Insulin/high-density lipoprotein cholesterol ratio: A newly-discovered predictor of esophageal varices in patients with hepatitis C virus-related cirrhosis in the absence of diabetes mellitus

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ABSTRACT

Background/Aims: *Insulin resistance (IR) is closely linked with chronic hepatitis C virus (HCV) and its complications, particularly hepatic fibrosis. The aim of the present study was to investigate some biochemical markers that are potentially related to IR as predictors of esophageal varices (EV) in patients with compensated HCV cirrhosis who do not have diabetes or metabolic syndrome.*

Materials and Methods: *One hundred subjects without diabetes with compensated HCV-related cirrhosis who did not fulfill the diagnostic criteria of metabolic syndrome were subjected to clinical, laboratory, ultrasonographic, and endoscopic assessments.*

Results: *EV were evident in 73 patients with lower platelet counts and high-density lipoprotein cholesterol (HDL-C) levels. On the contrary, the fasting values of both insulin and glucose, the homeostatic model assessment for insulin resistance (HOMA-IR) score, and the bipolar diameter of the spleen of patients with EV were higher than those of other patients who were varices-free. Multivariate analysis confirmed insulin/HDL-C ratio (P=0.01) and HOMA-IR score (P=0.039) as predictors for the presence of varices. The best cut-off values above which the risk of the latter occurrence increased were 0.147 (sensitivity 89%) and 2.24 (sensitivity 72.6%) for both predictors, respectively.*

Conclusion: *The present study recorded two valid predictors of HCV-related EV: HOMA-IR score and insulin/HDL-C ratio. The latter is more sensitive and is likely more convenient in the case of individuals without diabetes. The validity of two IR-related predictors in the absence of metabolic syndrome confirmed the suggestion that the mechanism of IR-related HCV is different from that of the traditional metabolic syndrome.*

Keywords: *Insulin/HDL ratio, homeostasis model of assessment-insulin resistance, hepatitis C virus, predictors of esophageal varices, Insulin resistance, metabolic syndrome*

INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem worldwide with considerable morbidity and mortality (1). One of the main mechanisms responsible for HCV complications is insulin resistance (IR), as the virus per se is thought to decrease the sensitivity of insulin receptors (2,3). Several studies have linked HCV-induced IR with more hepatic inflammation and fibrosis (4,5).

Accordingly, as long as hepatic fibrosis correlates with the development of esophageal varices (EV), IR is thought to be associated with the occurrence of the latter (6). On the other hand, endoscopic screening of all patients with cirrhosis for any variceal evidence has been recommended (7). However, patients with early stages of cirrhosis often display much discomfort with such invasive procedures. Therefore, the poor compliance of those "asymptomatic" individuals has challenged the researchers to identify several predictors of variceal development with a view to reducing the need for diagnostic endoscopy (8,9).

In the context of IR, Camma et al. (10) identified the homeostatic model assessment for insulin resistance (HOMA-IR) score as a predictor of EV. The study was conducted on patients with Child A cirrhosis with HCV etiology. Further, it included comorbid subjects with obesity and/or diabetes mellitus.

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Nevertheless, even in patients with chronic HCV who are not obese or having diabetes, IR is well acknowledged to aggravate fibrosis (11-14). It is noteworthy, however, that the presence of obesity and/or diabetes is thought to adversely impress the course of liver cirrhosis (12,15). Furthermore, the state of IR is initiated in the early stages of chronic HCV, and its mechanisms are different from that of the more prevalent lifestyle-associated IR (3,16-18).

Therefore, we hypothesized that HOMA-IR scoring could be valid as a predictor of EV for patients with compensated cirrhosis with underlying HCV etiology in the absence of diabetes and metabolic syndrome. This was the key objective of the current study.

MATERIALS AND METHODS

We recruited 100 patients without diabetes with well compensated (Child-Pugh A) HCV-induced cirrhosis who did not meet the criteria of metabolic syndrome. Patients were subjected to thorough history taking and complete physical examination, searching for manifestations of chronic liver disease and diabetes, with special stress on any previous antiviral administration with its results.

