Increased Carotid Intima-Media Thickness and Retinal Vascular Disorders in Patients with Non-Alcoholic Fatty Liver Disease

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Introduction: In this study we examined the association between the type of liver histology, value of carotid intima-media thickness and retinal vascular disorders in patients with Non-Alcoholic Fatty Liver Disease (NAFLD).
Material and method: We correlated the type of liver histology in 12 Non-Alcoholic Fatty Liver Disease patients with the measurements of carotid intima-media thickness evaluated by ultrasonography and the retinal vessel changes which were observed on retinal photography.
Results: The incidence of NAFLD was more increased in women (58.33%) than in men (41.66%). Dyslipidemia was detected in all 12 patients. The values of ALT were more increased than the one of ASAT. Moreover, the severity of liver findings and the degree of steatosis, necroinflammation or fibrosis were associated with the increase of carotid IMT and the occurrence of retinal vascular disorders ($p<0.001$ for all).
Conclusions: The results suggest that the type of liver histology is associated to the value of IMT and moreover to the incidence of retinal vascular disorders. Further controlled studies are needed to confirm the results.

Keywords: Non-Alcoholic Fatty Liver Disease, intima-media thickness, retinal vascular disorders

Received: 15 May 2012 / Accepted: 4 October 2012

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is nowadays considered a major health problem in developed countries. The gold standard for its diagnose remains the percutaneous liver biopsy. The manner in which liver findings in NAFLD patients are associated with the progression of atherosclerosis is still poorly understood [1].

The increase of carotid artery intima-media thickness (IMT), an early marker of atherosclerosis, in NAFLD patients has been demonstrated by several recent studies [2–5].

Retinal arterial disorders can be caused by carotid artery disease, atherosclerosis being the inciting event in the majority of cases and one of the most frequent mechanisms is embolism, usually with originating from a plaque of the carotid artery [6].

We investigated the association between the severity of liver findings, carotid IMT and retinal vascular changes in patients with NAFLD.

Material and method

Our study included 12 patients, 7 female and 5 male, mean age 49.6±2.50 (min: 44, max: 52, SD: 2.5) with NAFLD and retinal vascular changes. Patients were admitted to the Department of Gastroenterology of the County Emergency Hospital of Craiova between 2010–2011, presenting increased liver enzymes or fatty liver infiltration.

Inclusion criteria were: chronically increased liver enzymes, hepatic steatosis detected by ultrasonography, alcohol intake <20 g/day confirmed by at least one family member, no other cause of chronic liver disease (viral hepatitis B or C, autoimmune liver disease, Wilson's disease, hemochromatosis, α1-antitripsin defficiency) or drugs known to produce steatosis.

Standard laboratory procedures were used to determine blood measurements. All 12 patients underwent a percutaneous liver biopsy and the assessment of liver histology was classified according to NAFLD Activity Score = NAS (0–8). Ultrasonography of the carotid artery was performed in all patients, in order to determine the value of intima-media thickness. For the assessment of retinal vascular changes, retinal photography was performed using a non-midriatic retinal camera. The Keith-Wagener-Barker system was used to classify retinal changes.

Results

The most important clinical and laboratory findings are listed in Table I.

The incidence of NAFLD was more increased in women (58.33%) than in men (41.66%). All patients had increased levels of liver enzymes – aspartate aminotransferase (ASAT): 142±24 IU/L and alanine aminotransferase (ALT): 159±21 IU/L. Dyslipidemia was detected in all 12 patients: 8 of them had hypertriglyceridemia (66.66%, mean value: 218±46 mg/dl) and 4 of them had hypercholesterolemia (mean value: 208±26 mg/dl). Hypertension was observed in 9 patients (75%).

The biopsy showed: mild steatosis (grade 1) in 3 patients, moderate steatosis (grade 2) in 5 patients and severe steatosis (grade 3) in 4 patients. Steatosis alone was described in 5 patients, the rest of 7 patients had associated steatosis and lobular inflammation, hepatocellular ballooning or fibrosis.

