Relationship between Hepatic Artery Resistive Index and Liver Fibrosis Score in Non-Alcoholic Fatty Liver Disease Patient

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ABSTRACT:
Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most important precursors of chronic liver disease all over the world. Doppler ultrasonography is an essential part of evaluating the vascular haemodynamic variation seen within NAFLD.
Objective: Assessment of the role of Hepatic Artery Resistive Index (HARI) in NAFLD patient and the relation between HARI and grading of fatty liver by ultrasound.
Patients and methods: One hundred Egyptian patients diagnosed to have NAFLD based on ultrasound abdomen 35, 35, and 30 patients in grade1, grade 2, and grade3 NAFLD, respectively and 20 healthy subjects as control group were subjected to hepatic artery Doppler study. The study was carried out in the Outpatient Clinic of Internal Medicine Department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.
Results: Our study results showed high statistical significant difference (p-value < 0.001) between studied groups as regards hepatic artery resistance index. There was an inverse relationship between HARI and different grades of fatty liver in patients (p < 0.001). Hepatic artery resistance index (RI) decreased as the severity of diffuse fatty infiltration increases.
Conclusion: Hepatic artery resistance index (RI) decreases as the severity of diffuse fatty infiltration increases.
Keywords: Hepatic artery resistive index, Non-alcoholic fatty liver disease, NAFLD fibrosis score.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD), affects around one fourth of the general population worldwide. Nonalcoholic steatohepatitis (NASH), the active form of NAFLD, characterized by histological lobular inflammation and hepatocyte ballooning, is associated with faster fibrosis progression and affects around 1.5% to 6.5% of the general population **[1]**. NAFLD is frequently associated with metabolic comorbidities such as obesity, type 2 diabetes, hyperlipidemia, hypertension, and metabolic syndrome **[2]**.

Although the most common cause of death in patients with NAFLD is cardiovascular disease, independent of other metabolic comorbidities, NAFLD is becoming a major cause of liver disease-related morbidity (cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and liver transplantation) as well as mortality **[3]**.

As a non-invasive, extremely safe, widely available and inexpensive modality, ultrasonogram is the common method used for detecting fatty liver and assessing the stages of NAFLD. The bright liver, consisting of hyperechogenic liver tissue with fine, tightly packed echoes on US examination, ultrasonogram considered characteristics for fatty liver **[4]**. The degree of fatty infiltration was graded by gray-scale US as follows: Grade 0 (none): Normal liver echogenicity. Grade 1(mild): minimally increased diffuse liver echogenicity, intrahepatic vessels and diaphragm could be visualized. Grade 2 (moderate): moderately increased diffuse liver echogenicity; intrahepatic vessels and the diaphragm could be visualized slightly. Grade 3 (severe): markedly increased diffuse liver echogenicity, weak penetration through the liver by the gray-scale US evaluation **[5]**. Doppler ultrasonography of the liver is a useful test to evaluate arterial perfusion via calculation of resistance and plasticity indices **[6]**. And the resistance Index (RI) is the commonest Doppler parameter used for hepatic arterial evaluation **[7]**.

NAFLD fibrosis score (NFS) is one of the most commonly employed noninvasive tests to assess severity of hepatic fibrosis by using six commonly measured parameters. These include age, hyperglycemia, body mass index (BMI), platelet count, albumin level, and AST/ALT ratio **[8]**.

This study aimed to evaluate the role of HARI in NAFLD patient and the relation between HARI and grading of fatty liver by ultrasound.

PATIENTS AND METHODS

The study was carried out in the Outpatient Clinic of Internal Medicine Department, Faculty of Medicine, Al-Azhar University. One hundred Egyptian patients with hepatic steatosis (mild, moderate or severe) detected by ultrasound and twenty healthy volunteers (subjects without fatty infiltration) as control group were enrolled.

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Patients with Chronic viral hepatitis (B and C), patients consuming alcohol more than 20 g/day, patients with Wilson's disease, lipodystrophy, Abetalipoproteinemia, or congenital defects of the metabolism were excluded. Patients who are < 18 years old or pregnant female were also be excluded.

