TÜBİTAK

Original Article

Turk J Med Sci
2010; 40 (3): 335-342
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0906-22

The role of ultrasonographic hepatic artery resistive index in the diagnosis of insulin resistance in obese children with non-alcoholic fatty liver disease

Şamil HIZLI[1], Ali KOÇYİĞİT[2], Nur ARSLAN[3], Sedat TUNCEL[2], Fatih DEMİRCİOĞLU[3], Handan ÇAKMAKÇI[2], Benal BÜYÜKGEBİZ[4]

Aim: To determine the role of hepatic artery resistive index (HARI) measurement in the prediction of insulin resistance (IR) in obese children with nonalcoholic fatty liver disease (NAFLD).

Materials and methods: A total of 64 obese subjects with NAFLD (13.5 ± 1.36 years of age, 34 male) and 32 age- and gender-matched control subjects (13.8 ± 1.24 years of age, 16 male) were enrolled in the study. All subjects underwent a physical examination, laboratory tests, and ultrasonographic and Doppler examinations of the liver. The homeostasis model assessment of IR (HOMA-IR) was used for the IR diagnosis.

Results: Obese subjects with NAFLD had significantly higher HARI, insulin, alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), and HOMA-IR than the control subjects. Obese subjects with NAFLD and IR had significantly higher HARI compared to obese subjects with NAFLD but without IR (0.761 ± 0.04 vs. 0.732 ± 0.04, P = 0.006). Changes in HARI correlated significantly to changes in BMI, SDS-BMI, MAC, TSF, MAC, ALT, TC, insulin, and HOMA-IR (r = 0.578, P = 0.001; r = 0.547, P = 0.001; r = 0.549, P = 0.001; r = 0.504, P = 0.001; r = 0.549, P = 0.001; r = 0.223, P = 0.029; r = 0.306, P = 0.002; r = 0.315, P = 0.011; r = 0.295, P = 0.018, respectively). As an optimal cutoff point, a HARI level of 0.715 determined IR with 81.2% sensitivity and 71.9% specificity.

Conclusion: Our findings suggest that HARI might be used as a simple and non-invasive screening method to predict IR in obese children with NAFLD.

Key words: Obesity, insulin resistance, nonalcoholic fatty liver disease, hepatic artery resistive index, adolescent, Doppler ultrasonography

Non-alkolik yağlı karaciğer hastalığı olan obez çocuklarda insulin rezistansının belirlenmesinde ultrasonografik hepatik arter rezistif indeksinin rolü

Amaç: Bu çalışmanın amacı non-alkolik yağlı karaciğer hastalığı olan obez çocuklarda insülin rezistansının (IR) belirlenmesinde ultrasonografik hepatik arter resistif indeksi (HARI) ölçümünün yerinin değerlendirilmesidir.

Yöntem ve gereç: Non-alkolik yağlı karaciğer hastalığı tanısı almış olan toplam 64 obez çocuk (13,5 ± 1,36 yıl, 34 erkek) ile yaş ve cinsiyet açısından farklı olmayan 32 çocuk (13,8 ± 1,24 yıl, 16 erkek) kontrol olarak alındı. Tüm çocuklar fizik inceleme, laboratuar testleri, ultrasonografi ve Doppler ile değerlendirildi. IR tanısı koymak için insülin rezistansı homestaz modeli değerlendirme (HOMA-IR) yöntemi kullanıldı.

Bulgular: Non-alkolik yağlı karaciğer hastalığı olan obez çocukların HARI, insülin, alanin aminotransferaz (ALT), total kolesterol (TC), trigliserit (TG) ve HOMA-IR değerleri kontrol hastalarından yüksekti (P < 0,05). Non-alkolik yağlı

