

Impact of Insulin Resistance on Therapeutic Response to Oral Treatment of Chronic Hepatitis C Virus Infection

Magda S. Hassan¹, Soha Saoud Abd El Monem¹, Ahmad F. Hasanain¹, Rasha Hosny Sayed¹, Amal Abdel Aziz²

1 Department of gastroenterology and hepatology, Assiut Univeristy, Egypt;

2 Department of clinical pathology, Assiut Univeristy, Egypt.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Correspondence to: Rasha Hosny Sayed, Department of gastroenterology and hepatology, Assiut Univeristy, Egypt.

Email: rashahosny86@yahoo.com

Telephone: +2001093241729

Received: December 10, 2019

Revised: December 20, 2019

Accepted: December 22, 2019

Published online: February 21, 2020

ABSTRACT

AIM: HCV infection is one of the major health problems in our country. Prevalence of DM is higher among patients with chronic HCV infection. Insulin resistance (IR) is common in such and its impact on sustained virological response (SVR) is not well studied. This work was designed to assess impact of IR on SVR.

METHODS: Between July 2016 and June 2017; two hundred patients with chronic HCV infection were enrolled in a prospective study. Exclusion criteria included decompensated cirrhosis, hepatocellular carcinoma or extrahepatic malignancy, co-infection with HBV or HIV infection. HOMA and IR were assessed at baseline of therapy and 3-months post-therapy. Patients received sofosbuvir and daclatasvir for 3 months (chronic hepatitis) and for 6 months in (liver cirrhosis).

RESULTS: Mean age of patients was 49.89 ± 9.01 years, 111 (55.5%) patients were male and 180 (90%) achieved SVR. Baseline

IR had insignificant difference between responders and non-responders (93% vs. 90%; $p = 0.45$), while baseline HOMA was significantly higher in non-responders (10.11 ± 3.03 vs. 8.48 ± 2.98 ; $p = 0.01$). Also, post-therapy IR had insignificant difference between both groups (73.3% vs. 85%; $p = 0.05$), while post-therapy HOMA was significantly higher in non-responders (7.12 ± 2.31 vs. 5.06 ± 1.34 ; $p = 0.01$). Predictors of non-responders were age (> 40 years), low serum albumin and post-therapy IR.

CONCLUSION: Baseline IR had no impact on SVR but it showed significant improvement in presence of SVR.

Key words: Insulin resistance; Homeostatic model assessment; Sustained virological response

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Hassan MS, El Monem SSA, Hasanain AF, Sayed RH, Aziz AA. Impact of Insulin Resistance on Therapeutic Response to Oral Treatment of Chronic Hepatitis C Virus Infection. *Journal of Gastroenterology and Hepatology Research* 2020; 9(1): 3088-3092 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2756>

INTRODUCTION

Globally, hepatitis C virus (HCV) is considered a major cause morbidity and death. Worldwide, more than 185 million individuals are infected with HCV, about 350000 patients from them die annually. It has been estimated that while the incidence of HCV infection seems to decrease in the developed world, mortality secondary related to HCV infection will continue to increase over the next 20 years^[1].

In Egypt, HCV infection is considered one of the major causes of chronic liver diseases that may be associated with serious sequelae as cirrhosis (LC), hepatocellular failure, and hepatocellular carcinoma (HCC)^[2].

In fact, HCV treatment passed through two important treatment phases; pegylated interferon/ribavirin (Peg IFN/RBV) therapy and direct-acting antiviral (DAAs) therapy. In the former treatment, the protocol is complicated, associated with more side effects and lower cure rates, in contrast to the latter^[3].

There is a causal relationship between HCV and diabetes mellitus (DM). Its known that the prevalence of HCV is higher among diabetic patients and a higher frequency of DM is noticed among

patients with HCV-related liver disease also have a higher prevalence of diabetes mellitus^[4].

Also, those patients with HCV-related liver disease had higher incidence of insulin resistance (IR). IR in patients with HCV infection is responsible for reduced response to PegIFN/RBV therapy, steatosis, liver fibrosis, and cirrhosis complications, especially varices and hepatocellular carcinoma^[5].