Diagnosis of cirrhosis was based on the clinical, biochemical, and ultrasonographic criteria (19). The severity of the disease was assessed by the Child-Pugh score (1973). Patients administering insulin-sensitizing drugs, alcohol, or β blocker or having advanced cirrhosis, portal vein thrombosis, or severe comorbid diseases were excluded from the study. Patients with coinfection with hepatitis B virus or meeting the diagnostic criteria of diabetes mellitus (fasting blood glucose ≥126 mg/dL, 2-hour postprandial ≥200 mg/dL, and/or patient was already under therapy) or metabolic syndrome were also excluded.

Metabolic syndrome was defined based on the National Cholesterol Education Program Adult Treatment Panel III as the presence of three or more of the following five criteria (or the patient was under therapy): waist circumference ≥40 in. (for men) or 35 in. (for women), blood pressure ≥130/85 mm Hg, fasting triglyceride level ≥150 mg/dL, fasting high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL (for men) or 50 mg/dL (for women), and fasting blood sugar ≥100 mg/dL (20).

Laboratory investigations

After a 12-hour overnight fasting, a venous sample was extracted to determine the serum levels of insulin, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, total cholesterol, HDL-C, triglycerides, and plasma glucose (using a fully automated chemistry analyzer, Beckman Coulter AU480), as well as prothrombin time and viral markers (HCV antibody (Ab) and hepatitis B virus surface antigen (HBsAg)). The 2-hour postprandial plasma glucose concentration was assessed by another appropriate sample.

Hepatitis C virus Ab was determined by immunofluorescence assay (bioMérieux SA, France), with HBsAg assayed by enzyme-linked immunosorbent assay (ELISA; Biomedica, Sorin, Italy). On the other hand, prothrombin time was measured by a coagulometer (Coatron M1, TECO, Neufahrn, Germany) using a reagent (DiaMed GmbH, Ottobrunn, Germany).

Serum insulin was measured by chemiluminescence (Immulite, Siemens, UK). Thereafter, IR was estimated by the HOMA equation: HOMA-IR=fasting insulin (μU/mL)*fasting glucose (mg/dL)/405 (21).

Abdominal ultrasonography

All patients were examined using an ultrasound (Aplio™ 500 Platinum, Toshiba, Japan), searching for findings suggestive of cirrhosis, such as coarse heterogeneous echo pattern, surface nodularity, attenuated blood supply, and caudate lobe hypertrophy. Findings suggestive of portal hypertension were also reported. The bipolar diameter of the spleen, as well as diameters of the portal vein and the right liver lobe, was all measured.

Endoscopy

Upper gastrointestinal endoscopy was performed by the same endoscopist for all the included population using the PENTAX Medical EPK-i5000 video processor (PENTAX Medical, Japan). EV were detected and graded from 1 to 4 as classified by de Franchis et al. (22).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences version 22 (IBM Corp.; Armonk, NY, USA). Quantitative data were expressed as mean±standard deviation and analyzed by independent t-test or one-way analysis of variance (ANOVA) as appropriate. Qualitative data were expressed as number and analyzed by χ^2 test.

The correlation was made using a Pearson correlation test, and logistic regression was applied to evaluate the significant risk factors for EV. A $p<0.05$ was considered as statistically significant.

Receiver operating characteristic (ROC) curves were elaborated to determine the best cut-off values and to identify the area under the ROC curve (AUC) of the independent variables associated with the presence of EV. The specificity and sensitivity of the significant predictors were compared.

Ethical approval

The study was approved by the local research and ethics committee of the Al-Azhar University School of Medicine and performed in accordance with the principles of the Declaration of Helsinki and its appendices. Informed consent was obtained from the participants with a full explanation of the study protocol.

