Hepatic artery resistive index (HARI) and non-alcoholic fatty liver disease (NAFLD) fibrosis score in NAFLD patients: cut-off suggestive of non-alcoholic steatohepatitis (NASH) evolution

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Abstract

Purpose of the study Conventional ultrasound (US) is reliable to reveal the presence of non-alcoholic fatty liver disease (NAFLD), but it is neither sensitive nor specific to reveal fibrosis clues, except in advanced stages where signs of cirrhosis are evident. NAFLD fibrosis score is a non-invasive parameter that predicts well the presence of significant fibrosis, but correlations with US parameters are lacking. The aim of this study was, therefore, to compare resistive index of hepatic artery (HARI) of NAFLD patients with different severity degrees of diffuse fatty liver disease vs HARI of controls, and to compare HARI of NAFLD patients with different NAFLD fibrosis scores vs HARI of controls.

Methods This was a spontaneous, no-profit observational study conducted in our US department between December 2013 and July 2014. Patients with NAFLD with different severity of disease and healthy controls were included. Echogenicity and size of liver and spleen, maximum portal vein velocity, RI, peak systolic velocity (PSV), and end diastolic velocity (EDV) of splenic artery, PSV, EDV, and RI of hepatic artery, and NAFLD fibrosis score were acquired and compared between groups.

Results HARI was significantly lower in NAFLD patients than controls ($p < 0.0001$). A significant difference was also found between the groups of NAFLD severity ($p < 0.0001$). There was also a difference between HARI of NAFLD patients with different NAFLD fibrosis scores vs HARI of controls ($p < 0.0001$) with a positive correlation between HARI and NAFLD fibrosis score.

Conclusion and discussion Conventional Doppler US can be helpful to detect NAFLD patients with the risk of fibrous tissue accumulation. HARI tends to exceed the range of controls for patients with NAFLD fibrosis score greater than 0.675. The detection of HARI greater than 0.9 in NAFLD patients, regardless of the US degree of severity of steatosis, might suggest the execution of biopsy to predict the risk of progression to steatohepatitis and fibrous tissue accumulation. Low values of HARI may be expression of lower risk, which does not necessitate any biopsy.

Keywords Hepatic artery resistive index · Non-alcoholic fatty liver disease · NAFLD fibrosis score · Non-alcoholic steatohepatitis · Ultrasound · Color Doppler

Sommario

Scopo dello studio L'ecografia convenzionale è risultata affidabile nel rilevare la presenza di steatosi epatica, tra cui la forma non alcolica (NAFLD), ma non è né sensibile né specifica nel rivelare indizi suggestivi di fibrosi, tranne che in fase avanzata dove sono presenti segni conclamati di cirrosi. Il NAFLD fibrosis score è un parametro non invasivo che predice bene la presenza di fibrosi significativa, ma non ci sono dati in letteratura riguardanti una possibile correlazione con i parametri ecografici. Lo scopo di questo studio è stato quindi quello di confrontare HARI dei pazienti con NAFLD a differente grado di severità di

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steatosi epatica vs l'HARI dei controlli, e di confrontare HARI dei pazienti affetti da NAFLD a differente NAFLD fibrosis score vs l'HARI dei controlli.

Metodi Studio osservazionale spontaneo, no-profit condotto nel nostro Dipartimento tra il dicembre 2013 e il luglio 2014. Venivano inclusi i pazienti con NAFLD a differente severità di malattia e controlli sani. Venivano registrati e confrontati tra gruppi i seguenti parametri: ecogenicità, dimensioni del fegato e della milza, velocità massima della vena porta, indice di resistenza (RI), velocità di picco sistolico (PSV), velocità tele-diastolica finale (EDV) di arteria splenica, e PSV, EDV e RI dell'arteria epatica (HARI) ed il NAFLD fibrosis score.

Risultati HARI risultava significativamente più basso nei pazienti affetti da NAFLD rispetto ai controlli ($p < 0.0001$). Una differenza significativa veniva trovata anche tra i gruppi a differente severità di steatosi ($p < 0.0001$). Veniva riscontrata anche una differenza tra HARI dei pazienti con NAFLD a differente NAFLD fibrosis score vs HARI dei controlli ($p < 0.0001$) con una correlazione positiva tra HARI e NAFLD fibrosis score.

