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The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA)

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ABSTRACT

Introduction: We characterized the association of 3 metabolic conditions – obesity, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) – with increased inflammation and subclinical atherosclerosis.

Methods: We conducted cross-sectional analysis of 3976 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) with adequate CT imaging to diagnose NAFLD. Obesity was defined as BMI $\geq$ 30 kg/m^2, metabolic syndrome by AHA/NHLBI criteria, and NAFLD using non-contrast cardiac CT and a liver/spleen attenuation ratio (L/S) < 1. Increased inflammation was defined as high sensitivity C-reactive protein (hsCRP) $\geq$2 mg/L and subclinical atherosclerosis as coronary artery calcium (CAC) > 0. We studied the association of a stepwise increase in number of these metabolic conditions (0–3) with increased inflammation and CAC, stratifying results by gender and ethnicity.

Results: Mean age of participants was 63 (±10) years, 45% were male, 37% white, 10% Chinese, 30% African American, and 23% were Hispanic. Adjusting for obesity, metabolic syndrome and traditional risk factors, NAFLD was associated with a prevalence odds ratio for hsCRP $\geq$2 mg/L and CAC >0 of 1.47 (1.20–1.79) and 1.37 (1.11–1.68) respectively. There was a positive interaction between female gender and NAFLD in the association with hsCRP $\geq$2 mg/L (p = 0.006), with no interaction by race. With increasing number of metabolic conditions, there was a graded increase in prevalence odds ratios of hsCRP $\geq$2 mg/L and CAC >0.

Conclusion: NAFLD is associated with increased inflammation and CAC independent of traditional risk factors, obesity and metabolic syndrome. There is a graded association between obesity, metabolic syndrome, and NAFLD with inflammation and CAC.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is an important condition with an estimated worldwide prevalence of 20% [1]. There is increasing recognition that NAFLD is associated with cardiovascular disease (CVD). Cross-sectional epidemiologic studies have shown NAFLD to be linked to a higher prevalence of CVD independent of traditional risk factors [2]. NAFLD has also been associated with an increased risk of CVD events in patients with type 2 diabetes independent of obesity, other metabolic syndrome components, and traditional risk factors [3]. Indeed, the most common cause of death among individuals with NAFLD is CVD [1].

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In addition to manifest CVD, NAFLD has been associated with increased inflammation [4–7] and subclinical atherosclerosis [8–12] both of which are well known predictors of CVD in asymptomatic patients [13–19]. NAFLD has also been closely associated with obesity and metabolic syndrome – two conditions known to be associated with CVD, subclinical atherosclerosis, and systemic inflammation [20–24]. The associations of these metabolic conditions with inflammation and subclinical atherosclerosis have not been well characterized. As a result, some investigators have contended that NAFLD is an epiphenomenon as opposed to a mediator in the development of CVD [25]. The relationship between NAFLD, obesity, metabolic syndrome, and CVD is further complicated by the known ethnic differences in the prevalence of both NAFLD and metabolic risk factors [26].

We hypothesized that NAFLD would be associated with high sensitivity C-reactive protein (hsCRP) as well as coronary artery calcium (CAC) independent of obesity and metabolic syndrome, and that this relationship would be similar across ethnic groups. Furthermore, we hypothesized that there would be a graded association between the number of these metabolic conditions present and the prevalence of high hsCRP and CAC.

2. Methods

2.1. Study design

MESA is an observational cohort of 6814 men and women aged 45–84 years without known CVD at the time of enrollment. White, Black, Chinese, and Hispanic individuals were enrolled at six different US field centers (Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York City, New York; and St. Paul, Minnesota) from July 2000 through September 2002. The MESA study design has been described in detail previously [27]. The study was approved by the institutional review board of each site, and all participants gave written informed consent.

