Insulin resistance and hepatitis C infection: a bidirectional relationship independent of diabetes and metabolic syndrome

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Introduction
Hepatitis C virus (HCV) infection is known to be associated with insulin resistance (IR). The latter occurs early in the course of the disease and adversely affect it. The mechanism of this association seems to be different from that occurring in the metabolic syndrome. The aim of the study was to test this relationship in non-diabetic patients with early cirrhosis who are not fulfilling the criteria of metabolic syndrome.

Patients and methods
This cross-sectional study, included 100 patients with Child A cirrhosis induced by HCV. The patients were subjected to clinical, laboratory, ultrasonographic, and endoscopic evaluation. On the basis of homeostasis model assessment for insulin resistance (HOMA-IR) categorization, the patients were divided into two groups, with and without IR.

Results
A total of 63 patients had a higher HOMA-IR score, hence assigned as group 1, with significant elevation of liver enzymes, less albumin levels and more esophageal varices than in group 2. In a cohort of patients previously eradicated from the virus, HOMA-IR is lower than the non-treated patients.

Conclusion
Even in the absence of diabetes and metabolic syndrome, IR is evident in nearly two-thirds of patients having early HCV-induced cirrhosis. This link is associated with more inflammation of the liver and more drawbacks on the portal circulation. Sustained clearance of the virus improves insulin sensitivity.

Keywords:
hepatitis C virus, insulin resistance, liver cirrhosis, metabolic syndrome

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Introduction

The prevalence of insulin resistance (IR) in patients with chronic hepatitis C virus (HCV) is significantly higher than that in the general population [1]. This has been reported to occur early during HCV infection [2]. Furthermore, the latter may be viewed as a metabolic disease closely related to the metabolic syndrome [3,4].

The relationship between IR and HCV infection, however, is thought to be bidirectional; IR, in turn, influences the natural history of chronic HCV infection in different aspects; first, it is linked with fibrosis progression [2,5]. Second, it shares in the pathogenesis of portal hypertension [6]. Third, it is thought to be associated with the development of hepatocellular carcinoma [7]. Fourth, IR was reported to be associated with a poor response to antiviral treatment [8].

Therefore, patients with HCV infection have a higher homeostasis model of assessment for insulin resistance (HOMA-IR) index than nonhepatic patients matched for age, sex, and BMI [9]. Moreover, the underlying mechanisms responsible for HCV-induced IR are potentially different from that of the metabolic syndrome and type 2 diabetes mellitus [10]. In contrast, both obesity and diabetes have been found to impact the natural history of compensated cirrhosis [11–13]. Consequently, it becomes wise to evaluate the relationship between IR (measured by HOMA-IR) and the early HCV-induced cirrhosis in non-diabetic patients not fulfilling the metabolic syndrome criteria, and that was the aim of this study.

Patients and methods

This was a cross-sectional study, carried out on 100 patients at the Internal Medicine Department, Al-Azhar University Hospital in New Damietta from October 2016 to September 2017. Patients

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who were shown to have early HCV-related cirrhosis but not known to be diabetic or fulfilling the criteria of diagnosis of diabetes or metabolic syndrome were included in the study.

All patients were subjected to thorough history taking and clinical examination. In addition, they were examined by abdominal ultrasonography for findings suggestive of cirrhosis such as coarse surface, irregular border, and attenuated blood supply, as well as measurement of the hepatic and splenic size, and the portal vein diameter (normally up to 13 mm).

Using the HOMA-IR index (categorical; ≥2.5 vs. <2.5), the patients were divided into two groups: group 1, included 63 patients having IR, and group 2, 37 patients without IR.

From the patient histories taken, a group of 27 patients were shown to receive oral antiviral therapy in the recent past and achieved sustained virological response (SVR) with documented HCV clearance after 6 months of the end of treatment. This group was subjected to a statistical comparison with the other patients.

Diagnosis of cirrhosis was dependent on the clinical, biochemical, and ultrasonographic features [14], while the metabolic syndrome was identified based on the National Cholesterol Education Program Adult Treatment Panel III. The diagnosis was confirmed on the presence of three or more of the following five criteria: waist circumference of more than 102 cm (men) or 88 cm (women), blood pressure of more than 130/85 mmHg (or under therapy), triglyceride level of more than 150 mg/dl, high-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar of more than 100 mg/dl (or under therapy) [15].

