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BRIEF ARTICLES

Carotid lesions in outpatients with nonalcoholic fatty liver disease

Stefano Ramilli, Stefano Pretolani, Antonio Muscari, Barbara Pacelli, Vincenzo Arienti

Stefano Ramilli, Stefano Pretolani, Vincenzo Arienti, Department of Internal Medicine, Maggiore Hospital, 40133 Bologna, Italy
Antonio Muscari, Department of Internal Medicine, Aging and Nephrological Diseases, University of Bologna, 40138 Bologna, Italy
Barbara Pacelli, Epidemiology Unit, Local Health Authority, 40124 Bologna, Italy
Author contributions: Ramilli S, Pretolani S and Arienti V designed the study; Ramilli S performed carotid ultrasound assessments; Pacelli B performed statistical analysis of the data; Ramilli S , Pretolani S , Pacelli B and Muscari A wrote the paper; Muscari A and Arienti V critically revised the manuscript.
Supported by (in part) A grant from Gruppo Italiano di Ultrasonologia in Medicina Interna (GIUMI)
Correspondence to: Antonio Muscari, MD, Professor, FESC, Department of Internal Medicine, Aging and Nephrological Diseases, University of Bologna, S.Orsola-Malpighi Hospital, Via Albertoni 15, 40138 Bologna, Italy. antonio.muscari@unibo.it
Telephone: +39-51-6362280 Fax: +39-51-6362210
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Abstract

AIM: To ascertain whether carotid lesions are more prevalent in outpatients with incidental findings of nonalcoholic fatty liver disease (NAFLD) at abdominal ultrasound (US).

METHODS: One hundred and fifty-four consecutive outpatients (age range 24-90 years, both sexes) referred by general practitioners for abdominal US, and drinking less than 20 g alcohol/day, underwent carotid US for an assessment of carotid intima-media thickness (c-IMT) and carotid plaque prevalence. Hepatic steatosis, visceral fat thickness and subcutaneous fat thickness were also assessed at ultrasonography.

RESULTS: Higher c-IMT values were found in the presence of NAFLD (90 patients), even after adjustment for indices of general and abdominal obesity and for the principal cardiovascular risk factors (0.84 ± 0.10 mm *vs* 0.71 ± 0.10 mm, $P < 0.001$). The prevalence of carotid plaques was 57.8% in the patients with NAFLD *vs* 37.5% in the patients without this condition ($P = 0.02$). The adjusted relative risk of having carotid plaques for patients with NAFLD was 1.85 (95% CI: 1.33-2.57, $P < 0.001$).

CONCLUSION: An incidental finding of hepatic steatosis may suggest the presence of silent carotid atherosclerotic lesions.

Key words: Hepatic steatosis; Nonalcoholic fatty liver disease; Metabolic syndrome; Carotid atherosclerosis; Plaque; Intima-media thickness

Peer reviewer: Emmet B Keeffe, MD, Professor, Chief of Hepatology, Medical Director, Liver Transplant Program, Program Director, Gastroenterology Fellowship, Stanford University Medical Center, 750 Welch Road, Suite 210, Palo Alto, CA 94304, United States

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INTRODUCTION

Hepatic steatosis is a feature of the metabolic syndrome[1,2], a condition associated with a high cardiovascular risk and, in particular, an increased prevalence of carotid lesions[3]. In the last few years several studies have assessed the association between hepatic steatosis and carotid atherosclerosis. Some case-controlled and cross-sectional studies[4-8] showed a relationship between nonalcoholic fatty liver disease (NAFLD) and carotid intima-media thickness (c-IMT), an early independent predictor of cardiovascular events[9-11]. In addition, other studies also showed a relationship with the presence of more advanced atherosclerotic lesions in the carotid arteries[12-14]. However, the only study performed so far in the general population (4222 subjects) did not find any independent association between hepatic steatosis and c-IMT, showing an association with plaque prevalence only[15]. The lack of concordance of these results may be related to non-standardized measurement methods and to the use of low frequency linear ultrasound (US) probes.

A possible relationship between hepatic steatosis and carotid lesions might have important practical consequences, considering the frequent incidental finding of hepatic steatosis in subjects undergoing abdominal US for any reason. In these subjects, an US

assessment of carotid arteries might also be advisable.