Ethical approval and written informed consent:

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

All the patients enrolled in the study were subjected to the following:

History and Clinical Examination:

1- Complete history taking, which include history of other comorbid conditions such as DM, cardiac disease and renal failure.
2- Full clinical examination including assessment of general condition, vital signs (pulse, blood pressure, respiratory rate and temperature). Abdominal, chest and heart examination were assessed with focus on manifestations of chronic liver disease (such as jaundice, flapping tremors, lower limb edema, organomegaly and ascites). Anthropometric parameters were obtained. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Laboratory Investigations:

Blood samples were collected from patients and submitted to the following:

1- Complete blood picture (CBC), hemoglobin concentration (Hb %), red blood cells (RBCs) count, differential white blood cells (WBCs) count and platelet count.
2- Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and total bilirubin.
3- Renal function tests: serum creatinine.
4- Fasting blood glucose level & Hemoglobin A1c.
5- Lipid profile includiong total cholesterol, low-density lipoprotein, very low density lipoprotein, high-density lipoprotein and triglycerides.

Imaging: Study patients were submitted to screening with the following procedures:

1- Abdominal Ultrasonography: The following parameters were involved in ultrasonographic evaluation:

- Assessment of the liver for its size in both midline and mid-clavicular line, surface of the liver and echogenicity. NAFLD will be diagnosed by ultrasonography using a high-resolution B-mode ultrasound system by professional ultrasound doctors according to the guidelines for the diagnosis and management of nonalcoholic fatty liver disease. participants who possessed two of the following three characteristics could be diagnosed as fatty liver: (i) the near-field echo of the liver is diffusely increased and more than in the kidney; (ii) the intrahepatic duct structure is not clear; (iii) the far-field echo of the liver is decreased gradually **[9]**.
- Severity of the fatty liver was then graded based on the USG findings into grade 1 (mild) if the echogenicity was slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders, grade 2 (moderate) if the echogenicity was moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels and grade 3 (severe) if the echogenicity was markedly increased with poor visualization of the diaphragm, the intrahepatic vessels and the posterior portion of the right lobe **[10]**.
- Hepatic focal lesion.
- Splenic size: were expressed as average (absence of splenomegaly) or enlarged.
- Presence or absence of ascites and Portal vein patency.

2- Doppler measurements:

The HARI was measured on the proper HA, at its crossing of the portal vein, by using a Doppler sample length of 3 to 9 mm. The peak systolic (S) and peak end-diastolic (D) Doppler frequency shifts were measured manually on the time-frequency Doppler spectrum by calipers, and the RI was automatically calculated as RI 5 (S-D)/S.

All Doppler ultrasound examinations were performed and interpreted by one investigator according to standard protocol using Aplio 500 Platinum ultrasound unit (Toshiba Medical Systems, Tokyo, Japan), with multifrequency 3.5 MHz convex transducer). All ultrasonographic examinations were performed by the same radiologist, who was blinded to the clinical and laboratory details of the patients.

Assessment of hepatic fibrosis:

Liver fibrosis was evaluated by the NAFLD fibrosis score, which includes serum glucose, platelet count, albumin, AST/ALT ratio) and readily available patient characteristics (age, BMI, and diabetes status). NAFLD liver fat score (NAFLD-LFS) was calculated according to this formula:

− 1.675 + 0.037 × age (years) + 0.094 × body mass index (BMI, kg/m2) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet (× 109/L) − 0.66 × albumin (g/dL). The result was interpreted as low NFS (<− 1.445), indeterminate NFS (− 1.445 to 0.676), and high NFS (> 0.676) **[11]**.