Received: 11.06.2009 – Accepted: 19.02.2010

[1] Department of Pediatric Gastroenterology, Hepatology and Nutrition Clinic, Dr Sami Ulus Children Research and Training Hospital, Ankara - TURKEY
[2] Department of Radiodiagnostics, Faculty of Medicine, Dokuz Eylül University, İzmir - TURKEY
[3] Department of Pediatric Gastroenterology, Hepatology and Nutrition, Faculty of Medicine, Dokuz Eylül University, İzmir-TURKEY
[4] 0-18 Clinic, Appetite and Growth Disorders Center, İstanbul - TURKEY
Correspondence: *Şamil HIZLI, Kuşçağız Mh. Sakız Ağacı Cad. Gündüz Sk. Asiller Ap. No: 26/22 Keçiören Ankara - TURKEY*
E-mail: shizli@yahoo.com

karaciğer hastalığı ve IR olan obez çocukların HARI ölçümleri IR saptanmayanlardan yüksekti (sırasıyla 0,761 ± 0,04 ve 0,732 ± 0,04, P = 0,006). HARI değişiklikleri beden kitle indeksi (BKİ), BKİ-SDS skoru, glukoz, ALT, TC, TG ve HOMA-IR değerlerinin önemli korelasyonu vardı (sırasıyla; r = 0,578, P = 0,001; r = 0,547, P = 0,001; r = 0,549, P = 0,001; r = 0,504, P = 0,001; r = 0,549, P = 0,001; r = 0,223, P = 0,029; r = 0,306, P = 0,002; r = 0,315, P = 0,011; r = 0,295, P = 0,018). HARI ölçümünün 0,715 ve üzerinde saptanması insülin rezistansını % 81,2 duyarlılık ve % 71,9 özgüllükte gösteriyordu.

Sonuç: Bulgularımız non-alkolik yağlı karaciğer hastalığı olan obez çocuklarda HARI ölçümünün IR tanısının belirlenebilmesi için tarama amaçlı kullanılabilecek basit ve noninvazif bir tetkik olabileceğini düşündürmüştür.

Anahtar sözcükler: Obezite, insulin rezistansı, non-alkolik yağlı karaciğer hastalığı, hepatik arter rezistif indeksi, adölesan, doppler ultrasonografi

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a very frequent condition that is most commonly a complication of obesity and has been shown to be increasing all over the world both in adult and pediatric populations (1-3). NAFLD starts as fatty liver and may progress to nonalcoholic steatohepatitis (NASH). NASH is an inflammatory form of NAFLD that can progress to fibrosis, cirrhosis, and even to hepatocellular carcinoma (4). Insulin resistance (IR), which is detected by HOMA-IR, has been found to be strictly related with NASH pathogenesis (5,6). IR plays a pivotal role through oxidative stress, leading to endothelial dysfunction inflammatory changes in the microvasculature (7). Clinical examinations and biochemical laboratory tests including transaminases are unreliable in differentiating NASH progression and risk stratification**.** Liver histology is considered the gold standard for diagnosis of NASH but liver biopsy is associated with risks of complications, patient discomfort, and expense (8-11). Therefore, tracking of NASH progression and complication development cannot rely on repeated biopsies (11).

Hepatic artery resistive index (HARI) is a Doppler ultrasonography parameter that is used to follow up microcirculatory resistance in fatty liver, adult alcoholic liver disease, chronic hepatitis, and post-transplant liver patients and in children with severe cirrhosis secondary to biliary atresia (12-18).

The relation of HARI with HOMA-IR has not been explored in obese adolescents with NAFLD and there is no cut-off point of HARI to detect IR yet. The aim of this study was to determine the relation of HARI with HOMA-IR and the threshold value of HARI to detect IR in obese adolescents with NAFLD.

Subjects and methods

This was a case-control study conducted in adolescents diagnosed as obese and IR in Dokuz Eylül University Department of Pediatric Gastroenterology and Nutrition. A total of 64 obese subjects with NAFLD (13.5 ± 1.36 years of age; 30 female and 34 male patients) and 32 age- and gender-matched lean subjects (13.8 ± 1.24 years of age; 16 female and 16 male subjects) were included in this study. Age- and gender-matched children admitted due to mild dyspepsia without obesity (SDS BMI < +1 SD for age and gender) and normal liver at US were included in the study as controls.

