Nonalcoholic Fatty Liver Disease Is Associated With Arterial Distensibility and Carotid Intima-Media Thickness: (from the Multi-Ethnic Study of Atherosclerosis)

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Nonalcoholic fatty liver disease (NAFLD) is considered a potential independent risk factor for cardiovascular disease (CVD). The Multi-Ethnic Study of Atherosclerosis cohort enrolled 6,814 adults without previous CVD. We excluded 2,692 participants who had missing variables, were heavy drinkers, or history of steroid use and/or chronic liver disease. NAFLD was defined using noncontrast cardiac CT and a liver/spleen Hounsfield Unit attenuation ratio <1. Ultrasound-measured carotid arterial compliance and stiffness, was expressed as distensibility coefficient and Young's modulus. Common and internal carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) >0 were used as markers of subclinical CVD. A multivariate robust linear regression and logistic regression analysis were done to evaluate the association of NAFLD and this subclinical CVD markers. Our analysis of 4,123 participants showed 55% were female with a mean age of 63 (±10) years, 39% white, 10% Chinese, 28% black, and 23% were Hispanic. The prevalence of NAFLD was 17% (n = 729). Patients with NAFLD had higher distensibility coefficient and higher CIMT. Multivariate linear regression analysis showed the presence of NAFLD was associated with both the common carotid and internal carotid IMT and logCAC. Logistic analysis showed an independent association with CAC > 0 (odds ratio [OR] 1.44 95% confidence interval [CI] 1.18, 1.75) and CIMT > 1 mm (OR 1.30 95% 1.08, 1.56). When stratified by race the association with CIMT > 1 mm was significant in whites (OR 1.37 95% 1.00, 1.90) and Hispanic (OR 1.53 95% 1.08, 2. 17) and CAC > 0 was significant in Hispanics (OR 1.52 95% 1.06, 2.19). In conclusion, NAFLD is modestly associated with carotid IMT and coronary artery calcification in a multiethnic population. **(Am J Cardiol 2019;124:534−538)**

Nonalcoholic fatty liver disease (NAFLD) is considered an emerging disease globally and a leading cause of chronic liver disease in the western world, with a prevalence in the general adult population of approximately 15% to 30% and a steady increase to above 70% in patients with obesity or type 2 diabetes.[1−3] NAFLD is increasingly recognized as linked with increased cardiovascular disease (CVD) risk[4] and events.[1,4] In fact, the most common cause of death in patients with NAFLD is CVD.[1] It is unclear if the relation between clinical CVD and NAFLD extends to early atherosclerosis or subclinical disease. Such an association could provide insight regarding the higher risk of clinical CVD events in those with NALFD. We hypothesized that NAFLD was associated with arterial stiffness, carotid intima-media thickness (CIMT), and other markers of subclinical CVD in an asymptomatic population across different ethnic groups.

Methods

Multi-Ethnic Study of Atherosclerosis (MESA) is an observational cohort of 6,814 men and women aged 45 to 84 years without known CVD at the time of enrollment. White, Black, Chinese, and Hispanic patients were enrolled at 6 different US field centers (Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New

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York City, New York; and St. Paul, Minnesota) from July 2000 through September 2002. The MESA study design has been described in detail previously.[5] The study was approved by the institutional review board of each site, and all participants gave written informed consent.

A total of 4,384 patients had an adequate noncontrast cardiac CT imaging to diagnose fatty liver. We excluded 261 patients with a history of heavy alcohol use (>14 drinks/week for men and >7 drinks/week for women), known cirrhosis, oral corticosteroid, or amiodarone use.

CIMT images were obtained using B-mode sonography at the right and left common carotid artery and measured 1 cm starting from the bulb. Technicians, trained at Tufts Medical Center, at each MESA study site performed B-mode ultrasonography of the near and far walls of the common carotid artery for both the right and left arteries.[6]

Carotid artery distensibility coefficient (DC) was calculated after visualization of the instantaneous waveform of the common carotid diameter using a high-resolution B-mode ultrasound. The carotid DC was calculated as: $\frac{2\Delta D}{\Delta PD_s}$. Where D_s represents the internal arterial diameter at peak systole, D_d represents the internal diameter at end-diastole, and Δp represents the difference between the brachial artery systolic blood pressure (SBP) and diastolic blood pressure measurements (pulse pressure).[7,8]