Higher frequency of DM and IR among patients with HCV infection isn't clearly understood but there are many theories for this issue. B-cell dysfunction that increases with advancing of liver disease may explain occurrence of DM while IR was said to be secondary to direct inhibitory effect of HCV on insulin signaling pathway^[6].

Till our knowledge there were limited studies about effect of IR on response to DAA in patients with HCV, particularly in our country that had higher prevalence of DM and HCV infection. This work was designed to study impact of IR on response to DAA.

PATIENTS AND METHODS

Patients and study setting

After obtaining approval from Local Ethical Committee of Faculty of Medicine at Assiut University, Assiut, Egypt, a prospectively hospital based study was conducted at Outpatient Clinics of Al-Rajhi Liver Hospital. Two hundred patients with known HCV infection and were eligible for DAAs (based on HCV-antibody and HCV-RNA) were enrolled in the study in period between July 2016 and June 2017.

Patients who fulfilled the following criteria were excluded: non-HCV-related liver disease or combined HCV and other causes of liver disease, for example, hepatitis B virus and HCV co-infection, evidence of advanced decompensated liver disease defined as Child-Pugh C patients, hepatocellular carcinoma or extrahepatic malignancy, pregnant women, and those who were planning a pregnancy and presence of large esophageal varices (except after successful prophylactic banding).

Methodology

All patients underwent a thorough assessment of history, a complete physical examination, BMI calculation, liver function tests, renal function tests, complete blood count, international normalized ratio, α -fetoprotein, pregnancy test for fertile female patients, and serum HCV RNA count by PCR. Laboratory investigations were done at baseline, and 3 month after treatment.

Complete blood count (CBC: White blood cells count, Red blood cells count, Hemoglobin level, Platelets count) for all patients were done by ABX Pentra XL80 HORIBA ABX-France. Serum Glucose, urea, creatinine and liver function tests were measured by conventional methods using Cobas Integra c311 autoanalyzer, (Roche, Switzerland). Alpha fetoprotein (AFP) protein serum level was measured by Advia centaur immunoassay system.

The level of fasting Insulin in the serum was measured by the Sandwich enzyme-linked immunosorbent assay (ELISA) technique using an Immunospec. Corporation kit (Canoga Park, Catalogue No: E29-072).

Abdominal ultrasonography was in all patients. Also, degree of fibrosis was assessed by transient elastography (FibroScan; Echosens, Paris, France). Transient elastography measurement was performed in the supine position after 6-8h of fasting. Results were expressed as kilopascals (kPa). Degree of fibrosis was defined as following; F0-F1= 7, F2= 8-9, F3= 9-14, and F4 is defined with score > 14^[5].

Patients with platelets count less than or equal to $100 \times 10^3/\mu\text{l}$ and/or the presence of controlled ascites underwent upper gastrointestinal endoscopy. Esophageal band ligation was performed for small risky

varices or large ones^[7].

IR was measured using the homeostasis model assessment of insulin resistance (HOMA-IR). The HOMA-IR was calculated using the following equation: fasting insulin (mIU/l) \times fasting glucose (mg/dl)/405. A cutoff of HOMA-IR greater than 2.5 was used to identify patients with IR^[8].

Treatment regimens

Monitoring of therapy and treatment efficacy was performed according to European Association for the Study of the Liver guidelines. All patients were treated with DAAs (Sofosbuvir 400 mg and Daclatasvir 60 mg daily). The course of treatment was 3 months in chronic hepatitis C patients and 6 months in liver cirrhotic patients. Chronic hepatitis is defined as hepatitis that lasts more than 6 months with persistent positive HCV PCR. The diagnosis of cirrhosis was made on the basis of clinical, laboratory, ultrasonographic, and transient elastography^[5,9].

The primary endpoint was the impact of baseline IR on the response to the different DAA protocols as assessed by achievement of a SVR. The secondary endpoint was the change in IR in patients who achieved an SVR.