A total of 4384 individuals had an adequate non-contrast cardiac CT imaging to diagnose fatty liver. Compared to those who were excluded for inadequate CT imaging, our population was in general older, more likely to be female and had a higher prevalence of obesity, diabetes and hypertension. Those with adequate imaging were also more likely to be black and Hispanic but less likely to be Chinese. We excluded 285 individuals for a history of heavy alcohol use (>14 drinks/week for men, > 7 drinks/week for women), known cirrhosis, oral corticosteroid or amiodarone use. An additional 123 individuals were excluded for missing covariates. The final population consisted of 3976 participants.

2.2. HsCRP measurement

HsCRP was measured at the baseline examination using a particle-enhanced immunonepholometric assay on the BNII nephelometer (Dade-Behring, Inc., Deerfield, IL) [28] at the University of Vermont, Burlington, Vermont. We defined increased inflammation as hsCRP $\geq$2 mg/L [29].

2.3. CAC score measurement

Details of the MESA scanning protocol have been reported previously [30]. All participants underwent CAC scoring using computed tomography (CT) as part of the baseline examination. 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). Individuals were scanned twice, and mean CAC (Agatston) score was calculated and used for all analyses [31]. All images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute, Torrance CA). We defined subclinical atherosclerosis as CAC >0.

2.4. Liver fat assessment

Details of the liver fat measurement within MESA have been previously reported [26,32]. Briefly, baseline cardiac CT scans were utilized to measure hepatic and splenic attenuation values (Hounsfield Units) using a region of interest of $\geq$100 mm^2 in area. Two regions in the right hepatic lobe and one in the spleen were measured. The liver/spleen (L/S) attenuation ratio was calculated using the mean of the hepatic measurements divided by the splenic attenuation value. NAFLD was defined as L/S attenuation ratio <1.

2.5. Risk factor measurement

Information pertaining to demographics, medical history, cigarette smoking, and alcohol use was collected at the baseline visit using standardized questionnaires, as previously described [27]. 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, FL), systolic and diastolic blood pressure (SBP & DBP) were measured 3 times and the mean of the last two measurements was used. A central laboratory (Fairview-University Medical Center, Minneapolis, MN) measured levels of total and high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) after a 12-h fast. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Obesity was defined as BMI $\geq$30 kg/m^2. Metabolic syndrome was defined by the American Heart Association/National Heart, Lung, and Blood Institute criteria as at least 3 of the following: waist circumference $\geq$102 cm for men and $\geq$88 cm for women; TG $\geq$ 150 mg/dL or drug treatment for elevated TG; HDL-C < 40 mg/dl for men and <50 mg/dL for women or drug treatment for reduced HDL-C; SBP $\geq$130 mmHg or DBP $\geq$85 mmHg or drug treatment for hypertension; and fasting blood glucose level $\geq$100 mg/dL or drug treatment for elevated glucose [33].

2.6. Statistical analysis

We described baseline characteristics by presence or absence of NAFLD. We used logistic regression models to study the cross-sectional association between NAFLD and the outcomes of hsCRP $\geq$2 mg/L and CAC >0. The first model was adjusted for age, gender, and ethnicity as well as other CVD risk factors not included in the metabolic syndrome: smoking status, LDL-cholesterol, use of lipid-lowering medication, and level of education. In order to assess the strength of association for NAFLD independent of obesity and metabolic syndrome, a second logistic regression model was performed adjusting for obesity and components of the metabolic syndrome (each individual component coded as binary) in addition to the covariates used in model 1. These two logistic regression models were stratified by ethnicity and gender and estimates were calculated for each ethnicity or gender category. Formal multiplicative interaction testing was also performed for the ethnicity and gender variables with NAFLD. As a sensitivity analysis we adjusted for overweight rather than obesity and obtained unchanged results.

In order to assess a possible gradient-response, logistic regression (Model 1) was used to examine the association of a stepwise increase in the number (0–3) of metabolic conditions (NAFLD, obesity, metabolic syndrome) with increased inflammation and subclinical atherosclerosis. We also calculated the p-value for linear trend of the prevalence odds ratios.