Young's elastic Modulus (YEM), the ratio of stress and circumferential strain in the arterial wall, was calculated as: $\frac{D\Delta P}{\Delta Dh}$ where Dd is the internal arterial diameter at end-diastole, h is the arterial wall thickness at end diastole (external carotid artery diameter minus internal carotid artery diameter).[9] YEM and DC are inversely related; thus, increased arterial stiffness corresponds to a lower DC and a higher YEM. Reproducibility measurements were performed by a single reader with 25 blinded, replicate images as previously described.[7–9]

Details of the MESA scanning protocol have been reported previously.[10] CAC was measured with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, New York), or a multidetector CT (Baltimore, Forsyth County, St. Paul) at baseline. patients were scanned twice, and mean CAC (Agaston) score was calculated and used for all analyses.[11] All images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute, Torrance, California). We defined subclinical atherosclerosis as CAC > 0.[12]

Details of the liver fat measurement within MESA have been previously reported.[10] Baseline cardiac CT scans were utilized to measure hepatic and splenic attenuation values (Hounsfield units) using a region of interest of ≥100 mm^2 in area. Two regions in the right hepatic lobe and one in the spleen were measured. The liver/spleen attenuation ratio was calculated using the mean of the hepatic measurements divided by the splenic attenuation value. NAFLD was defined as liver/spleen attenuation ratio <1.

All the information on demographics, medical history, cigarette smoking, and alcohol use were collected at the baseline visit using standardized questionnaires, as previously described.[9] Waist circumference was measured at the umbilicus. Body mass index (BMI) was calculated as weight in kilograms divided by height divided in meters squared. Using an automated sphygmomanometer (Critikon, Tampa, Florida), SBP and diastolic blood pressure were measured 3 times and the mean of the last 2 measurements was used. Obesity was defined as BMI ≥ 30 kg/m^2. Metabolic syndrome was defined by the American Heart Association/National Heart, Lung, and Blood Institute criteria.[13]

A central laboratory (Fairview-University Medical Center, Minneapolis, Minnesota) measured levels of total and high-density lipoprotein cholesterol, and triglycerides after a 12-hour fast. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. High sensitivity c-reactive protein (HsCRP) was measured using a particle-enhanced immunonepholometric assay on the BNII nephelometer (Dade-Behring, Inc., Deerfield, Illinois) 28 at the University of Vermont, Burlington, Vermont.

Baseline characteristics of study subjects were compared by the presence or absence of NAFLD. We used multivariate robust linear regression models to study the cross-sectional linear association between NAFLD and CIMT (mm), DC (10^{-3} mm Hg^{-1}) and logCAC. A logistic regression analysis was also conducted for the association between NAFLD and CIMT > 1 mm, CAC > 0 and quartiles of DC (Q4 vs Q1). For all regression analyses, a hierarchical model approach was used, adjusting first for age, gender, and ethnicity and then simultaneously adjusting for other confounding factors including SBP, fasting glucose, use of lipid lowering medications, antihypertensive use, Low-density lipoprotein cholesterol, cigarette smoking, and C-reactive proteins. The logistic regression models were stratified by ethnicity and estimates were calculated for each ethnicity category.

All analyses were performed using STATA version 11.2 (Stata Corp, College Station, Texas).

Results

The characteristics of the study population stratified by the presence/absence of NAFLD are shown in Table 1. The prevalence of NAFLD was significantly different across the ethnic groups, with a predominance in the Hispanics, whereas Chinese Americans had the least prevalence. Patients with NAFLD had higher BMI, waist circumference, blood pressures, cholesterol, and prevalence of CAC > 0. Similarly, NAFLD subjects had higher CIMT and stiffer arteries evidenced by the lower DCs and the Young's elastic Modulus.

Our multilevel analysis showed the presence of NAFLD was linearly associated with both the common carotid and internal carotid IMT and CAC. From the step-wise logistic analysis NAFLD was independently associated with CAC > 0 and CIMT > 1 mm, see Tables 2 and 3. We also noted that the DC showed a linear association with NAFLD when adjusted for confounding variables, this association was however attenuated after adjusting for C-reactive protein.

Discussion

The results of our cross-sectional analysis from this multiethnic cohort demonstrates that the presence of NAFLD is associated with CIMT, arterial distensibility, and coronary calcifications. All of which are established makers of subclinical atherosclerosis.