Thus, we have prospectively examined a random group of consecutive outpatients undergoing abdominal US to establish whether those with NAFLD had an increased prevalence of early or advanced carotid lesions. The study was performed following the Mannheim Consensus[16], which proposed a standardized method for c-IMT measurement.

MATERIALS AND METHODS

Patients

From December 2006 to February 2007, we performed a cross-sectional study on 186 consecutive Caucasian outpatients, referred to our centre by general practitioners to perform an abdominal US assessment.

Body weight was measured in light clothing, without shoes, to the nearest 0.5 kg. Height was measured at the nearest 0.5 cm. Body mass index (BMI) was calculated as kilograms divided by square meters. Hypertension was diagnosed for values > 140/90 mmHg in non-diabetics and > 130/80 mmHg in diabetics, or when subjects were taking anti-hypertensive drugs[17].

The design of the study did not allow any biochemical measurements, since many US assessments were performed in the late morning and some patients were not fasting. However, demographic characteristics (sex and age), some cardiovascular risk factors (smoking, history of diabetes and/or dyslipidemia) and possible causes of steatosis [alcohol consumption, anti-retroviral drugs, tamoxifen, amiodarone, corticosteroids, jejunal-ileal bypass, inflammatory bowel diseases, hepatitis C virus (HCV), and Human Immunodeficiency virus (HIV)] were collected in a structured questionnaire. The presence of dyslipidemia or diabetes was assumed if subjects were taking lipid-lowering/antidiabetic drugs, or positively answered the questions: "do you know you have high cholesterol or triglyceride values?" and "do you know you have diabetes?". To quantify the number of cigarettes smoked, the total pack-years[18,19] was calculated: (number of cigarettes smoked daily/20) x years of smoking. Smoking was categorized into the 3 following levels: never smoked, up to 20 pack-years and more than 20 pack-years. The cut-off value of 20 corresponded to the 75th percentile of pack-years distribution excluding non-smokers.

Thirty-two patients (17%) were excluded due to significant alcohol consumption (> 20 g/d, average weekly consumption). No other exclusion criteria were utilized. Thus, our study group consisted of 154 patients (75 male, mean age 59.6 ± 14.2 years, range 24-90 years) who underwent an abdominal US assessment for the following reasons: abdominal pain (44.2%), biliary/kidney stones (5.2%), follow-up of benign cysts of the liver (24.7%), kidney (15.6%) and ovary (3.2%), and for colorectal cancer (5.8%) and hepatocellular carcinoma (1.3%) surveillance.

Ultrasound evaluation

All subjects underwent abdominal and carotid US in order to assess hepatic steatosis, visceral fat thickness (VFT), subcutaneous fat thickness (SFT) and c-IMT, and to ascertain the presence of carotid plaques. We used a Technos MP (Esaote, Italy), with convex probes (2.5-5 MHz) to scan the liver, and high frequency linear probes (7.5-13 MHz) to scan carotid arteries. All investigations were performed by two experienced operators (for abdominal and carotid US), blinded to each other regarding the respective US measurements and unaware of patients' clinical data.

Following the AGA classification of NAFLD[20], steatosis was defined as the presence of diffuse hyperechoic echotexture, bright liver[21], increased liver echotexture compared with the kidneys, vascular blurring and deep attenuation of the ultrasonic beam.

VFT and SFT were measured with the probe located 1 cm above the umbilicus, and defined as the distance between the linea alba and the anterior wall of the aorta, and as the distance between the skin and the linea alba, respectively[22,23]. VFT and SFT US measurements correlate with visceral and subcutaneous fat areas as measured by CT scan[24].

All measurements concerning c-IMT and plaques were performed according to the Mannheim Consensus[16]. Longitudinal images of both the left and right side at the level of the common carotid artery, bulb and internal carotid were obtained in each patient. The arterial wall was assessed with a high frequency linear probe with appropriate focus, frame rate and gain setting to obtain a symmetrical brightness on the near and far wall.

c-IMT was measured in the far wall of the common carotid artery, along a 15 mm section free of plaque from the bifurcation, as the distance between the leading edges of the lumen-intima and media-adventitia interfaces. Maximum rather than mean values of c-IMT were considered, and edge detection was performed manually. c-IMT measurements from the left and right side were averaged. Previous studies have shown that "normal IMT values" vary according to age and atherosclerosis-related risk factors, ranging from 0.60-0.75 mm (30-49 years) to 0.79-0.86 mm (70-79 years)[16]. Thus, values > 0.90 mm should be considered as increased in all cases.