Statistical analysis

Data were analyzed statistically using IBM SPSS Statistics version 20 for Windows (IBM Corporation; North Castle Drive, Armonk, New York, USA). Data are expressed as mean \pm SD for parametric data, and number with column percentage for nominal data. All *p* values are two-tailed, with values less than 0.05 considered statistically significant *p* = 0.01 considered highly significant, and *p* = 0.001 considered very highly significant.

Comparisons between two groups were performed using Student's *t*-test for parametric data. *Chi*² test and Fisher's exact test were used for categorical data analysis. Univariate and multivariate binary logistic regression was performed to detect the predictors of SVR development.

RESULTS

Baseline characteristics and laboratory data of patients based on response (Table 1)

Based on the current study, 180 (90%) patients achieved SVR while only 20 (10%) patients failed to achieve SVR. The mean age of those patients with SVR was significantly lower than those without (47.87 ± 12.74 vs. 53.03 ± 10.49 years; *p* < 0.04) where 76.1% of the responders were 40 years old or more and 85% of the non-responders were 40 years or more.

As regarding baseline laboratory data, only serum albumin was significantly lower in non-responders compared to the responders (3.19 ± 0.74 vs. 3.68 ± 0.68 ; *p* = 0.03). Other characteristics and laboratory data had insignificant differences between the two groups.

Data expressed as mean (SD), frequency (percentage). *P* value was significant if < 0.05. AST, aspartate transaminase; ALT, alanine transaminase.

Assessment of fibrosis degree and disease severity of patients based on response (Table 2)

Findings of abdominal ultrasonography are summarized at table 2. Fibrosis degree and disease severity were significantly higher among the non-responders compared to the responders (*P* < 0.05). All the study population was classified as Child A regarding Child-Pugh classification.

Data expressed as mean (SD), frequency (percentage). HCV:

Table 1 Baseline characteristics and laboratory data of patients based on response.

	Responders (n = 180)	Non-responders (n = 20)	P value
Age (years)	47.87 ± 12.74	53.03 ± 10.49	0.04
Age group			0.02
< 40 years	43 (23.9%)	3 (15%)	
> 40 years	137 (76.1%)	17 (85%)	
Sex			
Male	99 (55%)	12 (60%)	0.42
Female	45 (45%)	8 (40%)	
Body mass index (kg/m ²)	29.63 ± 6.42	28.38 ± 6.44	0.59
Smoking	55 (30.6%)	7 (35%)	0.06
Family history	42 (23.3%)	4 (20%)	0.49
Hypertension	42 (23.3%)	3 (15%)	0.29
Diabetes mellitus	64 (35.6%)	10 (50%)	0.15
Complete Blood Count			
Haemoglobin (g/dL)	13.70 ± 1.48	13.75 ± 1.63	0.98
Platelets (× 10 ³ /mL)	220.36 ± 72.87	201.80 ± 78.83	0.43
White blood cells (× 10 ³ /mL)	6.45 ± 2.21	6.11 ± 1.98	0.09
Liver function tests			
Total bilirubin (mg/dL)	0.75 ± 0.42	0.86 ± 0.54	0.45
Direct bilirubin (mg/dL)	0.21 ± 0.1	0.22 ± 0.10	0.11
AST (U/L)	35.11 ± 10.98	44.58 ± 11.56	0.53
ALT (U/L)	44.58 ± 12.78	45.70 ± 16.89	0.22
Serum albumin (g/dL)	3.68 ± 0.68	3.19 ± 0.74	0.01
Kidney function tests			
Serum creatinine (μmol/L)	111.34 ± 11.45	100.98 ± 23.13	0.67
Urea (mmol/L)	6.78 ± 1.99	4.57 ± 1.46	0.41
Prothrombin time (seconds)	13.39 ± 1.82	14.34 ± 2.90	0.34
Random blood glucose (μmol/L)	5.78 ± 1.87	6.11 ± 1.45	0.12

Data expressed as mean (SD), frequency (percentage). P value was significant if < 0.05. AST, aspartate transaminase; ALT, alanine transaminase.

hepatitis C virus infection; APRI: aspartate aminotransferase/platelets ratio index; FIB-4: fibrosis- 4 index; MELD: model for end stage liver disease. P value was significant if < 0.05.