Conclusione e discussione L'ecografia Doppler può essere utile per individuare pazienti con NAFLD a rischio di evoluzione fibrotica. HARI tende a superare i valori dei controlli per i pazienti con NAFLD fibrosis score superiore a 0.675. La rilevazione di HARI superiore a 0.9 nei pazienti con NAFLD, indipendentemente dal grado di severità di steatosi, potrebbe indicare l'esecuzione della biopsia al fine di prevedere il rischio di progressione a steatoepatite e fibrosi. Bassi valori di HARI potrebbero essere invece espressione di rischio più basso che non necessiterebbero di alcuna biopsia.

Background

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by histopathological or imaging evidence of diffuse fatty liver disease that occurs usually in presence of metabolic risk factors (e.g., hypercholesterolemia and/or diabetes) and without an identifiable etiology of liver disease [1]. NAFLD is common in Western countries, presents inter-racial differences, and its prevalence has been estimated around 25–30 % in the general population, while the incidence varies according to the populations studied (from 29/100,000 to 86/1000) [2, 3]. Two NAFLD groups can be distinguished, NAFLD, where there is no evidence of hepatocytes ballooning or fibrosis, and non-alcoholic steatohepatitis (NASH), in which inflammation with hepatocyte injury predominates, with or without fibrosis [1]. The distinction between these two conditions is essential, because NASH patients are at higher

risk of liver failure, cirrhosis, and hepatocellular carcinoma [1]. Liver biopsy is the gold standard technique to detect early liver fibrosis, but is an invasive procedure and not free of complications. In the last years, some clinical/laboratory scores have been created to assess the risk of NASH evolution and the need of biopsy in these patients [1]. Among all, NAFLD fibrosis score seems to predict well the presence of significant fibrosis [4–6]. Although the traditional ultrasound (US) is an excellent diagnostic technique to reveal the presence of diffuse fatty liver disease, it is neither sensitive nor specific to reveal fibrosis, except in advanced stages where signs of cirrhosis are evident. Previous studies have demonstrated that hepatic artery resistive index (HARI) is significantly altered in patients with NAFLD, with significant reduction of this parameter with increasing of severity of diffuse fatty liver disease [7–10].

Conversely, HARI in cirrhotic patients tends to increase [11], but there is no evidence so far of a putative correlation between HARI and severity of fibrosis in NAFLD patients. Fibrosis risk assessment in NAFLD patients is crucial, because the presence of advanced fibrosis in these subjects is associated with the risk of severe hepatic dysfunction, consequent mortality, and the risk of malignant progression [12].

The aim of this study was to compare HARI of NAFLD patients with different severity degrees of diffuse fatty liver disease vs HARI of controls, and to compare HARI of NAFLD patients with different NAFLD fibrosis scores vs HARI of controls.

Methods

Study design

This was a spontaneous, no-profit observational study conducted in our US department between December 2013 and July 2014. Patients of both sexes and aged ≥ 18 years were considered eligible for this study. Inclusion criteria were risk factors for NAFLD (obesity—body mass index, BMI ≥ 30 —, hypercholesterolemia and/or hypertriglyceridemia, type 2 diabetes mellitus).

Patients were excluded if they had fatty liver disease from identifiable cause, such as alcohol consumption (≥ 20 g/day for women, ≥ 30 g/day for men), viral hepatitis (B and C), Wilson's disease, lipodystrophy, total parenteral nutrition, abetalipoproteinemia, pregnancy, congenital defects of the metabolism, such as LCAT deficit, Wolman's disease. Patients with rhythm and/or conduction disorders and current neoplasia were also excluded.

Written informed consent was obtained from all participants. The study has been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its late amendments.

Study procedures

For each patient included in the study, complete medical history was acquired. The following laboratory tests were also recorded: complete blood count, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-gt, total bilirubin, total cholesterol (TC), triglycerides (TG), fasting glucose, and serum albumin.

After complete fasting for at least 12 h, all study participants underwent US examination.

The examination was performed by two trained operators, certified by the Italian Society for Ultrasound in Medicine and Biology (SIUMB). The same US device (Aloka Prosound Alpha 10 with convex multifrequency probe) was used.