A plaque was defined as a focal structure encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value, or having a thickness > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. The presence of plaques was evaluated in a 30 mm-long segment both in the left and right common carotid, internal carotid and bulb. Quality controls (phantom scans and proper US calibration) were performed monthly.

Statistical analysis

Analyses were performed using SPSS (14.0, Chicago, Il. USA) and Stata (8.0, StataCorp LP, Tx. USA) software. Quantitative characteristics were expressed as mean ± SD, or *n* (%). The study sample was divided into two groups according to the presence or absence of hepatic steatosis. Comparisons between groups were made by analysis of variance (ANOVA) and Kruskal Wallis' test for continuous

data, and using the χ^2 test with Yates correction for nominal data. ANOVA and Spearman's test were used to investigate the associations between c-IMT and demographic, clinical, anthropometrical and US characteristics. Multivariable analysis was performed with respect to c-IMT by means of analysis of covariance (ANCOVA). The mean scores of c-IMT, adjusted for the main risk factors (age, sex, BMI, diabetes, dyslipidemia, hypertension and smoking) were estimated in subjects with and without steatosis. To determine whether the adjusted mean scores of the two groups were significantly different, we tested the hypothesis that the steatosis coefficient was null using a multiple-partial *F* test. The assumption of parallelism was assessed by comparing a fitted model and expanded model with interaction terms with a multiple-partial *F* test. Adjusted R^2 was used to estimate the percentage of c-IMT variability explained by the model.

The adjusted relative risk of the presence of plaques associated with hepatic steatosis was assessed as prevalence ratio by the Cox regression model with equal time of follow-up assigned to all individuals and robust variance estimates, so that the calculated hazard ratio equaled the correct prevalence ratio[25]. This method is preferred in cross-sectional studies with frequent outcomes, such as in this case, to avoid the overestimation of prevalence ratios obtained by odds ratios[25]. Two-tailed tests were performed throughout and a P value < 0.05 was considered statistically significant.

RESULTS

Table 1 reports the clinical, anthropometrical and US characteristics of the population sample. No patients had chronic liver disease (except for two HCV-positive subjects), HIV-positivity, inflammatory bowel disease, abdominal surgery or received parenteral nutrition. None had taken drugs that could lead to hepatic steatosis.

Significantly higher BMI, VFT and SFT values were found in the subjects with NAFLD, who also reported a higher prevalence of dyslipidemia. Age, sex and smoking did not differ between the two groups (Table 2).

c-IMT was significantly associated with all cardiovascular risk factors, except for sex and SFT (Table 3). In univariate analysis c-IMT was also associated with NAFLD (Table 4).

In multivariable analysis, after adjustment for age, sex, BMI, smoking, hypertension, dyslipidemia and diabetes, c-IMT was still greater in the NAFLD group. The full regression model explained 46.4% of the variability of c-IMT.

The prevalence of plaques in the subjects with NAFLD was 52/90 (57.8%) *vs* 24/64 (37.5%) in those without ($P = 0.02$), which corresponded to a relative risk of 1.54; this risk even increased (1.85, $P < 0.001$) after adjustment for confounding factors (Table 4).

DISCUSSION

This study has shown that an incidental finding of NAFLD is associated with c-IMT and predicts the presence of carotid plaques in outpatients undergoing abdominal US assessment.