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Table I. Clinical and laboratory characteristics of NAFLD patients (mean±SD)

Age (years)	49.6±2.50
BMI (kg/m^2)	28.1±2
Waist circumference (cm)	93±5
Systolic blood pressure (mmHg)	125±13.7
Diastolic blood pressure (mmHg)	70.5±5.35
Total cholesterol (mg/dl)	208±26
Triglycerides (mg/dl)	218±46
Glucose (mg/dl)	97±7
ASAT (IU/L)	142±24
ALT (IU/L)	159±21
γ GT (IU/L)	57±16
Creatinine (mg/dl)	0.6±0.4

Table II shows that the value of carotid IMT was associated to the severity of steatosis and to the degree of retinal vascular disorders (p<0.001 for all). The lowest value of carotid IMT was determined in patients with grade 1 steatosis and mild narrowing of the retinal arterioles (stage I in Keith-Wagener-Barker classification), intermediate values of IMT in cases with grade 2 steatosis, moderate narrowing of retinal arterioles and arteriovenous crossing changes (stage II in Keith-Wagener-Barker classification). The highest values of IMT were observed in patients with copper-wire, silver-wire arterioles, arteriovenous nicking (stage III in Keith-Wagener-Barker classification).

Carotid IMT was significantly correlated with age (r=0.474, p=0.04), waist circumference (r=0.453, p=0.007), BMI (r=0.472, p=0.03), systolic blood pressure (r=0.359, p=0.035) and triglyceride level (r= 0.466, p=0.038).

The severity of liver findings and the degree of steatosis, necroinflammation or fibrosis were associated with the increase of carotid IMT and the occurrence of retinal vascular disorders (p<0.001 for all).

Table II. Clinical and laboratory characteristics of NAFLD patients (mean±SD)

Liver histology	N	Carotid IMT (mm)	Retinal vascular changes
Steatosis			
grade 1	3	0.91+0.02	mild arteriolar narrowing
grade 2	5	1.10+0.02	moderate arteriolar narrowing, arteriovenous crossing changes
grade 3	4	1.18+0.02	copper-wire, silver-wire arterioles, arteriovenous nicking, retinal vascular occlusion
Necroinflammation			
grade 1	3	1.03+0.03	arteriovenous crossing changes
grade 2	2	1.12+0.01	copper-wire, silver-wire arterioles, arteriovenous nicking
grade 3	2	1.22+0.01	retinal vascular occlusion
Fibrosis			
grade 1	3	1.04+0.02	copper-wire, silver-wire arterioles
grade 2	3	1.18+0.01	arteriovenous nicking
grade 3	2	1.24+0.01	retinal vascular occlusion

Discussion

NAFLD is considered a major health problem in developed countries with a prevalence of 20% to 40% in the general population and also the most frequent cause of increased liver enzymes in asymptomatic patients having an increased chance to progress to cirrhosis [7].

An association between carotid IMT, as a marker of atherosclerosis evaluated by ultrasonography and NAFLD has been reported in previous studies [2–5,8].

Our study included 12 patients with NAFLD and retinal vascular changes. The results showed that the values of carotid IMT evaluated by ultrasonography are increased in patients with NAFLD, well correlated with the severity of histological lesions. The lowest value of carotid IMT was described in patients with mild steatosis, intermediate values in patients with moderate steatosis and the highest values of carotid IMT were determined in patients with severe steatosis, associated with fibrosis.

The way in which liver findings in NAFLD patients could be associated with the progression of atherosclerosis is not entirely clarified. In order to elucidate the pathogenetic pathways some authors described the implication of endothelial dysfunction, insulin resistance, oxidative stress, inflammation and inflammatory cytokines and an abnormal lipoprotein metabolism [7,8].

The internal carotid artery provides blood to the eye, therefore the pathology due to arteriosclerosis of these arteries may have a direct impact on retinal circulation and may coexist with retinal arteriosclerosis [6].

The clinical importance of our study is highlighted by our results and we strongly suggest carotid ultrasound to be performed in patients with NAFLD in order to detect early atherosclerosis. Moreover, retinal photography is required to evaluate retinal vascular changes in NAFLD patients.

One of the limitations of our study is the reduced number of patients, further controlled studies on larger groups are needed to confirm these results.

Conclusions

The study proves that patients with histologically proven NAFLD have an increased value of carotid IMT, which is strongly correlated with the degree of liver steatosis. Carotid IMT is higher in patients with severe steatosis than in those with simple steatosis. Moreover, there is an increased incidence of retinal vascular changes in patients with NAFLD. Further controlled studies will confirm the results.

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