The following information was acquired: echogenicity and size of liver and spleen (longitudinal diameter of the right lobe of the liver, color Doppler parameters, such as maximum portal vein velocity (MPVV), RI, peak systolic velocity (PSV), end diastolic velocity (EDV) of splenic artery, and PSV, EDV, and RI of hepatic artery (Fig. 1).

Patients with evidence of fatty liver disease was assigned to the NAFLD group, and further divided according to severity of diffuse fatty liver disease (mild—mS, moderate—MS, or

severe—SS) on the basis of US beam attenuation [13, 14]; otherwise, they were assigned to the group of controls.

Finally, NAFLD fibrosis score was calculated using a standardized formula that included variables as age, BMI, GOT, GPT, presence or not of fasting hyperglycemia or diabetes mellitus II, platelet count, and serum albumin. NAFLD fibrosis score was defined as low risk of fibrosis (L) if <-1.455 , intermediate risk of fibrosis (I) if ≥ -1.455 and ≤ -0.675 , and high risk of fibrosis (H) if >0.675 .

Statistical analysis

Statistical analysis and graphics were done using GraphPad Instat and Prism for Windows, respectively. Mean $\pm$ standard deviation (SD) was calculated of all the investigated parameters. B-mode and Doppler US parameters were compared in the different study groups using the one-way ANOVA test.

Statistical significance was defined with a p value <0.05 .

Results

Baseline characteristics of the study population

Table 1 shows the baseline characteristics of the patients and controls. A total of 49 NAFLD patients and 13 controls were included in the study. There was no significant difference between the two groups for age and laboratory exams as hemoglobin, platelet count, creatinine, AST, ALT, gamma-gt, total bilirubin, TG, fasting glucose, and serum albumin. Only TC was significantly higher in NAFLD patients than controls ($p < 0.05$).

US features of liver, spleen, portal vein, and splenic artery are reported in Table 2. Longitudinal diameter of the right lobe of the liver was significantly higher in patients with NAFLD with different severity of diffuse fatty liver disease vs controls ($p < 0.0001$). Portal vein diameter did not differ significantly between patients suffering from NAFLD with different severity of diffuse fatty liver disease vs controls.

Furthermore, there was also no significant difference between MPVV, splenic area, and PSV and EDV of splenic artery of NAFLD patients and controls. Splenic artery RI was significantly higher in NAFLD patients vs controls ($p < 0.001$).

HARI of NAFLD patients with different severity of diffuse fatty liver disease vs controls

There was no significant difference between hepatic artery PSV and EDV of NAFLD patients vs controls (Table 2).

Fig. 1 **a** Portal triad with hepatic artery visualization by Color Doppler US (arrows). **b** Hepatic artery resistive index (HARI), PSV, and EDV assessment for this subject (arrow)

Table 1 Baseline characteristics of the patients included in the study ($n = 62$, mean $\pm$ SD)

	NAFLD patients ($n = 49$)	Controls ($n = 13$)	p^*
Characteristic			
Age (years)	62.31 $\pm$ 12.35	64.38 $\pm$ 18.15	NS
Male sex, n (%)	25 (51.02)	9 (69.23)	
Obesity, n (%)	21 (42.85)	0 (0)	
Dyslipidemia, n (%)	27 (55.10)	6 (46.15)	
Type 2 diabetes mellitus, n (%)	18 (36.73)	5 (38.46)	
Arterial hypertension, n (%)	36 (73.46)	8 (61.53)	
Laboratory tests			
Hemoglobin (g/dl)	13.69 $\pm$ 1.61	13.25 $\pm$ 1.94	NS
Platelets ($\times 10^3/\mu\text{l}$)	226.65 $\pm$ 74.44	225.31 $\pm$ 97.84	NS
Creatinine (mg/dl)	0.96 $\pm$ 0.40	1.21 $\pm$ 0.59	NS
AST	29.26 $\pm$ 18.24	27 $\pm$ 14.96	NS
ALT	45.10 $\pm$ 46.18	38.38 $\pm$ 18.98	NS
Gamma-gt	57.85 $\pm$ 76.16	62.85 $\pm$ 65.09	NS
Total bilirubin	0.77 $\pm$ 0.57	0.76 $\pm$ 0.3	NS
Total cholesterol	191.41 $\pm$ 44.29	158.67 $\pm$ 42.58	<0.05
Triglycerides	194.51 $\pm$ 128.22	132.75 $\pm$ 62.28	NS
Fasting glucose (mg/dl)	127.71 $\pm$ 49.32	121.82 $\pm$ 57.90	NS
Serum albumin (g/l)	40.09 $\pm$ 5.98	37.88 $\pm$ 7.19	NS
Therapy, n (%)			
ACE inhibitors	12 (24.48)	1 (7.69)	
Angiotensin II receptor antagonists	4 (8.16)	5 (38.46)	
β -Blockers	11 (22.44)	2 (15.38)	
Diuretics	11 (22.44)	1 (7.69)	
Calcium channel blockers	5 (10.20)	3 (23.07)	
Statins	8 (16.32)	5 (38.46)	
Metformin	10 (20.40)	0 (0)	
Sulfonylureas	6 (12.24)	2 (15.38)	
Insulin	4 (8.16)	1 (7.69)	
Aspirin	8 (16.32)	2 (15.38)	

