as hypertension and diabetes was taken out as shown in (Tab.3).

Among 108 patients with carotid lesions, CIMT > 1 was observed in 67 (34.9%) patients while 41 (21.4%) patients demonstrated carotid plaque on ultrasound. These carotid lesions were causing variable severity of carotid stenosis in 33 (30.6%) patients while no stenosis was observed in 75 (69.4%) patients, as shown in (Tab.4).

Variables		Mean ± SD%
Age (years)		43.18± 10.02 (18-60years)
Weight (kg)		76.97±11.28 (kg)
Height (m)		1.68 ± 0.08 (m)
BMI (kg/m^2)		27.26 ± 4.28 (kg/m^2)
Gender	Male	89(46.4%)
	Female	103(53.6%)
Hypertension	Yes	79(41.1%)
	No	113(58.9%)
Diabetes mellitus	Yes	51(26.6%)
	No	141(73.4%)
Smoking status	Smokers	69(35.9%)
	Non-smokers	123(64.1%)

Table 1: Demographic details of patients with NAFLD (n=192).

Grades of Fatty Liver (%)	Number of patients (%)	Carotid Lesion (%)	
		Yes	No
Grade I (Mild)	79(41.1%)	49 (25.5%)	30 (15.6%)
Grade II (Moderate)	72(37.5%)	34 (17.7%)	38 (19.8%)
Grade III (Severe)	41(21.4%)	25 (13.0%)	16 (8.3%)

Table 2: The frequency of Grades of fatty liver and Carotid lesions (n= 192).

Variables		Carotid lesion		p value
		Yes n (%)	No n (%)	
Age group	18 -40	46 (24.0%)	38 (19.8%)	0.714
(years)	> 40	62 (32.3%)	46 (24.0%)	
Gender	Male	47 (24.5%)	42 (21.9%)	0.372
	Female	61 (31.8%)	42 (21.9%)	
BMI (kg/m^2)	Normal	14 (7.3%)	10 (5.2%)	0.210
	Overweight	47(24.5%)	47 (24.5%)	
	Obese	47 (24.5%)	27 (14.1%)	
Hypertension	Yes	47 (24.5%)	32 (16.7%)	0.449
	No	61 (31.8%)	52 (27.1%)	
Diabetes mellitus	Yes	29 (15.1%)	22 (11.5%)	0.918
	No	79 (41.1%)	62 (32.3%)	
Smoking status	Smokers	40 (20.8%)	29 (15.1%)	0.719
	Non smokers	68 (35.4%)	55 (28.6%)	

Table 3: Stratification by demographics, and comorbidities with carotid lesions (n= 192).

Types of Carotid Lesions		Grade of Fatty Liver			Total
		Grade I	Grade II	Grade III	
CIMT> 1mm		42 (62.7%)	20 (29.8%)	5 (7.5%)	67
Carotid Plaque		7 (17.1%)	14 (34.1%)	20 (48.8%)	41
Severity of Carotid Stenosis	No stenosis	49 (45.4%)	21 (19.4%)	5 (4.6%)	75
	< 50% stenosis	0	8 (7.4%)	11 (10.2%)	19
	≥ 50% stenosis	0	5 (4.6%)	9 (8.4%)	14

Table 4: Descriptive Analysis of the Carotid lesions according to Grades of fatty liver (n= 108).

Discussion

Metabolic associated fatty liver disease (NAFLD) has emerged as a global public health concern due to its association with genetic, socioeconomic, and lifestyle variables, as well as metabolic syndromes that leads to increased risk of cardiovascular dysfunction, ischemic heart diseases, peripheral vascular disease, cardiovascular mortality.[5,20,21] This study was designed to assess the frequency of carotid lesions in adult patients with an ultrasound diagnosis of uncomplicated metabolic associated fatty liver disease (MAFLD) as mentioned in the literature that values of CIMT are reliable to detect early atherosclerosis and also to predict the ongoing atherosclerosis process in the body.[4,11,20]