Statistical analysis

Data were studied utilizing a Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were evinced as mean ± standard deviation (M ± SD). Qualitative data were expressed as frequency and percentage. Chi-square test was utilized in comparison of non-parametric data. A one-way analysis of variance (ANOVA) was utilized in comparison of more than two means. P-values were established statistically significant at $P \leq 0.05$**.**

RESULTS

Baseline characteristics:

The mean age of patients group was 42.8 ± 4.9 years, 62 were males (62%). The mean BMI was 31.3 ± 4.9 kg/m², 66 patients were smokers (66%), 19 patients were diabetic patients and 26 patients were prediabetics. Regarding laboratory profile , results showed that the mean fasting blood glucose, HA1c, ALT, AST, S. albumin, S. bilirubin and S. creatinine were 114.9 mg/dl, 6%, 48 U/L , 29.3 U/L , 4.1 mg/dl, 0.71 mg/dl, and 0.89 mg/dl, respectively.

Regarding lipid profile, the mean of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were 209 mg/dl, 39.1 mg/dl, 93.7 mg/dl and 210 mg/dl, respectively.

Among controls, the mean age of patients group was 43.5 ± 6.8 years, 16 were males (80%). The mean BMI was 28.75 ± 2.95 kg/m², 10 patients were smokers (50%), two patients were diabetic patients and two patients were prediabetics.

Regarding laboratory profile, results showed that the mean fasting blood glucose, HbA1c, ALT, AST, S. albumin, S. bilirubin and S. creatinine were 96.5 mg/dl, 5.6 %, 35.6 U/L , 30 U/L , 4.3 mg/dl, 0.8 mg/dl, and 1 mg/dl, respectively. Regarding lipid profile, the mean of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were 177.9 mg/dl, 40 mg/dl, 93.9 mg/dl and 153.9 mg/dl, respectively.

Analysis of the Doppler measurements:

Our study results showed high statistical significant difference (p-value < 0.001) between studied groups as regards hepatic artery resistance index.

There was an inverse relationship between HARI and different grades of fatty liver in patients (p < 0.001). Hepatic artery resistance index (RI) decreased as the severity of diffuse fatty infiltration increases.

Table (1): Comparison between studied groups as regards demographic data

		Patients (N = 100)		**Control (N = 20)**		**P-value**
Age (years)	Mean	42.8		43.50		0.614 NS
	±SD	4.9		6.80		
Sex	Male	62	62%	16	80%	0.123 NS
	Female	38	38%	4	20%	
BMI (kg/m^2)	Mean	31.3		28.75		0.026 S
	±SD	4.9		2.95		
Smoking	Non	66	66%	10	50%	0.175 NS
	Smoker	34	34%	10	50%	

This table showed statistically significant difference (p-value < 0.05) between studied groups as regards BMI.

Table (2): Comparison between studied groups as regard laboratory data

		Patients (N = 100)	Control (N = 20)	P-value
Hb% (g/dl)	Mean	14.9	13.3	0.244 NS
	±SD	2.7	1.9	
WBCs ($x10^3$/ul)	Mean	6.0	6.1	0.829 NS
	±SD	1.9	1.7	
PLTs ($x10^3$/ul)	Mean	213.2	235.6	0.141 NS
	±SD	59.7	20.0	
FBG (mg/dl)	Mean	114.9	96.5	**0.034 S**
	±SD	6.3	8.2	
HbA1C (%)	Mean	6.0	5.6	0.142 NS
	±SD	1.2	0.9	
CHOL (mg/dl)	Mean	209.1	177.9	**0.004 S**
	±SD	46.7	16.1	
TG (mg/dl)	Mean	210.0	153.9	**0.012 S**
	±SD	9.7	8.2	
HDL (mg/dl)	Mean	39.1	40.0	0.660 NS
	±SD	7.9	9.8	
LDL (mg/dl)	Mean	93.7	93.9	0.966 NS
	±SD	16.0	10.4	
ALT (U/L)	Mean	48.0	35.6	**0.009 S**
	±SD	7.9	4.3	
AST (U/L)	Mean	29.3	30.0	0.853 NS
	±SD	5.9	7.6	
ALB (g/dl)	Mean	4.1	4.3	0.165 NS
	±SD	0.4	0.4	
T. Bilirubin (mg/dl)	Mean	0.71	0.8	0.379 NS
	±SD	0.19	0.2	
Creatinine (mg/dl)	Mean	0.89	1.0	0.101 NS
	±SD	0.18	0.2	

This table showed statistically significant differences (p-value < 0.05) between studied groups regarding serum levels of FBG, CHOL, ALT & TG.