Body size measurements were obtained in the standing position with the head and eyes directed forward and the upper limbs hanging by the sides. Height was measured in stocking feet to the nearest millimeter. Body weight was recorded using calibrated scales in light clothing to the nearest 0.1 kg. Height and body weight measurements were taken twice and the mean of the 2 readings was calculated. Triceps skinfold thickness was measured by a single observer using a Holtain (Crymych, UK) skinfold caliper. Each patient was measured 3 times; the average of the measurements was recorded. In addition, midarm circumference was measured with the measuring tape kept horizontal. BMI of patients was calculated according to the formula kg m^2 (19). The criterion for diagnosing obesity was defined according to the World Health Organization classification as the body mass index standard deviation score (SDS-BMI) being over +2 SD of the same gender and age (WHO) (19,20).

A detailed history was obtained and a physical examination (including evaluation for syndromes and endocrine pathologies) was performed in all subjects.

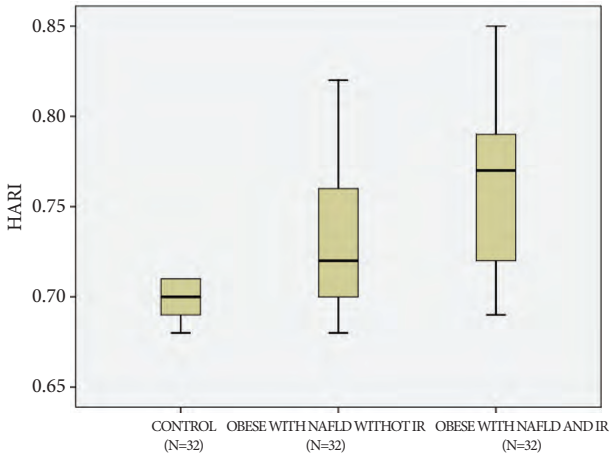

Figure 1. Hepatic artery resistive index of control, and obese with NAFLD with IR and without IR groups.

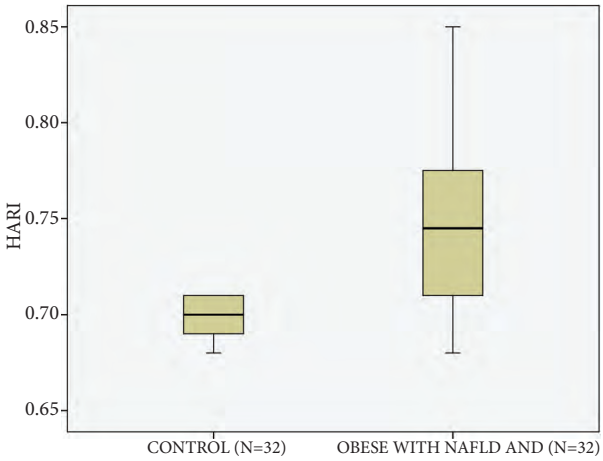

Figure 2. Hepatic artery resistive index of control and obese with NAFLD groups.

None of the subjects was taking drugs or had a history or evidence of metabolic, cardiovascular, respiratory or hepatic disease, and laboratory evaluation (thyroid function tests and diurnal variation of cortisol). The children with syndromal and endocrine causes (Cushing's syndrome, complete gonadal dysgenesis, hypothyroidism, etc.) of obesity were excluded.

Biochemical tests of patients were performed after 12 h of fasting. Venous blood samples were obtained to measure plasma glucose and insulin levels in the morning at 0800 by venipuncture after overnight fasting. After clotting, the serum was separated and immediately explored for analyses. Levels were measured for fasting serum glucose, alanine aminotransferase (ALT), total cholesterol (TC), and triglycerides (TG) by enzymatic colorimetric method. Plasma liver tests were determined by standard laboratory procedures. Serum-fasting glucose, TC, and TG levels were measured. Normal ranges for serum aminotransferase levels, in our laboratory, were 5 to 45 U/L for children. Hepatotropic viruses, serum copper and ceruloplasmin levels, serum α1-antitrypsin level, and autoantibodies against nuclear, smooth muscle, liver, and kidney microsomal type-1 antigens were screened to eliminate infectious, metabolic, and immunological liver pathologies. IR was estimated using the homeostasis model assessment for IR (HOMA-IR; fasting insulin X fasting glucose/22.5) and equal or greater than 4 was accepted as IR for pubertal subjects (HOMA-IR ≥ 4) (21).