Insulin resistance of the study population based on response (Table 3, Figures 1, 2)

It was noticed that frequency of pre-therapy IR in both responders and non-responders was 169 (93%) and 18 (90%), respectively with insignificant differences while baseline HOMA was significantly higher in non-responders (10.11 ± 3.03 vs. 8.48 ± 2.98; *p* = 0.01 respectively).

Also, post-therapy IR had insignificant difference between both groups (132 (73.3%) vs. 17 (85%); *p* = 0.05 respectively), while post-therapy HOMA was significantly higher in non-responders (7.12 ± 2.31 vs. 5.06 ± 1.34; *p* = 0.01 respectively).

Delta HOMA (baseline 12-week post-treatment HOMA) was significantly higher in responders (2.99 ± 0.76 vs. 2.01 ± 0.11; *p* = 0.01 respectively) in comparison to non-responders.

Predictors of sustained virologic response among the study patients with chronic hepatitis C virus infection (Table 4)

The current study showed that predictors for non-response to HCV therapy were age (> 40 years) (OR = 1.43, 95%CI= 1.03- 3.11; *p* = 0.03), low serum albumin (OR = 1.33, 95%CI= 1.05- 3.33; *p* = 0.03), and post-therapy IR (OR = 1.98, 95% CI = 0.76- 2.35; *p* = 0.01).

Table 2 Fibrosis degree and disease severity of patients based on response.

	Responders (n = 180)	Non-responders (n = 20)	P value
Abdominal ultrasonography			
Liver assessment			
Normal findings	129 (71.7%)	11 (55%)	0.06
Diffuse hepatic pathology	34 (18.9%)	4 (20%)	0.57
Liver cirrhosis	17 (9.4%)	5 (25%)	0.04
Splenomegaly	22 (12.6%)	7 (35%)	0.01
FIB-4	1.28 ± 0.80	2.57 ± 1.17	0.01
APRI	0.49 ± 0.12	0.75 ± 0.33	0.04
Fibroscan (kPa)	10.78 ± 2.01	12.45 ± 2.84	0.03
MELD score	8.14 ± 2.33	8.61 ± 1.90	0.01
Child score	5.38 ± 1.34	5.98 ± 1.11	0.01

Data expressed as mean (SD), frequency (percentage). HCV: hepatitis C virus infection; APRI: aspartate aminotransferase/platelets ratio index; FIB-4: fibrosis- 4 index; MELD: model for end stage liver disease. P value was significant if < 0.05.

Table 3 HOMA and IR of patients based on response.

	Responders (n = 180)	Non-responders (n = 20)	P value
Baseline			
HOMA	8.48 ± 2.98	10.11 ± 3.03	0.01
Insulin resistance	169 (93%)	18 (90%)	0.45
Post-therapy			
HOMA	5.06 ± 1.34	7.12 ± 2.31	0.01
Insulin resistance	132 (73.3%)	17 (85%)	0.05
Delta HOMA	2.99 ± 0.76	2.01 ± 0.11	0.01

Data expressed as mean (SD), frequency (percentage). P value was significant if < 0.05. HOMA: homeostatic model assessment.

Table 4 Predictors of SVR among the study patients with chronic HCV infection

	Odd's ratio	95% Confidence Interval	P value
Age (> 40 years)	1.43	1.03- 3.11	0.03
Low serum albumin	1.33	1.05- 3.33	0.03
Liver cirrhosis	0.41	0.10- 1.56	0.67
Splenomegaly	0.67	0.11- 3.04	0.09
FIB-4	1.04	0.56- 1.65	0.06
APRI	1.22	1.03- 2.67	0.77
Fibroscan (> F3)	2.87	1.67- 4.78	0.11
MELD score	1.07	0.06- 1.90	0.09
Child score	0.76	0.76- 1.11	0.45
Baseline IR	0.76	0.11- 1.98	0.67
Post-therapy IR	1.98	0.76- 2.35	0.01

P value was significant if < 0.05. IR: insulin resistance, SVR: sustained virologic response; HCV: hepatitis C virus.