Table 1. Statistical evaluation of demographic and clinical data of patients with EV in comparison with patients without EV

	Patients with EV (n=73) Mean±SD	Patients without EV (n=27) Mean±SD	t (χ2)	p
Age (years)	50.16±8.57	48.41±8.35	0.916	0.36
Gender (M/F)	52/21	19/8	0.007	0.93
BMI (kg/m2)	23.27±1.68	23.89±1.14	-1.771	0.08
Family history of T2 DM (no)	4	3	0.96	0.32
Smokers (no)	14	8	1.25	0.26
HTN (no)	10	5	0.35	0.54
SBP (mm Hg)	120.00±7.63	120.37±7.58	-0.216	0.83
DBP (mm Hg)	77.47±6.01	78.15±5.90	-0.506	0.61

EV: esophageal varices; BMI: body mass index; T2 DM: type 2 diabetes mellitus; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2. Statistical evaluation of laboratory and ultrasonographic data of patients with EV in comparison with patients without EV

	Patients with (n=73) Mean±SD	Patients without EV (n=27) Mean±SD	t	p
ALT (Iμ/L)	46.74±16.46	47±21.68	0.064	0.949
AST (Iμ/L)	40.47±14.10	39.7±17.23	0.22	0.822
Bilirubin (mg/dL)	0.91±0.38	1±0.62	0.855	0.39
Albumin (g/dL)	3.98±0.36	4±0.58	-1.19	0.234
INR	1.263±0.2239	1.359±0.2832	-1.772	0.079
HDL-C (mg/dL)	44.59±10.26	56.02±13.27	4.55	<0.001
Fasting BG (mg/dL)	105.29±10.19	87.22±17.68	6.35	<0.001
Postprandial BG (mg/dL)	128.05±20.29	132.48±23.2	-0.931	0.354
Insulin (μU/mL)	22.49±15.98	9.64±8.93	3.94	<0.001
HOMA-IR	5.94±4.38	2.27±2.30	4.131	<0.001
Triglycerides (mg/dL)	120.82±26.56	118.89±25.01	0.32	0.744
Hb (g/dL)	12.11±1.11	12.44±1.16	1.31	0.19
WBC (10^3/mm)	6.69±1.97	6.71±2.21	0.061	0.95
Platelet (10^3/mm)	129.37±43.67	151.59±61.28	6.0433	0.047
Portal vein diameter (mm)	13.07±2.23	13±1.494	0.147	0.883
Right liver lobe diameter (mm)	149.45±25.86	153.52±23.526	0.714	0.477
Bipolar diameter of the spleen (mm)	131.26±27.37	120.19±14.31	1.99	0.048

EV: esophageal varices; ALT: alanine aminotransferase (N up to 45 Iμ/L); AST: aspartate aminotransferase (N up to 40 Iμ/L); INR: international normalized ratio (N 0.8-1.2); HDL-C: high-density lipoprotein cholesterol; BG: blood glucose, fasting insulin (N<25 μU/mL); HOMA-IR: homeostatic model assessment for insulin resistance (N<2.5); WBC: white blood cell; Hb: hemoglobin

RESULTS

The study included 100 (71 male and 29 female) patients with HCV-related cirrhosis. The mean age of the patients was 49.69±8.50 (range 30-69) years, and the mean body mass index was 23.47±1.63 (range 19.42-27.15) kg/m^2. Demographic and clinical criteria were comparable between patients with and without varices (Table 1). All patients showed the sonographic criteria for liver cirrhosis without ascites or focal lesions. EV were evident in 73 patients, with grade 1 in 20 (27.4%), grade 2 in 39 (53.4%), and grade 3 in 14 (19.2%). Cases with grade 4 EV were not recorded in the present study.

Throughout the univariate comparison of variables, we found no significant association between the classic liver function tests and the occurrence of EV. On the contrary, we recorded a significant increase in serum insulin, fasting plasma glucose (though not in the diabetic range), HOMA-IR score, and bipolar diameter of the spleen, with a significant decrease in HDL-C levels and platelet counts in patients with EV than the others (Table 2).

After exclusion of serum insulin and fasting glucose to avoid multicollinearity, multivariate logistic regression analysis of the above significant variables revealed high HOMA-IR score to be the only independent predictor of the existence of varices (odds ratio (OR), 1.303; 95% confidence interval (95% CI), 1.014-1.6741; p=0.039) (Table 3, test 1).