Before the ultrasound examination, the subjects were instructed to rest quietly in a temperature-controlled dark room for 10 to 15 min. All HARI measurements were made by the same radiologist, who was blinded to the clinical and laboratory data of the patients. All subjects were examined at 1200 after 12 h of fasting in order to avoid the prandial effect. Convex transducers with frequency of 2-5 MHz were used for the Doppler US examination (ATL HDI 5000-Philips Medical Systems, Bothell, WA, USA). Doppler US evaluations of the hepatic artery of patients and controls were performed after lying for 15 min in the supine or left posterior oblique position during deep inspiration. The Doppler angle was set at 60° during spectral analysis. The HARI result of each subject was calculated as the mean of 3 measurements made automatically by US machine using the following formula: [(hepatic artery peak systolic flow – hepatic artery end diastolic flow) / hepatic artery peak systolic flow]. The hepatic artery was examined at the point where it crosses the portal vein and HARI measurements were done as previously described (16-18). Hepatic steatosis was investigated by US and presented as positive or negative. Presence of hepatic steatosis was confirmed by another radiologist, who was uninformed about HARI measurements.

Statistical Analyses

SPSS (version 16.01 for Windows; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The data were expressed as mean ± SD for numerical

variables and as percentages (%) for categorical variables. A P value of less than 0.05 was considered to be statistically significant. We compared the differences in variables between control subjects and obese subjects with and without IR with Student's t-test compared after ascertaining that the data were normally distributed. A chi-squared test was used for comparing percentages. The cut-off point of HARI to determine IR was evaluated by Receiver Operating Characteristics (ROC) analysis. Then sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of this cut-off point were calculated.

The study conformed to the guidelines established in the Helsinki Declaration II. The local ethics committee of the University approved the study protocol and informed consent was obtained from the study subjects. No complications or side effects were encountered.

Results

The clinical and laboratory characteristics of the control subjects and obese subjects with and without IR are summarized in Tables 1 and 2.

Gender distribution and mean age at admission were similar in the control, obese with IR, and obese without IR groups. The obese subjects had significantly higher ALT, TC, TG, and HARI. Changes in HARI correlated significantly to changes in BMI, SDS-BMI, MAC, TSF, MAC, ALT, TC, insulin, and HOMA-IR ($r = 0.578$, $P = 0.001$; $r = 0.547$, $P = 0.001$; $r = 0.549$, $P = 0.001$; $r = 0.504$, $P = 0.001$; $r = 0.549$, $P = 0.001$; $r = 0.223$, $P = 0.029$; $r = 0.306$, $P = 0.002$; $r = 0.315$, $P = 0.011$; $r = 0.295$, $P = 0.018$, respectively, Table 3). Obese subjects with NAFLD (n = 64) had significantly higher HARI, insulin, HOMA-IR, ALT, TG, and TC than the control subjects. Obese subjects

Table 1. Clinical and laboratory findings of obese and control subjects.

	Obese with NAFLD (n = 64)	**Control (n = 32)**	**P**
Age (mean, year ± SD)	13.5 ± 1.36	13.8 ± 1.24	NS
Gender (F/M)	30 / 34	16 / 16	NS*
BMI (kg/m^2)	30.3 ± 3.13	20.1 ± 1.07	**0.001**
SDS-BMI	2.6 ± 0.34	0.29 ± 0.49	**0.001**
Glucose (mg/dL)	89.8 ± 8.5	87.8 ± 6.3	NS
ALT (U/L)	22.9 ± 14.8	16.6 ± 4	**0.002**
TC (mg/dL)	163.3 ± 29.5	138.4 ± 20.1	**0.001**
TG (mg/dL)	105.8 ± 39.3	84.7 ± 17.2	**0.001**
HARI	0.7463 ± 0.043	0.6962 ± 0.011	**0.001**

Data are given as means ± SD, difference at $P < 0.05$ level.
BMI, body mass index;
SDS-BMI: body mass index-standard deviation score;
ALT, alanine aminotransferase;
TC, total cholesterol;
TG, triglycerides;
HARI, hepatic artery resistive index;
NS, not significant,
* χ^2 test

Table 2. Clinical and laboratory findings of obese subjects with and without IR.