Any of the following were considered as an exclusion criterion: advanced cirrhosis (Child B or C), any underlying cause of cirrhosis rather than HCV, severe comorbid diseases, and administration of alcohol or β-blockers as well as the presence of diabetes mellitus or metabolic syndrome.

Laboratory investigations

After 12-h overnight fasting, 5 ml of blood was drawn to assess the liver functions [serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, prothrombin, and albumin], total cholesterol, HDL-C, triglycerides, fasting plasma glucose, HCV antibodies (Biomarieux SA, Marcy-l'Étoile, France), and hepatitis B virus surface antigen (Biomedica, Sorin, Italy). Another sample was taken to determine the 2-h postprandial plasma glucose concentration. Serum insulin was measured by chemiluminescence (Immulite; Siemens Healthcare Products Ltd, Surrey, UK). IR was estimated by the HOMA equation: HOMA-IR=fasting insulin (μU/ml)×fasting glucose (mg/dl)/405 [16].

Endoscopic evaluation

Aiming at the detection of esophageal varices as complications of cirrhosis [17], an endoscopic examination was performed by the same endoscopist using a flexible video gastroscope (The PENTAX Medical EPK-i5000 video processor; PENTAX Medical, Tokyo, Japan).

Statistical analysis

The collected data were statistically analyzed using the statistical package for the social sciences (SPSS Inc., Chicago Illinois, USA), version 19. Quantitative data were expressed as the mean±SD and analyzed by the sample unpaired *t*-test. While qualitative data were expressed as number and percentage distribution and analyzed by χ^2-test. A *P* value of less than 0.05 was considered significant.

Ethical approval

The study was performed in accordance with the principles of the Declaration of Helsinki and its appendices. An informed consent was obtained from each participant after full explanation of the study protocol. The study was approved by the Local Research Ethics Committee of the Faculty of Medicine, Al-Azhar University.

Results

Demographic criteria of the patients are shown in Table 1. Out of 100 patients included in the study,

Table 1 General characteristics of the whole study population (*N*=100)

Variables	Mean±SD
Age (years)	49.69±8.50
Sex (male/female) (*n*)	71/29
Weight (kg)	71.07±7.43
Height (m)	1.74±0.08
BMI (kg/m^2)	23.47±1.63
SBP (mmHg)	123.10±10.98
DBP (mmHg)	78.65±6.27
HOMA-1R≥2.5 (*n*)	63
Smokers (*n*)	22
Family history of DM (*n*)	7
HTN (*n*)	15

DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; SBP, systolic blood pressure.

63 was having a HOMA-IR score of at least 2.5, and accordingly, the patients were divided into two groups. Group 1 had 63 patients with IR and group 2 had 37 patients without IR (Tables 2 and 3). Regarding demographic data, there were no significant differences between both the groups (Table 2).

There were statistical differences between groups 1 and 2 in terms of ALT (P=0.005), AST (P=0.009), HDL-C (P<0.001), and serum albumin (P=0.006). The prevalence of esophageal varices in the group of patients with IR was significantly higher (88.9%) than the other group (45.9%) (P=0.024) (Table 3).

On comparing the cohort of patients having varices to those with no evidence of varices, we found statistically higher HOMA-IR in the former (5.94±4.38 vs. 2.27±2.30) (P<0.001) (Fig. 1).

Throughout the direct questionnaire, 27 patients in our study population were found to receive antiviral therapy (in the form of sofosbuvir–daclatasvir regimen) with documented SVR, defined as the persistent absence of HCV-RNA in serum 6 months or more after completing antiviral treatment. The remaining patients had no previous history of receiving antiviral therapy. We noted a significant decrease in HOMA-IR score in the treated than in the nontreated patients (P=0.039) (Table 4).

Discussion

Despite the exclusion of patients with metabolic syndrome and diabetes in this study, approximately two-third of our patients with chronic HCV were having elevated HOMA-IR (group 1). In that group, patients had elevated liver enzymes (ALT and AST), and decreased serum albumin levels in comparison to patients in group 2 (P=0.005, 0.009, 0.006, respectively). This may reflect a consequence of more severe inflammation associated with IR [18,19].