The statistically significant "paradoxical" alteration of both insulin and HDL-C values between patients with and without varices and within the variceal grades (Table 2, Figure 1) has inspired us to test a ratio between them as another predictor of variceal existence. Therefore, we applied the

Table 3. Multivariate analysis of predictors of esophageal varices

		B	Wald	p	Odds ratio	95% confidence interval for Exp (B)	
						Lower bound	Upper bound
Test 1	Intercept	2.093	0.663	0.416			
	HOMA-IR	0.265	4.274	0.039	1.303	1.014	1.674
	HDL-C	-0.056	3.017	0.082	0.946	0.888	1.007
	Platelets	-0.005	0.797	0.372	0.995	0.984	1.006
	Splenic diameter	0.012	0.783	0.376	1.012	0.986	1.038
Test 2	Intercept	-0.770	0.213	0.644			
	Insulin/HDL-C	2.655	6.639	0.010	14.220	1.888	107.126
	Platelets	-0.007	1.934	0.164	0.993	0.982	1.003
	Splenic diameter	0.015	1.462	0.227	1.015	0.991	1.040

HOMA-IR: homeostatic model assessment for insulin resistance; HDL-C: high-density lipoprotein cholesterol
Test 1 used HOMA-IR; test 2 used insulin/HDL-C ratio instead

Table 4. Multivariate analysis of predictors of esophageal varices in a cohort of patients with SVR after successful antiviral therapy

		B	Wald	p	Odds ratio	95% confidence interval for Exp (B)	
						Lower bound	Upper bound
Test 3	Intercept	0.651	0.055	0.815			
	HOMA-IR	0.583	3.287	0.070	1.791	0.954	3.361
	Platelets	-0.004	0.321	0.571	0.996	0.981	1.011
	Spleen	-0.007	0.085	0.770	0.993	0.947	1.041
Test 4	Intercept	1.150	0.152	0.697			
	Platelets	-0.004	0.266	0.606	0.996	0.982	1.011
	Spleen	-0.010	0.146	0.703	0.990	0.941	1.042
	Insulin/HDL-C	5.767	2.656	0.103	319.661	0.311	328,794.549

SVR: sustained virologic response; HOMA-IR: homeostatic model assessment for insulin resistance; HDL-C: high-density lipoprotein cholesterol
Test 3 used HOMA-IR; test 4 used insulin/HDL-C ratio instead

insulin/HDL-C ratio in the multivariate regression instead of HOMA-IR to avoid multicollinearity (as both include the serum insulin value as a component), assuming to be a predictor of varices, with the advantage of not including the glucose value as an element. Fortunately, the regression test revealed a more significant independent association between high insulin/HDL-C ratio and the occurrence of varices (OR, 14.220; 95% CI, 1.888-107.126; p=0.01) than that of the high HOMA-IR score (Table 3, test 2).

Moreover, the ROC curve performed to compare those independent predictors revealed an insulin/HDL-C ratio

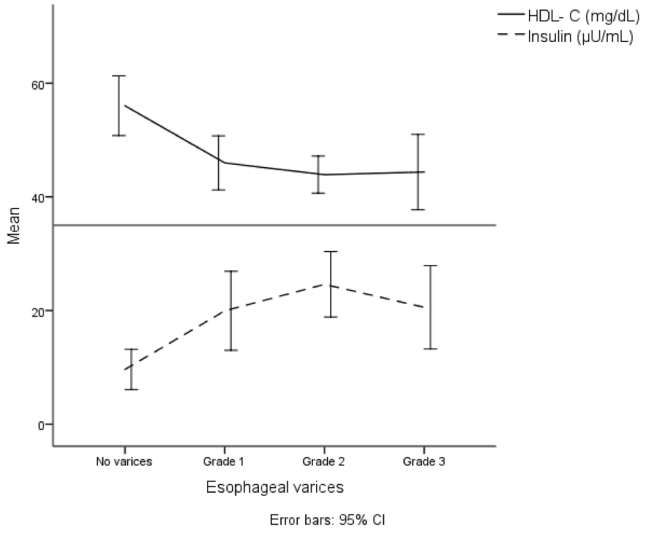

Figure 1. Paradoxical alteration of both levels of high-density lipoprotein cholesterol and serum insulin within different grades of esophageal varices