AST aspartate aminotransferase, ALT alanine aminotransferase

* Student T test

However, HARI was significantly lower in NAFLD patients (MS and SS groups) than controls ($p < 0.0001$). Furthermore, a significant difference was also found between the groups of severity ($p < 0.0001$, Fig. 2). There was no significant difference between HARI of mS NAFLD patients vs controls.

HARI of NAFLD patients with different NAFLD fibrosis scores vs controls

There was a significant difference between HARI of NAFLD patients with different NAFLD fibrosis scores vs HARI of controls, with significant differences between L and H, and I and H ($p < 0.0001$). No significant difference was found between L and I (Fig. 3).

Discussion

In this study, we found a significant inverse correlation between HARI and severity of diffuse fatty liver disease in NAFLD patients, with a significant decrease in HARI as severity of fatty disease increases. These results substantially confirm the data published previously [7, 9].

We also found a new, positive correlation between HARI of NAFLD patients and NAFLD fibrosis score, with increasing HARI values at increasing NAFLD fibrosis score.

While the conventional US is sensitive and specific in the diagnosis of fatty liver disease, it cannot distinguish, with traditional parameters, patients at high risk of fibrosis. Data of previous studies suggest that clues of

Table 2 Standard ultrasound (US), hepatic artery parameters in NAFLD patients vs controls ($n = 62$, means $\pm$ SD)

	NAFLD patient's severity of fatty liver disease			Controls (<i>n</i> = 13)	<i>p</i> *
	mS (<i>n</i> = 16)	MS (<i>n</i> = 21)	SS (<i>n</i> = 12)		
Standard US parameters					
Longitudinal diameter of the right lobe of the liver (mm)	143.87 ± 15.80	148.43 ± 19.79	161.17 ± 15.21	124.23 ± 16.34	<0.0001
VP (mm)	9.94 ± 1.12	10.55 ± 1.33	11.03 ± 1.45	9.85 ± 1.28	NS
MPVV (cm/s)	26.51 ± 4.64	26.48 ± 3.31	23.26 ± 7.29	31.66 ± 5.72	NS
Splenic area (cm ²)	37.31 ± 9.81	36.92 ± 5.95	41.51 ± 16.06	31.02 ± 9.37	NS
Splenic artery PSV (cm/s)	80.07 ± 36.64	64.13 ± 21.72	55.75 ± 25.06	65.43 ± 32.09	NS
Splenic artery EDV (cm/s)	29.84 ± 15.92	33.97 ± 17.57	18.08 ± 12.16	32.32 ± 20.17	NS
Splenic artery RI	0.59 ± 0.07	0.53 ± 0.11	0.67 ± 0.09	0.54 ± 0.07	<0.001
Hepatic artery parameters					
PSV (cm/s)	66.39 ± 33.39	68.32 ± 23.86	55.23 ± 33.48	58.15 ± 24.85	NS
EDV (cm/s)	14.08 ± 6.91	18.51 ± 8.04	19.07 ± 12.71	11.23 ± 6.84	NS
RI	0.81 ± 0.06	0.73 ± 0.04	0.61 ± 0.10	0.85 ± 0.01	<0.0001

VP portal vein diameter, MPVV maximum portal vein velocity, PSV peak systolic velocity, EDV end diastolic velocity, RI resistive index, mS mild steatosis, MM moderate steatosis, SS severe steatosis