Carotid duplex ultrasound is easily available non-invasive imaging modality to measure the CIMT and to assess carotid stenosis, that ultimately help in early diagnosis of atherosclerosis and considered as an independent predictor of cardiovascular risk. That s why it is widely used to evaluate the severity of carotid atherosclerosis in clinics due to its advantages like radiation free, safe, convenient and painless modality.[11]

The patients in the current study showed a cluster of abnormalities related to metabolic disorders like obesity, diabetes mellitus and hypertension, like in previous studies.[4,12,21,22] In this study, the majority of patients were >40 years of age and the frequency of carotid lesions was increased as age increased which is comparable to the studies.[3,20,21] In this study, women had more carotid lesions than men. These observations agreed with studies that showing metabolic syndrome have a stronger effect on cardiovascular dysfunction among women than men.[3,22]

Our study showed carotid lesions in 29 diabetes participants only. Multiple studies were done to assess the link between MAFLD, diabetes and carotid lesions because hepatic steatosis is extremely common in people with diabetes. Most studies reported that hepatic steatosis didn t demonstrate link with carotid atherosclerosis[3,5] showing agreement with our findings but few studies supported the relationship between MAFLD and increased CIMT.[23] Possible explanations for this variation may include the technique for detecting fatty liver (ultrasound, CT, MR Spectroscopy), different population/ethnic disparities or sample size. Our findings are consistent with those studies which have supported the association between hepatic steatosis and increased CIMT.[3,10,17,24] The current study showed increased CIMT in 34.9% participants and carotid plaque in 21.4% participants which were causing carotid stenosis in 30.6% (17.6% in <50% vs. 13.0% in ≥50%) participants. These results are comparable to a study[17] done on Chinese people of ≥ 40 year-old to investigatethe connection between ultrasound diagnosed hepatic steatosis and carotid artery disease found that those with NAFLD had a greater incidence of increased CIMT (30% vs. 21.1%), carotid stenosis (12.9% vs. 4.6%) and carotid plaque (21.9% vs. 15.0%) as compared to individuals without NAFLD. A meta-analysis conducted by Khoshbatenet al[5] on 59 observational studies has shown link of NAFLD with higher CIMT and higher incidence of carotid plaque. The study done on 98 diabetes participants by Zhen et al[11] found no statistical difference in CIMT between no NAFLD and mild NAFLD participants while there was increase in CIMT in participants with moderate to severe NAFLD, as seen in our study which showed more intimal thickening as carotid plaque (CIMT ≥ 1.5mm) in grade III fatty liver. He also didn t found significant differences in PSV among different grades of NAFLD but in contrast to this, our study showed carotid stenosis with variation in PSV during different grades of hepatic steatosis. These variations may be due to different population and insufficient sample size so further research is needed to refine/confirm these results. Elaborating the mechanism by which MAFLD lead to formation of carotid lesions is beyond the scope of this study. This study suggests that if hepatic steatosis

found incidentally then search for carotid lesions but if it is associated with increased CIMT (≥ 1 mm) or carotid plaque then an assessment for other silent arterial lesions should be recommended. Although numerous studies have shown that increased CIMT is associated with increased risk of stroke, myocardial infarction and peripheral vascular disease but only few studies have done to show the frequency of carotid plaque. So now it is necessary to study the influence of MAFLD on carotid plaque and effect on PSV in the future research.

This study had several limitations. First, due to the cross-sectional design, the study was unable to assess the temporal nature of the link between NAFLD and carotid lesions. Second, the ultrasonography used to diagnose NAFLD had lower sensitivity than a liver biopsy, which may have biased the results about the disease's frequency. In the end, the individuals who participated could not be considered representative of the whole Pakistani population because they were all from a single center. Further and multicenter studies as well as clinical trial focusing on whether the management of MAFLD can result in a reduced risk of cardiovascular disease are warranted.

Conclusion

This study concluded that the carotid lesion is highly prevalent in patients with uncomplicated metabolic associated fatty liver disease. Metabolic associated fatty liver disease may be a predictor of early carotid atherosclerosis, with carotid lesions serving as surrogate indicators. Maintaining a healthy lifestyle and managing the condition over the long term are essential for both preventing and treating MAFLD.

Conflict of Interest: None.

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