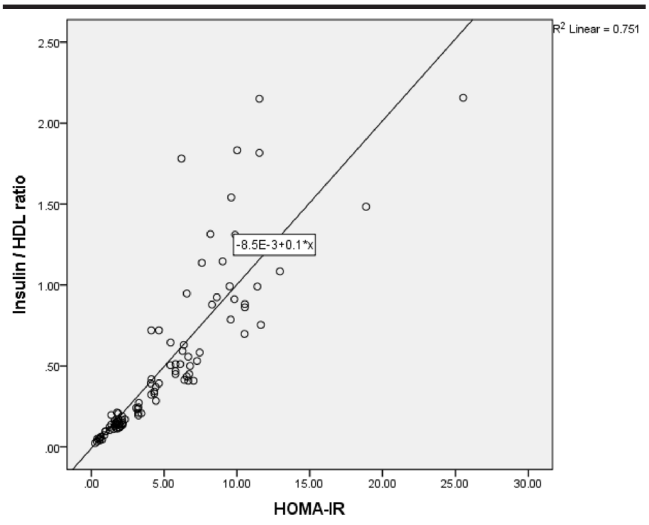

Figure 3. Strong positive correlation between values of homeostatic model assessment for insulin resistance and insulin/high-density lipoprotein cholesterol ratio in the population of the study (r=0.867, p<0.001)

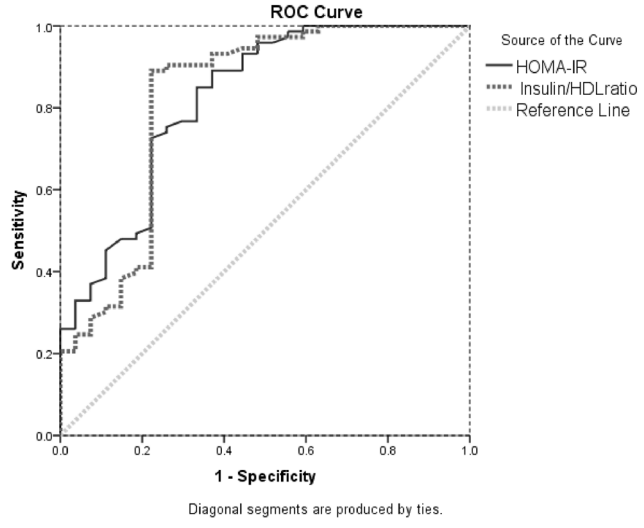

Figure 2. Receiver operating characteristic curve based on the evidence of any esophageal varices: HOMA-IR score (solid line) (AUC, 0.82; p<0.001; 95% CI, 0.722-0.919) and insulin/HDL-C ratio (dashed line) (AUC, 0.822; p<0.001; 95% CI, 0.712-0.931)
HDL-C: high-density lipoprotein cholesterol

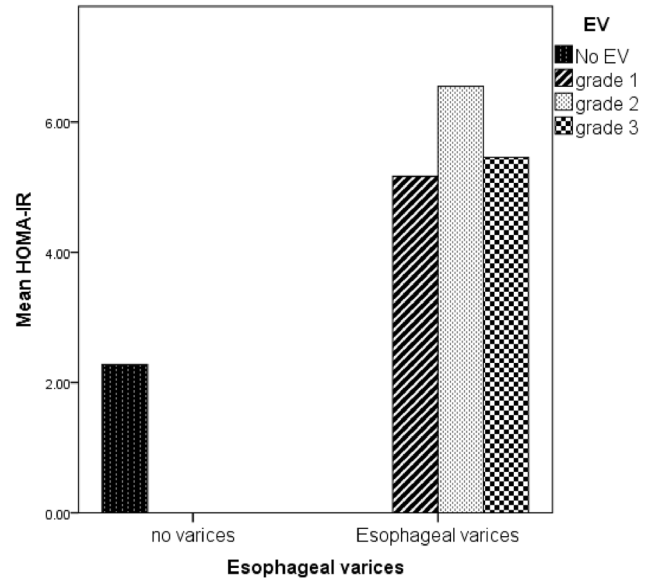

Figure 4. Mean values of HOMA-IR in patients with different grades of esophageal varices and in the absence of varices (p<0.001)