The higher prevalence of IR in this kind of liver disease compared with that in the general population is well acknowledged [20]. It was suggested that the direct viral effects of HCV on insulin signaling or the inflammatory response to that infection contributes to the development of IR [2,21]. Therefore, it is likely that the underlying mechanism of IR, in this case, is different from that occurring in diabetic or obese population [22].

Table 2 Demographic data of group 1 in comparison with group 2

	Group 1 (mean±SD)	Group 2 (mean±SD)	*P*
Age (years)	50.29±8.89	48.68±7.81	0.363
Sex (male/female) (*n*)	44/19	27/10	0.739
BMI (kg/m^2)	24.52±1.46	23.37±1.89	0.666
SBP (mmHg)	123.02±11.59	132.24±10.02	0.921
DBP (mmHg)	78.97±6.49	82.11±5.93	0.511
Smoker [*n* (%)]	14 (22.2)	8 (21.6)	0.944
FH of DM [*n* (%)]	5 (7.9)	2 (5.4)	0.632
HTN [*n* (%)]	10 (15.9)	5 (13.5)	0.750

DBP, diastolic blood pressure; FH of DM, family history of diabetes mellitus; HTN, hypertension; SBP, systolic blood pressure.

Table 3 Laboratory, ultrasonographic, and endoscopic findings of both groups

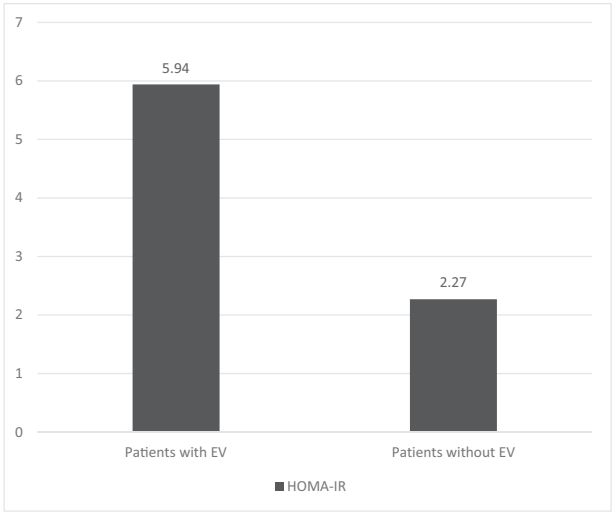
Parameters	Group 1 (mean±SD)	Group 2 (mean±SD)	*P*
ALT (IU/l)	50.79±14.95	39.54±20.31	0.005
AST (IU/l)	43.22±13.64	35.22±15.84	0.009
Bilirubin (mg/dl)	0.93±0.40	0.95±0.55	0.857
Albumin (g/dl)	3.92±0.37	4.17±0.50	0.006
INR	1.31±0.22	1.27±0.31	0.503
HDL-C (mg/dl)	42.66±10.86	56.22±9.36	<0.001
Triglycerides (mg/dl)	122.84±27.04	115.97±23.97	0.205
Postprandial plasma glucose (mg/dl)	128.70±6.21	132.24±5.69	0.218
Fasting plasma glucose (mg/dl)	108.62±11.21	86.43±14.61	<0.001
Fasting insulin (μU/ml)	26.51±15.02	6.28±2.19	<0.001
HOMA-IR	8.19±4.57	1.36±0.60	<0.001
PV diameter (mm)	13.16±2.27	13.24±1.99	0.852
Esophageal varices [*n* (%)]	56 (88.9)	17 (45.9)	0.024

ALT, alanine aminotransferase (N up to 45 IU/l); AST, aspartate aminotransferase (N up to 40 IU/l); fasting insulin (N<25 μU/ml); HDL-C, high-density lipoprotein cholesterol; HOMA-R, homeostatic model assessment for insulin resistance (N<2.5); INR, international normalized ratio (N: 0.8–1.2); PV, portal vein.

Once developed, HCV-related IR initiates the activation of the stellate cells resulting in the progression of the fibrosis process in the liver [23]. Throughout direct and indirect mechanisms (e.g. endothelial dysfunction), this fibrosis shares in the development of portal hypertension and esophageal varices [24].

Our results have shown a higher prevalence of varices in a cohort of patients with IR (group 1) compared with the other group (88.9 vs. 45.9%, respectively, P=0.024). Moreover, there was a statistically elevated HOMA-IR score in patients having esophageal varices compared with those without evidence of varices (P<0.001).