An association between hepatic steatosis and c-IMT has already been reported in some previous studies[4-8,12-15], and even in children[26]. In 85 healthy, non-obese, male volunteers, Targher *et al*[4] found a significant increase in c-IMT in the presence of non-alcoholic hepatic steatosis, and both conditions seemed to be due to visceral fat accumulation. In our sample, hepatic steatosis was independently associated with c-IMT, while VFT was associated with c-IMT in univariate analysis, but not in multivariable analysis. This may be explained by differences in sample composition and statistical analysis. Other studies that found an association between visceral obesity and c-IMT did not assess hepatic steatosis[24,27,28]. One study reported that the association between NAFLD and c-IMT concerned only the patients with metabolic syndrome[8]. On the other hand, two studies showed that the same relationship is absent,

Table 1 Clinical, anthropometrical and ultrasound characteristics of the study sample (n = 154)

Variable	Value
Age (yr)	59.6 ± 14.2
Gender (male)	75 (48.7)
BMI (kg/m^2)	26.1 ± 4.3
Diabetes	15 (9.7)
Hypertension	61 (39.6)
Dyslipidemia	53 (34.4)
Smoking	
Never	82 (53.3)
1-20 pack-years[1]	56 (36.4)
> 20 pack-years[1]	16 (10.4)
SFT (mm)	19.1 ± 6.3
VFT (mm)	51.6 ± 21.7
NAFLD	90 (58.4)
c-IMT (mm)	0.80 ± 0.18
Carotid plaque	76 (49.4)

Data are mean ± SD, or n (%). [1]Both current and former smokers. BMI: Body mass index; Pack-years: Packs of cigarettes smoked daily x years of smoking; SFT: Subcutaneous fat thickness; VFT: Visceral fat thickness; NAFLD: Nonalcoholic fatty liver disease; c-IMT: Common carotid intima-media thickness.

Table 2 Univariate associations of NAFLD with cardiovascular risk factors

Variable	No NAFLD (n = 64)	NAFLD (n = 90)	P value[1]
Age (yr)	60.1 ± 15.6	59.3 ± 13.2	0.72
Gender (male)	29 (45.3)	46 (51.1)	0.59
BMI (kg/m^2)	24.5 ± 3.4	27.2 ± 4.5	< 0.001
Diabetes	3 (4.7)	12 (13.3)	0.13
Hypertension	22 (34.4)	39 (43.3)	0.34
Dyslipidemia	16 (25.0)	37 (41.1)	0.05
Smoking			
Never	34 (53.1)	48 (53.3)	0.93
1-20 pack-years	24 (37.5)	32 (35.6)	
> 20 pack-years	6 (9.4)	10 (11.1)	
SFT (mm)	17.6 ± 5.2	20.2 ± 6.9	0.01
VFT (mm)	43.9 ± 16.7	57.0 ± 23.4	< 0.001

Data are mean ± SD, or n (%). [1]χ^2 test (nominal data); ANOVA or Kruskal Wallis when appropriate (continuous data).

Table 3 Univariate associations of c-IMT with cardiovascular risk factors

Variable	c-IMT		*P* value[1]
	mean ± SD (mm)	Rho	
Gender			0.27
Male	0.81 ± 0.19		
Female	0.78 ± 0.17		
Age (yr)		0.45	< 0.001
BMI (kg/m^2)		0.3	< 0.001
< 25	0.76 ± 0.18		0.02
25-30	0.82 ± 0.14		
> 30	0.86 ± 0.22		
Hypertension			< 0.001
Yes	0.88 ± 0.17		
No	0.74 ± 0.17		
Dyslipidemia			0.006
Yes	0.85 ± 0.18		
No	0.77 ± 0.17		
Diabetes			0.001
Yes	0.95 ± 0.21		
No	0.78 ± 0.17		
Smoking			0.03
Never	0.79 ± 0.18		
1-20 pack-years	0.78 ± 0.18		
> 20 pack-years	0.91 ± 0.19		
VFT (mm)		0.21	0.01
SFT (mm)		0.08	0.32

Rho: Spearman's correlation coefficient between continuous variables and c-IMT; [1]ANOVA (nominal data) or Spearman's Rho (continuous data).