Table 1
Baseline characteristics of study population

Clinical, anthropometric, and biochemical Characteristics	Overall (n = 4,123)	Nonalcoholic fatty liver disease		p Value
		Yes (n = 729)	NO (n = 3,394)	
Mean age, (years)	63(10)	61(10)	63(11)	0.001
Female	55%	53%	56%	0.18
White	39%	34%	40%	
Chinese American	10%	11%	9%	
Black	28%	19%	31%	
Hispanic	23%	36%	20%	<0.001
Never smoker	53%	55%	52%	
Current smoker	35	33%	36%	
Former smoker	12	12%	12%	0.245
Body mass index (kg/m^2)	28 ± 5	31 ± 5	28 ± 5	<0.001
Waist circumference(cm)	98 ± 13	105 ± 13	97 ± 14	<0.001
Systolic blood pressure(mm Hg)	127 ± 21	130 ± 21	127 ± 22	0.002
Diastolic blood pressure(mm Hg)	72 ± 10	72 ± 10	74 ± 11	<0.001
Hypertensive	47%	53%	45%	<0.001
Hypertensive medications	39%	45%	38%	<0.001
Baseline heart rate (bpm)	63 ± 10	65 ± 10	63 ± 10	<0.001
LDL-cholesterol (mg/dl)	117 ± 31	118 ± 31	115 ± 31	0.029
HDL-cholesterol(mg/dl)	51 ± 15	45 ± 12	52 ± 15	0.001
Triglycerides(mg/dl)	132 ± 93	180 ± 149	122 ± 72	<0.001
Diabetics	13%	21%	11%	<0.001
Fasting glucose(mg/dl)	98	108	95	<0.001
Lipid lowering medication	16%	16%	17%	<0.651
Coronary artery calcification > 0	50%	53%	49%	0.071
Coronary artery calcification > 100	23%	24%	22%	0.151
Distensibility coefficient, 10^{-3} mm Hg^{-1}	2.4(1.1)	2.4 (0.9)	2.48 (1.1)	<0.001
Young's elastic modulus, (mm Hg)	1301(±612)	1299(±618)	1310(±580)	0.035
Common carotid intima-media thickness(mm)	0.88(±0.2)	0.88(±0.18)	0.87(±0.2)	0.003
Internal carotid intima-media thickness(mm)	1.08(0±.6)	1.10(±0.6)	1.07(±0.6)	0.887
Internal carotid IMT > 1	37%	41%	37%	0.05

Our findings support previous studies that demonstrated significant relations between NAFLD and subclinical CVD.[14–19] Although there is increasing evidence of the association between NAFLD and CIMT and arterial stiffness, the association with CAC has been mixed. Because some studies have demonstrated increased burden of CAC in NAFLD patients' independent of traditional risk factors,[14–18] others argued otherwise.[20,21] In a previous subgroup analysis of MESA, NAFLD was not associated with CAC among a cohort of black and white subjects from a single field center in North Carolina.[20] Compared with our study, however, their sample was small (n = 398). Another study from the Coronary Artery Risk Development in Young Adults Study, reported no association between NAFLD and CAC in 2,424 white and black patients.[21] However, this population was younger. Recently however, Al Rifai et al demonstrated that NAFLD is associated with increased inflammation and CAC independent of traditional risk factors, obesity, and metabolic syndrome. They also showed a graded association between obesity, metabolic

Table 2
Robust regression of liver fat and subclinical disease/distensibility coefficient/young elastic modulus

	Internal carotid IMT (β-coefficient)	Common carotid IMT (β-coefficient)	LogCAC (β-coefficient)	Distensibility coefficient, 10^{-3} (β-coefficient)	Young's elastic modulus (β-coefficient)
Model 1	0.037	0.010	0.384	−0.036	30.51
	(0.005-0.069)*	(−0.004 to 0.024)	(0.29-0.47)***	(−0.111 to 0.039)	(−8.97 to 69.99)
Model 2	0.063	0.024	0.320	−0.137	43.77
	(0.030-0.096)***	(0.013-0.040)***	(0.14-0.50)**	(−0.199 to 0.075)***	(5.38-82.16)*
Model 3	0.042	0.015	0.183	−0.068	13.81
	(0.008-0.076)*	(0.003-0.030)*	(−0.001 to 0.38)*	(−0.125 to 0.004)*	(−24.71 to 52.32)
Model 4	0.035	0.013	0.186	−0.060	15.13
	(0.001-0.069)*	(0.001-0.025)*	(−0.005 to 0.371)	(−0.120 to 0.0012)	(−22.38-56.54)

*p <0.05, **p <0.005, ***p <0.001.