DISCUSSION

Egypt used to be on the top of the countries with heavy HCV burden. The highest prevalence of HCV infection is present in Egypt, with 92.5% of patients infected with genotype 4, 3.6% patients with genotype 1, 3.2% patients with multiple genotypes, and < 1% patients with other genotypes^[10].

Many studies evaluated the association between HCV chronic infection and IR, yet, the results were conflicting. Insulin resistance is associated with a higher risk for worse outcomes of HCV infection,

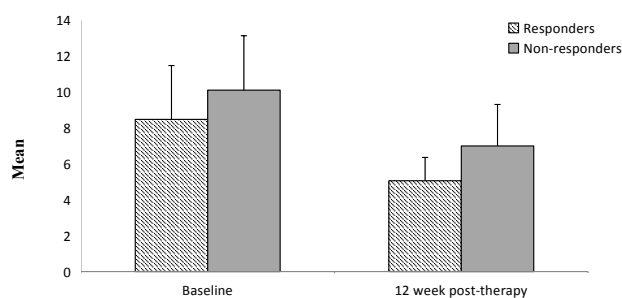


Figure 1 HOMA of the study population based on response. HOMA: homeostatic model assessment.

including progression to fibrosis and cirrhosis, and higher risk for development of hepatocellular carcinoma (HCC)^[11].

The relationship between the use of DAAs and IR was not extensively studied except in a limited number of studies. Our study aimed to determine the prevalence of insulin resistance among the patients with chronic hepatitis C virus infection, to find out the impact of insulin resistance as a predictor of SVR in patients with chronic hepatitis C after 3 months of therapy and in patients with liver cirrhosis after 6 months of therapy and to study the predictors of SVR among the study population.

In our study, we found a significant correlation between SVR and age of the patients. The mean age of those patients with SVR was significantly lower than those without (47.87 ± 12.74 vs. 53.03 ± 10.49 years; $p \leq 0.04$) where 76.1% of the responders were 40 years old or more and 85% of the non-responders were 40 years or more.

A previous study, matching ours, reported that age was a positive predictor of response at SVR12 and SVR24. However, given that the odds ratio (1.03) was very small, and that advanced age rarely leads to better clinical outcomes, this was likely statistical noise due to small power rather than a real effect of the predictor^[12].

On the contrary, a study by Snyder *et al*^[13] 2017, concluded that patients aged 70 years or older with genotype 1 achieved high rates of sustained virologic response with treatment with newer sofosbuvir-based DAAs without any undue adverse events.

In our study, we found that baseline laboratory data, serum albumin was significantly lower in non-responders while fasting blood glucose was significantly higher in non-responders. All oral DAAs effectively cured HCV in patients with advanced liver disease. Viral clearance was associated with improvement in liver function within 6 months compared to untreated patients^[14].

The long-term impact of HCV treatment in patients with decompensated cirrhosis remains to be determined. Patients with initial serum albumin < 35 g/L, aged > 65 or with low (< 135 mmol/L) baseline serum sodium concentrations were least likely to benefit from therapy^[14].

Ishigami *et al*^[15] (2017) reported that patients with advanced fibrosis presented a lower rate of SVR achieving only 90% of SVR compared to 95% of patients with mild liver disease.

We found that Post-treatment HOMA in non-responders was significantly lower compared with pre-treatment HOMA. In agreement with our findings, Butt *et al*^[16] (2019) concluded that HCV treatment significantly reduces the incidence and risk of subsequent diabetes, which appears to be driven largely by DAAs regimens. Treatment of HCV with DAAs regimens confer benefits beyond virologic control and may be useful in controlling or mitigating some of the extrahepatic complications of HCV.