* Anova test

Fig. 2 Hepatic artery resistive index (HARI) in NAFLD patients with different severity of diffuse fatty liver disease vs controls. mS mild steatosis, MM moderate steatosis; SS severe steatosis. * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$. Asterisk is used to mean comparison between NAFLD patients with different severity of fatty liver disease vs controls. SL vs SM, $p < 0.001$; SM vs SS, $p < 0.001$; SL vs SS, $p < 0.001$

steatohepatitis in NAFLD patients can be an increase in portal vein diameter, reduction of portal vein velocity, large splenic area, and an increase in RI of splenic artery [10, 15, 16]. In our baseline, similar characteristics were found in NAFLD patients with severe fatty liver disease (Table 2). However, there is a lack of evidence that these parameters can be helpful to predict the presence of fibrosis

Fig. 3 Hepatic artery resistive index (HARI) in NAFLD patients with different NAFLD fibrosis scores [low, L ($n = 12$) < -1.455 , mean value = 0.69 ± 0.08 ; intermediate, I ($n = 25$) ≥ -1.455 to ≤ -0.675 , mean value = 0.73 ± 0.08 ; high, H ($n = 12$) > 0.675 , mean value = 0.98 ± 0.02] vs controls ($n = 13$, mean value = 0.88 ± 0.03). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Asterisk is used to mean comparison between NAFLD patients with different NAFLD fibrosis scores vs controls. B vs I, NS; I vs A, $p < 0.001$; B vs A, $p < 0.001$

in NASH patients, as they are neither sensitive nor specific to detect fibrous tissue, unless US signs of overt cirrhosis manifest (e.g., irregular liver margins or echo-coarse

nodular pattern) [17–19]. NAFLD fibrosis score has demonstrated high sensitivity and specificity to predict the risk of fibrosis, but requires an algorithm, including several parameters (both clinical and laboratory) [4]. No single conventional US parameter has demonstrated so far, a full reliability to predict fibrous tissue in NAFLD patients. The recent development of novel techniques, such as elastography, has led to great advances in the assessment of liver fibrosis, but these methods are currently not available everywhere, are expensive, and need additional US equipment [20–22].

A positive correlation between HARI and NAFLD fibrosis scores also suggests that the conventional Doppler US can be helpful to detect NAFLD patients with the risk of fibrous tissue accumulation. HARI tends to exceed the range of controls for patients with NAFLD fibrosis score greater than 0.675, and HARI increase may result from high tissue stiffness secondary to fibrous tissue accumulation that can translate into increased arterial rigidity secondary to fibrous tissue compression and, therefore, rise of resistance to flow.

However, some limitations affect our study. First, sample size (both patients and controls) was limited; therefore, these results should be considered as preliminary and should be validated by large studies before considering them in clinical practice. Second, hepatic artery is a vessel of difficult US approach and is not always well visualized, in particular in obese patient with severe fatty liver disease, resulting often in not diriment examinations or in false-positive reduction of HARI. Third, comparisons were made between HARI and NAFLD fibrosis scores, that is a parameter calculated on clinical and laboratory variables, and not with tissue results obtained directly from liver biopsy. Despite these limitations, the use of non-invasive and rapid assessment of HARI can be promising in clinical practice. In particular, the detection of high HARI value in NAFLD patients, regardless of the US degree of severity of steatosis, might suggest the execution of biopsy to predict the risk of progression to steatohepatitis and fibrous tissue accumulation. Conversely, low values of HARI may be expression of lower risk, which does not necessitate any biopsy. However, before biopsy, non-invasive evaluation of fibrosis should be performed by means of fibroscan or elastography. If these results will be confirmed by future trials, the assessment of HARI in NAFLD patients could be integrated with NAFLD fibrosis score to assess patients at high risk of developing fibrosis and, therefore, candidates for liver biopsy.

Compliance with ethical standards

Conflict of interest Dr. Claudio Tana received a Grant from the Italian Society of Ultrasound in Medicine and Biology (SIUMB) for the best oral communication presented at the 25th SIUMB Congress.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All patients provided written informed consent to enrolment in the study and to the inclusion in this article of information that could potentially lead to their identification.

Human and animal studies The study was conducted in accordance with all institutional and national guidelines for the care of humans, and did not include laboratory animals.

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