Model 1: unadjusted Model 2: adjusted for age, gender, ethnicity. Model 3: model 2 +Systolic blood pressure, fasting glucose, lipid lowering medications, hypertension medications, Low Density Lipoprotein-Cholesterol, cigarette smoking. Model 4: Model 3 + C-reactive protein.

Table 3
Logistic regression of liver fat and subclinical disease markers

	Common carotid IMT > 1 mm	Internal carotid IMT > 1 mm	CaC>0	Distensibility coefficient Q4 vs Q1
Model 1	0.91	1.25	1.16	0.96
	(0.74-1.12)	(1.06-1.47)**	(0.99-1.36)	(0.79-1.16)
Model 2	1.07	1.47	1.54	0.76
	(0.87-1.31)	(1.24-1.74)***	(1.28-1.85)***	(0.62-0.93)**
Model 3	0.91	1.22	1.41	0.90
	(0.72-1.13)	(1.01-1.47)*	(1.18-1.75)**	(0.72-1.13)

*p <0.05, **p <0.005, ***p <0.001.

Model 1: unadjusted Model 2: adjusted for age, gender, ethnicity Model 3: model 2 + systolic blood pressure, fasting glucose, lipid lowering medications, hypertension medications, Low-density lipoprotein-cholesterol, cigarette smoking, body mass index and logC-reactive protein.

syndrome, and NAFLD with inflammation and CAC.[12] In our study, we noted there was an association between the presence of NAFLD and increased CIMT as well as increased arterial stiffness measured by their DCs. Similarly, other studies across the globe have presented evidence of the association between NAFLD and both CIMT and arterial stiffness.[19,22–24] It is however relevant to note that these associations are different across ethnic populations in a subanalysis.

A recent study from Europe noted a decrease in the severity of NAFLD was is independently associated with reduced CIMT progression in an 18-month study.[25] This further establishes the role of NAFLD in subclinical CVD progression. From another large cohort study, persistent NAFLD was associated with an increased risk of subclinical carotid atherosclerosis development.[26] The authors elucidated that this association was explained by metabolic factors that act as potential mediators of the effect of NAFLD. They also noted that markers of liver fibrosis were associated with subclinical carotid atherosclerosis. They found that the risk of subclinical carotid atherosclerosis was higher in participants with high NAFLD fibrosis score, FIB-4 scores, or levels of gamma-glutamyl transferase at baseline.[26]

NAFLD has been linked with insulin resistance, obesity, and metabolic syndrome; conditions known to be associated with CVD and subclinical atherosclerosis.[19,22] Because the associations of NAFLD and subclinical atherosclerosis have not been well characterized; some investigators have argued that the association is an epiphenomenon as opposed to being a mediator in the development of CVD.[27] This relation further is complicated by the known ethnic differences in the prevalence of both NAFLD and metabolic risk factors.[28] The rising evidence of the association between NAFLD and subclinical CVD may suggest that NAFLD is not merely a marker of CVD, but also may be actively involved in its pathogenesis.[22] It is important to note that a recent Mendelian randomization study in 2 large European cohorts argued that there was no evidence for a causal relation between NAFLD and CVD examining genetic variants in the PNPLA3 and TM6SF2 genes. Santos et al argued that it may be reasonable to speculate that the association between NAFLD and CVD is mediated by the classical risk factors for atherosclerosis and unmeasured confounders, although more data are needed to confirm the role of genetic risk in this association.[29]

Our study provides further evidence of the association between NAFLD and subclinical atherosclerosis. It also provides hints that this relation may be different across different ethnic populations.

The main strength of this analysis is the ethnic diversity of the MESA cohort. Most previous studies evaluating the impact of NAFLD on subclinical atherosclerosis have been performed in ethnically homogeneous cohorts.

This study has a few limitations. Firstly, we have presented a cross-sectional data from the MESA cohort, thus temporality cannot be inferred. Secondly, NAFLD was diagnosed using CT which has limited specificity compared to using histology or magnetic resonance spectroscopy.[30]

In conclusion, NAFLD is independently associated with markers of subclinical atherosclerosis in a multiethnic population. This study reaffirms the role of NAFLD in early atherosclerosis and endothelial dysfunction. This may provide an opportunity to explore strategies for early screening for subclinical CVD and targeted aggressive strategies for prevention. Further research looking at the longitudinal association of NAFLD with subclinical atherosclerosis is imperative and the role of ethnic diversity in the association should be explored.

Disclosures

The authors have no conflicts of interest to disclose.

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