Our study revealed that insulin resistance (IR) was present among 169 (93.9%) of the responders before therapy but after 12 weeks of antiviral therapy; the rate of IR decreased to 132 (73.3%)

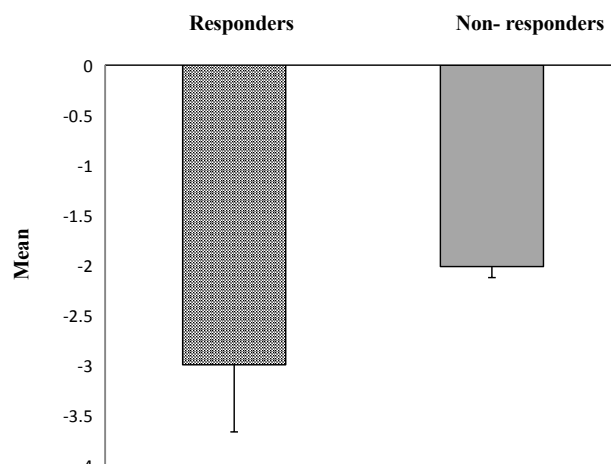


Figure 2 Delta HOMA of the study population based on response.

of those patients but in case of the non-responders, IR was present among 18 (90%) of the non-responders but after 12 weeks of antiviral therapy, the rate of IR decreased to 17 (85%) of those patients.

Elhelbawy *et al*^[17] (2019) reported that IR does not impair the response of patients with HCV treated with DAAs and improves significantly in patients who achieve an SVR (3). Also, Saad *et al.*, (2013) reported that pretreatment IR was not a predictor of SVR among Egyptian patients with HCV infection.

Among 200 chronic HCV patients were treated with sofosbuvir & daclatasvir, insulin resistance was insignificantly lower after end of treatment, rate of IR (73.3% vs. 85; $p = 0.05$). Among our study population, comparing responders to non-responders, post-treatment HOMA (5.06 ± 1.34 vs. 7.12 ± 2.31 ; $p = 0.01$) and were significantly lower.

These findings are in agreement with Pavone *et al*^[18] (2016) who reported that HCV suppression with DAA therapy produced a significant improvement in insulin resistance. In addition, Hum *et al*^[19] (2017) found that eradication of HCV with DAA therapy lead to improved insulin resistance.

The association between HCV genotype and IR has also been investigated with one study revealing an SVR-induced reduction in IR in patients with HCV genotype 1^[20].

As the most prevalent genotype of HCV in Egypt is genotype 4, we did not determine the HCV genotype of our patients and consequently, we could not determine if the insulin resistance or glycaemic improvement with DAAs was genotype-related or not. However, insulin resistance among patients with HCV infection is not genotype dependent^[21].

Baseline HOMA was significantly higher in non-responders (10.11 ± 3.03 vs. 8.48 ± 2.98 ; $p = 0.01$). So our findings are in contrast with a study by Elhelbawy *et al*^[13] (2019) who concluded that a pretreatment HOMA was not different in responders and non-responders.

At the end of treatment, there was a reduction in HOMA-IR among our study population. Agreeing with our results, it was found that the mean IR declined after antiviral therapy for HCV^[17].

The non-diabetic patients achieved SVR and showed a 21% reduced risk of T2DM compared to those who did not achieve SVR during after an average of 3.7 years of follow-up suggesting that the eradication of HCV by DAAs may have a positive impact on reducing the incidence of T2DM^[22].

Improvement of glycaemic control in HCV patients treated with DAAs is greater in patients without family history of T2DM, short duration of diabetes, and mild liver disease (Child-Pugh class A) but

is not related to age, sex, and BMI^[23].

In conclusion, IR does not impair the response patients with HCV treated with DAAs, and improves significantly in patients who achieve an SVR. The main limitations of our study included; relatively small sample size, no long term follow up of HOMA and lipid profile didn't be assessed. So, we recommended studying HOMA and IR in such patients in multi-center study with longer follow up of HOMA.

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