	Obese with NAFLD and IR (n = 32)	Obese with NAFLD without IR (n = 32)	P
Age (year)	13.4 ± 1.32	13.5 ± 1.43	NS
Gender (F/M)	11 / 21	19 / 13	NS‡
BMI (kg/m^2)	30.8 ± 3.5	29.8 ± 2.7	NS
SDS-BMI	2.7 ± 0.38	2.6 ± 0.29	NS
TSF (mm)	33.5 ± 8.9	30.9 ± 9.4	NS
MAC (cm)	31.5 ± 3.3	30.8 ± 3.9	NS
Glucose (mg/dL)	90.3 ± 9.2	89.5 ± 8	NS
ALT (U/L)	26.4 ± 17.9	19.6 ± 10	NS
TC (mg/dL)	164.3 ± 29.1	162.4 ± 3.3	NS
TG (mg/dL)	112 ± 43	99.6 ± 34.7	NS
Insulin (mU/mL)	22.7 ± 8.9	7 ± 2.2	**0.001**
HOMA-IR	6.2 ± 3.7	2.2 ± 0.68	**0.001**
HARI	0.761 ± 0.04	0.732 ± 0.04	**0.006**

Data are given as means ± SD, difference at $P < 0.05$ level.
BMI, body mass index;
SDS-BMI, body mass index-standard deviation score;
TSF, triceps skinfold;
MAC, middle arm circumference;
ALT, alanine aminotransferase;
TC, total cholesterol;
TG, triglycerides;
HOMA-IR: homeostasis model assessment for insulin resistance,
HARI, hepatic artery resistive index; NS, not significant;
‡ χ^2 test

with NAFLD and IR (n = 32) had significantly higher HARI compared to obese subjects without IR (n = 32). As an optimal cut-off point, a HARI level of 0.715 determined IR with 81.2% sensitivity and 71.9% specificity. In the diagnosis of IR, the area under the curve value was 0.808 ± 0.047 for HARI (P = 0.001). Positive and negative predictive values and diagnostic accuracy of this HARI cut-off were 59%, 70%, and 60.6%, respectively.

In the obese group with NAFLD and IR there were 5 subjects with ALT levels higher than the normal limits but none of them had ALT levels of twice the upper limit.

Discussion

Obesity is characterized by an impaired direct vasodilatory effect of insulin on microvasculature (22). Alteration in endothelial function is a common underlying event for vascular abnormalities observed in patients with obesity and IR most likely due to metabolic and inflammatory responses to the increased amount of stored fat. This impairment of endothelial function becomes obvious early on, long before any vascular abnormalities become clinically relevant and detectable. Recent studies have shown that reduced synthesis of vasodilator nitric oxide from L-arginine in endothelial cells is a major factor contributing to the impaired action of insulin in the

Table 3. Correlations between HARI, and anthropometric and laboratory parameters in obese subjects.

Variable		r	P
HARI			
	TSF	0.504	**0.001**
	BMI	0.578	**0.001**
	SDS-BMI	0.547	**0.001**
	TSF	0.549	**0.001**
	MAC	0.549	**0.001**
	ALT	0.223	**0.029**
	TC	0.306	**0.002**
	TG	0.121	NS
	Insulin	0.315	**0.011**
	HOMA-IR	0.295	**0.018**

BMI, body mass index;
SDS-BMI, body mass index-standard deviation score;
TSF, triceps skinfold;
MAC, middle arm circumference;
ALT, alanine aminotransferase;
TC, total cholesterol;
TG, triglycerides;
HOMA-IR: homeostasis model assessment for insulin resistance,
HARI, hepatic artery resistive index; NS, not significant.