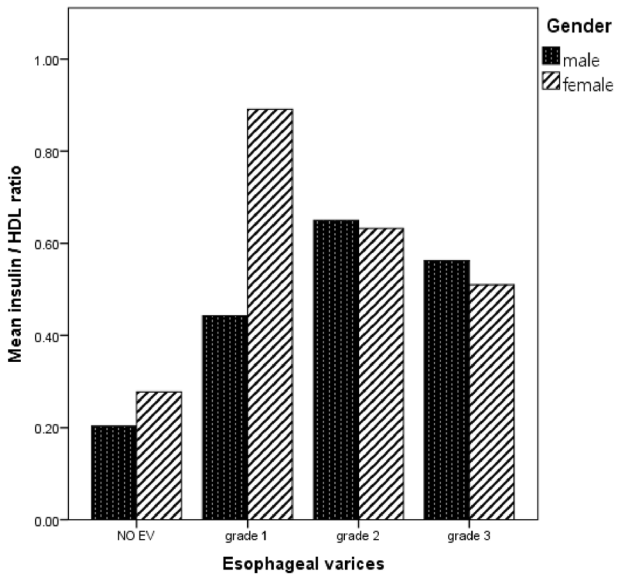

Figure 5. Mean values of insulin/high-density lipoprotein cholesterol ratio in patients with different grades of esophageal varices and in the absence of varices (p=0.007)

of 0.147 (AUC, 0.822; p<0.001; 95% CI, 0.712-0.931; sensitivity 89.04%; specificity 77.7) and an HOMA-IR score of 2.24 (AUC, 0.82; p<0.001; 95% CI, 0.722-0.919; sensitivity 72.6%; specificity 62.96%) as the best cut-off values above which the risk of the occurrence of EV increased (Figure 2).

Furthermore, by applying the Pearson correlation test for studying the direct relationship between both independent predictors, we noticed a strong positive correlation (r=0.867, p<0.001) (Figure 3). On the contrary, on comparing the grades of EV in terms of either HOMA-IR score or insulin/HDL-C ratio separately, one-way ANOVA provided significant associations for both (p<0.001 and p=0.007, respectively) (Figure 4, 5).

Particularly, a cohort of 27 patients among our study population had already received specific anti-HCV therapy in the form of the sofosbuvir-daclatasvir regimen. They all had a sustained virologic response, with documented HCV-RNA below the detection limit after at least 6 months of stopping the treatment. It is noteworthy that the statistical application of the above two independent predictors in that group revealed no significant associations with the presence of varices (Table 4, tests 3, 4).

DISCUSSION

Insulin resistance is relatively an early phenomenon during the course of HCV infection that plays a significant role in the pathogenesis of hepatic fibrosis (3-5,11,16-18). Consequently, it may be linked with the development of EV (10).

In contrast, it is well acknowledged that HCV infection is also associated with type 2 diabetes mellitus, in which hyperglycemia is another additional risk for more hepatic fibrosis (18). Moreover, the role of obesity per se in perturbing the course of compensated cirrhosis has been recognized (11,15).

To the best of our knowledge, this is the first study to evaluate HOMA-IR score as a predictor of EV in patients with HCV, independent of the comorbidity of diabetes or even metabolic syndrome.

In the case of variceal existence in the present study, we recorded higher HOMA-IR scores. This positive association remained existing within different variceal grades. Moreover, the high HOMA-IR score was an independent predictor for the presence of EV in our cohort.

Previous studies investigated the association of IR with portal hypertension or EV in different situations. A recent Japanese study examined 53 patients with heterogeneous kinds of chronic liver diseases and found a close link between IR and impaired portal hemodynamics (23). The Japanese study did not exclude, however, patients who are obese or have diabetes. A similar finding was reported by a similarly designed Egyptian study (24). Degré et al. (25) linked IR with EV in alcoholic liver disease, whereas Jeon et al. (26) investigated the role of IR in the case of hepatogenous diabetes and demonstrated a significant link between IR and episodes of variceal hemorrhage in that kind of patients.