Table (3): Comparison between studied groups as regards hepatic artery Doppler measurements

		Patients (N = 100)	Control (N = 20)	P-value
PSV	Mean	60.0	65.9	0.015 S
	±SD	9.6	10.2	
EDV	Mean	14.7	13.9	0.214 NS
	±SD	2.3	2.2	
HARI	Mean	0.7	0.78	< 0.001 HS
	±SD	0.1	0.01	

Table (3) showed highly statistically significant differences (p-value < 0.001) between studied groups regarding hepatic artery resistive index.

Table (4): Relation between grades of fatty liver & HARI in patients group

		Grades of Fatty Liver in patients group			P-value
		Fatty grade I (n = 35)	Fatty grade II (n = 35)	Fatty grade III (n = 30)	
HARI	Mean	0.78	0.71	0.62	< 0.001 HS
	±SD	0.04	0.10	0.08	

This table showed high statistical significant difference **(p-value < 0.001)** between fatty liver grades (I, II & III) regarding HARI.

Table 5. Correlation study between NAFLD fibrosis score and hepatic artery Doppler measurements in patients group.

Correlations	Patients group	
	r	p-value
NAFLD Fibrosis score vs HARI	- 0.19	0.049 S

(r): Pearson correlation coefficient. S: p-value < 0.05 is considered significant.
NS: p-value > 0.05 is considered non-significant.

In patients group, there was statistically significant (p-value = 0.049) negative correlation (r = - 0.19) between NAFLD Fibrosis score vs HARI.

DISCUSSION

In the current study, we found highly statistical significant difference (p-value < 0.001) between studied groups as regards hepatic artery resistance index and there was an inverse relationship between HARI and different grades of fatty liver in patients (p < 0.001). Hepatic artery resistance index (RI) decreased as the severity of diffuse fatty infiltration increases. The results of current study are supported by **Balasubramanian *et al.*** [10] in which ninety patients were diagnosed to have NAFLD. HARI was assessed where the mean HARI in patients with fatty liver was 0.65 ± 0.06 when compared to controls of 0.75 ± 0.06 (p=0.001). HARI (r-value of -0.517) had a better negative correlation with the severity of NAFLD. The mean HARI in grade1, grade2 and grade3 NAFLD were 0.69, 0.66, and 0.61**,** respectively (P < 0.001) [10]**. Tana *et al.*** [12] evaluated a total of 49 NAFLD patients and 13 controls. HARI was significantly lower in NAFLD patients (MS and SS groups) than controls (p < 0.001). Furthermore, a significant difference was also found between the groups of severity (p < 0.001). There was a significant difference between HARI of NAFLD patients with different NAFLD fibrosis scores vs HARI of controls**.**

In accordance with the current study, **Mohammadinia *et al.*** [13] evaluated 60 patients and 20 normal healthy subjects by using color and spectral Doppler sonography. The level of fatty liver infiltration was graded by biopsy in patients and excluded by MRI in controls. The patients were allocated to four study, according to infiltration level as follows: normal (group A), mild (group B), moderate (group C), and severe (group D). Hepatic artery resistance index was 0.81 (60.02), 0.78 (60.03), 0.73 (60.03), and 0.68 (60.05), respectively, in groups A, B, C, and D. It was significantly different between groups (p < 0.001).

Mohammadi *et al.* [4] provided evidence about relationship between the degrees of fatty infiltration and reduced vascular compliance in NAFLD patients. In their study, two hundred and fourty subjects were enrolled. They were divided into 4 groups: 60 controls, 180 patient with fatty liver including 60 grade 1 fatty liver patients, 60 grade 2 fatty liver patients and 60 grade 3 fatty liver patients. There was an inverse relationship between HARI and different grades of fatty liver in patients (p = 0.001).

CONCLUSION

Hepatic artery resistance index (RI) decreases as the severity of diffuse fatty infiltration increases.

Conflict of Interest:

The authors of the study have no conflict of interest related to this publication.

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