Table 4 Unadjusted and adjusted associations of NAFLD with c-IMT and presence of plaque

Variable	No NAFLD (*n* = 64)	NAFLD (*n* = 90)	*P* value[1]
c-IMT (mm)	0.71 ± 0.15	0.86 ± 0.18	< 0.001
c-IMT adjusted (mm)	0.72 ± 0.10	0.84 ± 0.10	< 0.001
Carotid plaque [RR (95% CI)]	1	1.54 (1.07-2.22)	0.02
Carotid plaque adjusted [RR (95% CI)]	1	1.85 (1.33-2.57)	< 0.001

[1]ANCOVA (c-IMT) and Cox regression with constant risk period and robust variance estimate (RR of carotid plaque). Adjustments for age, sex, BMI, smoking, hypertension, dyslipidemia and diabetes. RR: Relative risk (prevalence ratio); CI: Confidence interval.

or present but largely explained by insulin resistance, in type 2 diabetic patients[29,30]. Finally, in the only large cross-sectional study to date, Volzke *et al*[15] described an independent association of hepatic steatosis with carotid plaques, but not with c-IMT. The discordance with our results might be due to the fact that these authors used low frequency (5 MHz) US probes, which are known to provide less accurate c-IMT measurements[16].

In the present study, with high frequency probes and a standardized protocol to measure c-IMT, we found that NAFLD was independently associated with both c-IMT and the presence of carotid plaques. Defining the role played by NAFLD in the formation of initial or advanced carotid lesions is beyond the scope of this study, which was only designed to ascertain whether an incidental finding of NAFLD in outpatients may suggest the search for carotid lesions. The cross-sectional design, together with the impossibility of measuring metabolic variables such as serum lipids, glucose and insulin, and to exclude with certainty the presence of HCV or HIV infection, are the main limitations of this study, and impede any assessment of causality. The lack of metabolic measurements, together with the low frequencies, may also explain why the associations of NAFLD with diabetes and dyslipidemia were borderline or not significant.

In agreement with Targher *et al*[4] it seems likely that abdominal obesity may be the common antecedent of both NAFLD and carotid atherosclerosis, with the metabolic syndrome as an intermediate. However, we previously showed that endothelial dysfunction was more prevalent in patients with NAFLD than in controls matched for age and sex and with similar features of the metabolic syndrome[31]. Moreover, in the present study the association between NAFLD and carotid lesions was independent from indicators of general and abdominal obesity, such as BMI, SFT and VFT. It thus seems possible that NAFLD may identify a subgroup of metabolic syndrome patients at higher cardiovascular risk.

In conclusion, hepatic steatosis is a marker of increased c-IMT and of the presence of carotid plaques in outpatients undergoing abdominal US. Any incidental US finding of hepatic steatosis should prompt medical practitioners not only to assess the metabolic risk, but also to consider the search for silent carotid lesions.

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) is often caused by abdominal obesity, which is also one of the main causes of insulin resistance and metabolic syndrome. The latter, in turn, is an important cardiovascular risk factor, and has been found to be associated with the presence of carotid atherosclerotic lesions. It is therefore understandable that an association may exist between NAFLD and carotid lesions.

Research frontiers

Although the association between NAFLD and carotid lesions is plausible and demonstrated, its practical implications have not been fully understood. This study highlights the possible relevance of these implications.

Innovations and breakthroughs

The association between NAFLD and early or advanced carotid lesions is not new, but in this study this association has been demonstrated for the first time in a random group of outpatients undergoing abdominal ultrasound. It is indeed in this type of patients that, not infrequently, a previously unknown hepatic steatosis is found. In the same patients an ultrasound assessment of the carotid arteries might prove particularly useful.

Applications

This study suggests that an incidental finding of hepatic steatosis may represent a new indication for performing an ultrasound assessment of the supra-aortic branches to search for silent arterial lesions.

Terminology

NAFLD is a general term including all cases of hepatic steatosis, with or without inflammation (steatohepatitis), which are not caused by alcohol abuse. It is often found associated with abdominal obesity and metabolic syndrome. Intima-media thickness (IMT) is the thickness of the two internal layers of the arterial wall, and is usually measured by ultrasound at the level of the common/internal carotid arteries. Its increase corresponds to the initial phase of the atherosclerotic process, and is associated with an increased cardiovascular risk.

Peer review

Although not novel, this is a well-conducted study that is reported quite concisely. The strengths over prior similar studies are the thorough design and the measurement of carotid intima-media thickness using the new Mannheim

consensus criteria. Moreover patients were enrolled consecutively, and pertinent demographic and clinical data were collected at the time of imaging, which was performed in a blinded fashion by experienced operators using high quality equipment.

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