Figure 1



Levels of homeostatic model assessment for insulin resistance (HOMA-IR) in patients with and without esophageal varices (EVs) (P<0.001).

In the context of HCV, a significant association between IR and esophageal varices in HCV-related cirrhosis has been reported by Camma *et al.* [25]. This study included, however, obese and diabetic patients. The antidiabetic drugs used by those patients may impact the results.

However, our novel results in patients without comorbidity of diabetes or metabolic syndrome are supported by data considering IR at the early stages of HCV infection [2,26]. Also, the precedence of HCV-related IR on the occurrence of diabetes has been reported [2,11]. Furthermore, Antuna-Puente *et al.* [27] demonstrated that the function of ß cells was upgraded in early HCV infection with normal plasma glucose resulting in higher HOMA-IR values.

In contrast, HCV infection in Egypt is almost always of genotype 4, in which IR starts early and facilitates the progression of hepatic fibrosis [28,29]. This is also in support of our results in a cohort of nondiabetic, nonobese patients (although we did not confirm the genotypes, and that is one of the limitations of this study). Conversely, patients infected with genotype 3 have lower HOMA-IR values than the patients infected with other genotypes even after adjustment for the effects of BMI [30].

The relationship between IR and treatment response of HCV is potentially bidirectional. In other words, the presence of IR has been shown to impair treatment response and, *vice versa*, regress following successful treatment outcome. Therefore, IR is associated with low response rates in chronic hepatitis C patients [8,31–33], while eradication of the virus results in

Table 4 Comparison between patients with sustained virological response and the nontreated patients

	Patients with SVR (N=27) (mean±SD)	Patients not receiving antiviral therapy (N=73) (mean±SD)	t (X_2)	P
Sex n (male/female)	20/7	51/22	0.1698	0.68
Age (years)	48.74±7.48	50.24±8.92	0.778	0.44
BMI (kg/m^2)	23.82±1.79	23.39±1.54	1.123	0.26
ALT (IU/l)	45.30±20.19	47.25±17.09	0.482	0. 631
AST (IU/l)	38±12.98	41.1±15.59	0.92	0.36
Albumin (g/dl)	4.03±0.48	4±0.43	0.267	0.79
INR	1.28±0.27	1.31±0.26	0.47	0.639
Triglyceride (mg/dl)	115.67±13.32	119.23±20.4	0.791	0.432
HDL-C (mg/dl)	50.11±12.47	46.82±12.08	1.162	0.248
Fasting plasma glucose (mg/dl)	97.74±17.10	101.4±16.28	0.984	0.73
Postprandial plasma glucose (mg/dl)	132.07±15.9	130.97±22.1	0.238	0.813
Fasting insulin (μU/ml)	15.99±12.7	20.15±16.32	1.198	0.234
HOMA-IR	4.640±3.77	6.563±4.19	2.091	0.039
Esophageal varices [*n* (%)]	19 (70.37)	54 (73.79)	0.1298	0.72

ALT, alanine aminotransferase (N up to 45 IU/l); AST, aspartate aminotransferase (N up to 40 IU/l); fasting insulin (N<25 μU/ml); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance (N<2.5); INR, international normalized ratio (N: 0.8–1.2); SVR; sustained virological response.

amelioration of IR [34,35]. In agreement with that, our results have shown a significant decrease in HOMA-IR in patients gained SVR after successful treatment than the remaining nontreated patients. Whether the use of insulin sensitizers or regulation of weight, diet, and lifestyle management can help in preventing the distinctive complications of HCV-associated IR have not yet been established. Also, the use of insulin sensitizers in the antiviral protocol for chronic HCV is still a matter of controversy [36–39].

This study included homogeneous populations. However, we did not measure the HCV-RNA, but the third-generation enzyme-linked immunosorbent assay-based diagnosis used detects all the HCV genotypes with a specificity and sensitivity of ~99% [40].

Conclusion

IR was frequent in patients in early stages of HCV-related cirrhosis and was associated with derangement of the functions of the liver and with more esophageal varices. The high frequency of IR, in that case, was independent of the presence of the more common disorders such as diabetes and metabolic syndrome. Successful eradication of the virus had a positive impact in mitigating IR.

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All authors contribute to the study design, data collection and interpretation, drafting, and/or revision of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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