vasculature of obese and diabetic subjects (23). Insulin derived endothelium-dependent vasorelaxation is reduced in rats with IR, hyperinsulinemia, hypertriglyceridemia, hyperlipidemia, and elevated blood pressure (24). The prevalence of IR is higher in obese children with NAFLD (25). IR state is an early sign of hepatic dysfunction in NAFLD (26). Although the Doppler flow pattern of hepatic veins has been shown to be altered in an obese population with liver steatosis (27), little information is available on hepatic arterial hemodynamics in obese adolescent subjects with NAFLD and IR. Although clamp techniques have been applied as a standard approach in the study of insulin sensitivity and insulin secretion during childhood, they are too invasive for general epidemiologic studies, and the HOMA has correlated well with clamp studies (23).

In the present study, we examined the relation of HARI evaluated by Doppler ultrasonography with anthropometric parameters such as BMI, SDS-BMI, TSF, and MAC, and laboratory parameters such as ALT, TC, TG, and HOMA-IR. Our results confirmed that ALT, TG, and TC levels and HARI level of obese subjects with fatty liver are significantly higher than those of lean subjects. Elevation in HARI level was also correlated significantly with BMI increase.

Hepatic artery resistive index is a Doppler ultrasonography parameter used to follow up microcirculatory resistance in fatty liver, alcoholic liver disease, chronic hepatitis, obesity, and post-transplant liver adult patients and in children with severe cirrhosis secondary to biliary atresia (12,15-18,27). Little information is available on hepatic arterial hemodynamics in obese adolescent subjects with NAFLD and insulin resistant lean subjects, and similarly, in our study, there was an important correlation between HARI and age and BMI, which is compatible with the results of earlier studies (26). Measurement of HARI may be useful for detection of the early hemodynamic changes related to liver dysfunction due to NAFLD and insulin resistant states in obese children. In the diagnosis of IR, the area under the curve value was 0.808 ± 0.047 for HARI (P = 0.001). Using a cut-off point of 0.715, HARI determined IR with 81.2% sensitivity and 71.9% specificity with positive and negative predictive values and diagnostic accuracy of 59%, 70%, and 60.6% respectively, in the determination of IR. Other laboratory tests were not significantly different in obese subjects with IR. Our findings reflect that this cut-off value has moderate accuracy in differentiating healthy subjects and individuals with IR. However, the lower positive and negative predictive values suggest that HARI cut-off may be used as a preliminary test for screening purposes. Larger studies with higher number of patients would be useful for determining the value of this test for diagnostic purposes.

Nadea et al. (25) and Schwimmer et al. (26) demonstrated that treatment of IR with metformin leads to improvement in the severity of fatty liver and ALT levels. Most of the pathogenetic factors for NAFLD (obesity, lipid profile changes, inflammation) are common for IR. Measurement of HARI may be informative about the microvascular pathology due to IR and indirect effect of NAFLD and may give a clue about risk stratification for that subject with fatty liver. This is the first case control clinical study to demonstrate the relation of HARI and IR in obese subjects.

Our study had a few limitations. First, we did not evaluate interobserver and intraobserver differences in measuring HARI. However, we followed strict guidelines for HARI measurements recommended in the literature, such as measurements must be done by a skilled radiologist using the same US equipment with the same hardware and software in standard conditions related to the patient (12). Measurements in this study were done by one skilled radiologist with the same machine at 1200 after 12 h of fasting in order to avoid the prandial effect. Another limitation was that we did not grade the degree of liver steatosis. Consequently, we did not investigate a possible relation between severity of steatosis and HARI.

The results of this study confirm the suggestion that the early recognition of IR and its effects on hemodynamics of liver is important, since steatohepatitis progression in NAFLD patients is strictly related to the presence of IR. In conclusion, we recommend that HARI be a preliminary candidate for the detection of early derangement of hepatic arterial perfusion due to IR. Further studies with larger series are warranted in order to determine the utility of HARI for screening and risk stratification purposes in obese children with NAFLD for development of IR.

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