On the other hand, Camma et al. (10) studied 104 patients with child a HCV-induced cirrhosis and concluded that high HOMA-IR is linked with the occurrence of EV. In contrast with the present study, 26% of their patients already had diabetes, and some were obese.

Previous studies, however, demonstrated the presence of IR before the occurrence of diabetes (3,11). These data are in accordance with our results in patients without diabetes or metabolic syndrome comorbidity. In addition, the underlying mechanism responsible for HCV-related IR (although beyond the scope of this article) is not po-

tentially the same as that of the "regular" metabolic syndrome (27). Furthermore, the use of insulin-sensitizing drugs, usually prescribed for that syndrome, remained a matter of controversy for the HCV-induced IR (28).

The striking result in our setting is the validity of the ratio of insulin/HDL-C as a new independent predictor of variceal development. Despite the current evidence of a strong correlation between them and although not far from the concept of IR, this novel predictor is potentially more sensitive than the traditional HOMA-IR scoring (OR, 14.220, p=0.010 and OR, 1.303, p=0.039, respectively). That is just what we have also confirmed from data of the ROC curve (the sensitivity of the cut-off values was 89% for insulin/HDL-C ratio versus 72% for HOMA-IR scoring).

Another advantage of this newly identified predictor is that it does not include blood glucose as an element in its component. Hence, it may be more credible in patients without diabetes or even impaired glucose homeostasis, particularly as a considerable category of patients with HCV remains unsuffered from diabetes.

Interestingly, on performing the multivariate analysis in the subgroup of patients previously treated with direct antiviral drugs, no independent predictors resulted. Therefore, it appears that the above predictors might lose their reliability with the improvement of insulin sensitivity already gained by the successful viral clearance (29).

One of the limitations of the present study is the relatively limited sample size. In addition, the diagnosis of cirrhosis was based on the clinical and imaging criteria rather than the invasive liver biopsy. Finally, we did not test the HCV-RNA for all patients. Nevertheless, we have used the third generation ELISA-based diagnosis that detects all the HCV genotypes with an accuracy of 99% for both specificity and sensitivity (30). The main strength of this work came from performing the study on a homogeneous population with compensated HCV-induced cirrhosis who were assessed by the same endoscopist.

In conclusion, two independent predictors of EV in patients with child A HCV cirrhosis have been validated in the absence of diabetes or metabolic syndrome, HOMA-IR score and insulin/HDL-C ratio. The latter is a novel marker and is more sensitive. The predictors lose their validity if the patient is cleared of the virus using recent drugs. The identification of two predictors that are potentially related to IR in such population adds evidence to the previous data suggesting the underlying mechanism of HCV-related IR differs from that of type 2 diabetes and metabolic syndrome.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Al-Azhar University School of Medicine.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.N.E., M.S.B., T.E.; Design - K.N.E., M.S.B., T.E.; Supervision - K.N.E., M.S.B., T.E.; Materials - K.N.E., M.S.B., T.E.; Data Collection and/or Processing - K.N.E., M.S.B., T.E.; Analysis and/or Interpretation - K.N.E., M.S.B., T.E.; Literature Search - K.N.E., M.S.B., T.E.; Writing Manuscript - K.N.E., M.S.B., T.E.; Critical Reviews - K.N.E., M.S.B., T.E.

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REFERENCES

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57: 1333-42. [CrossRef]

2. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 2004; 126: 840-8. [CrossRef]

3. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology 2008; 134: 416-23. [CrossRef]

4. Stranges S, Trevisan M, Dorn JM, Dmochowski J, Donahue RP. Body distribution, liver enzymes, and risk of hypertension: evidence from the Western New York Study. Hypertension. 2005; 46: 1186-93. [CrossRef]

5. Banerjee A, Meyer K, Mazumdar B, Ray RB, Ray R. Hepatitis C virus differentially modulates activation of forkhead transcription factors and insulin-induced metabolic gene expression. J Virol 2010; 84: 5936-46. [CrossRef]

6. Svegliati-Baroni G, De Minicis S, Marzioni M. Hepatic fibrogenesis in response to chronic liver injury: novel insights on the role of cell-to-cell interaction and transition. Liver Int 2008; 28: 1052-64. [CrossRef]

7. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43: 167-76. [CrossRef]

8. de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol 2008; 49: 520-7. [CrossRef]

9. Zaman A, Hapke RJ, Flora K, Rosen HR, Benner KG. Changing compliance to the American College of Gastroenterology guidelines for

the management of variceal hemorrhage: a regional survey. Am J Gastroenterol 2004; 99: 645-9. [CrossRef]
10. Camma C, Petta S, Di Marco V et al. Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. Hepatology 2009; 49: 195-203. [CrossRef]
11. Hickman IJ, Powell EE, Prins JB, et al. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. J Hepatol 2003; 39: 1042-8. [CrossRef]
12. Petit JM, Bour JB, Galland-Jos C, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. J Hepatol 2001; 35: 279-83. [CrossRef]
13. El Ray A, Asselah T, Moucari R, et al. Insulin resistance: a major factor associated with significant liver fibrosis in Egyptian patients with genotype 4 chronic hepatitis C. Eur J Gastroenterol Hepatol 2013; 25: 421-7. [CrossRef]
14. Ziada DH, El Saadany S, Enaba M, Ghazy M, Hasan A. The interaction between insulin resistance, liver fibrosis and early virological response in Egyptian patients with chronic hepatitis C. Can J Gastroenterol 2012; 26: 325-9. [CrossRef]
15. Berzigotti A, Garcia-Tsao G, Bosch J, et al. for the Portal Hypertension Collaborative Group. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011; 54: 555-61. [CrossRef]
16. Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am J Pathol 2004; 165: 1499-508. [CrossRef]
17. Kralj D, Virović Jukić L, Stojsavljević S, Duvnjak M, Smolić M, Čurčić IB. Hepatitis C Virus, Insulin Resistance, and Steatosis. J Clin Transl Hepatol 2016; 4: 66-75. [CrossRef]
18. Petta S, Camma 'C, Di Marco V, et al. Insulin resistance, and diabetes, increase fibrosis in the liver of patients with HCV genotype 1 infection. Am Journal Gastroenterol 2008; 103: 1136-44. [CrossRef]
19. Gomez EV, Rodriguez YS, Bertot LC. the natural history of compensated HCV-related cirrhosis: A prospective long-term study. J Hepatol 2013; 58: 434-44. [CrossRef]
20. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung and Blood Institute scientific statement. Circulation 2005; 112: 2735-52. [CrossRef]
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9. [CrossRef]
22. de Franchis R, Pascal JP, Ancona E, et al. Definitions, methodology and therapeutic strategies in portal hypertension. A Consensus Development Workshop, Baveno, Lake Maggiore, Italy, April 5 and 6, 1990. J Hepatol 1992; 15: 256-61. [CrossRef]
23. Maruyama H, Kobayashi K, Kiyono S, Yokosuka O. Interrelationship between insulin resistance and portal haemodynamic abnormality in cirrhosis. Int J Med Sci 2017; 14: 240-5. [CrossRef]
24. Eslam M, Ampuero J, Jover M, et al. Predicting portal hypertension and variceal bleeding using non-invasive measurements of metabolic variables. Ann Hepatol 2013; 12: 588-98.
25. Degré D, Gustot T, Gerkens A, et al. Insulin resistance is associated with esophageal varices in alcoholic liver disease patients. Eur J Gastroenterol Hepatol 2016; 28: 792-6. [CrossRef]
26. Jeon HK, Kim MY, Baik SK, et al. Hepatogenous diabetes in cirrhosis is related to portal pressure and variceal hemorrhage. Dig Dis Sci 2013; 58: 3335-41. [CrossRef]
27. Yoneda M, Saito S, Ikeda T, et al. Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients. J Viral Hepat 2007; 14: 600-7. [CrossRef]
28. Kawaguchi T, Sata M. Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulin sensitization. World J Gastroenterol 2010; 16: 1943-52. [CrossRef]
29. Kawaguchi T, Ide T, Taniguchi E, et al. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. Am J Gastroenterol 2007; 102: 570-6. [CrossRef]
30. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J Viral Hepat 2001; 8: 87-95. [CrossRef]