

## Effect of Direct Acting Anti-viral Agents on Insulin Resistance in Chronic HCV Patients

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### ABSTRACT

**Background:** HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and hepatocellular carcinoma. Globally, it is estimated that up to 185 million people have been infected with HCV, and among these, according to the World Health Organization, ~ 130–150 millions are chronically infected. Recent estimates place to ~ 700,000 the yearly death toll of liver-related, long-term sequelae of HCV. In many regions of the world, where access to therapy is available, the number of deaths due to HCV has even surpassed.

**Aim of the work:** The goals of our study is to evaluate the effect of direct antiviral agents (DAAs) on insulin resistance in chronic HCV patients receiving (daclatasvir + sofosbuvir +/- ribavirin) for 12 weeks and 12 weeks post treatment.

**Methodology:** The study was conducted at, Gastroenterology and Hepatology Unit, Police Authority Hospitals. It included 80 patients with chronic HCV infection (treatment naive patients). Patients were classified in to 4 groups: Group 1: 20 non diabetic, non-obese patients; Group 2: 20 diabetic, non-obese patients; Group 3: 20 obese, non-diabetic patients and Group 4: 20 diabetic, obese patients.

**Results:** The current study showed highly significant decrease in HOMA-IR in all groups at end of treatment and 12 weeks post treatment.

**Conclusion:** Antiviral therapy (DAAs) improves insulin resistance during HCV treatment. These findings suggest that HCV plays an etiological role in the pathogenesis of impaired glucose homeostasis. Moreover, the decrease of insulin resistance through viral eradication implicates clinical benefits by readily available regimens.

**Recommendations:** Confirmation of the current results by conduction of larger scale studies.

**Keywords:** Direct acting anti-viral agents, HCV.

### INTRODUCTION

HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and hepatocellular carcinoma. Globally, it is estimated that up to 185 million people have been infected with HCV<sup>(1)</sup>, and among these, according to the World Health Organization, ~ 130–150 millions are chronically infected<sup>(2)</sup>. Recent estimates place to ~ 700,000 the yearly death toll of liver-related, long-term sequelae of HCV<sup>(3)</sup>. In many regions of the world, where access to therapy is available, the number of deaths due to HCV has even surpassed<sup>(4)</sup>.

Egypt has the highest prevalence rate of HCV in the world<sup>(5)</sup>, making it the most challenging public health problem facing the country. Studies showed that 14.7% of the Egyptian population carries HCV-antibodies and 10% have an active infection with predominance of genotype 4 (about 93.1 % of cases)<sup>(6)</sup>.

Optimal therapy for patients with hepatitis C virus genotype 4 (HCV-4) infection is changing rapidly; the standard of care for a long time has been a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), with modest response rates and considerable adverse events<sup>(7)</sup>.

Since the introduction of direct acting anti-viral agents (DAAs) e.g: sofosbuvir (SOF), and daclatasvir (DCV), the duration of treatment has been significantly shortened and response rates have increased with substantial improvements in the side effect profiles<sup>(8)</sup>.

Hepatitis C virus infection has been shown to be linked to a higher prevalence of type 2 diabetes. This association is due to B-cell dysfunction in the stage of chronic hepatitis, which becomes more advanced with the development of liver cirrhosis together with insulin resistance (IR) that occurs early in the course of the disease even in patients with or without minimal fibrosis. The mechanisms for HCV-induced IR are only partially understood and include a direct inhibitory effect of HCV on insulin signaling pathway. Insulin resistance in chronic HCV results in an increased rate of progression of hepatic fibrosis, cirrhosis and hepatocellular carcinoma<sup>(9)</sup>.

### AIM OF THE WORK

The goals of our study is to evaluate the effect of direct antiviral agents (DAAs) on insulin resistance in chronic HCV patients receiving

(daclatasvir + sofosbuvir +/- ribavirin) for 12 weeks and 12 weeks after the end of treatment.

## PATIENTS AND METHODS

A study of HCV infected patients who had positive serum RT HCV PCR and received sofosbuvir & daclatasvir with or without ribavirin as a dual or triple therapy for 3 month according to the recommendations of The Egyptian National Committee for Control of Viral Hepatitis. The study was carried out at Gastroenterology and Hepatology Unit, Police Authority Hospitals measuring insulin resistance by HOMA test (fasting insulin level x blood fasting blood glucose/22.5) pre and at end of treatment and 12 weeks after the end of treatment. Patients were considered insulin resistant when HOMA test > 2.5.

Treatment was considered successful when HOMA test <2.5 plus negative HCV RNA serum PCR at 12 weeks from the end of the treatment Therapeutic regimens.

### Patients classified into 4 groups:

**Group 1:** 20 non-diabetic, non-obese patients.

**Group 2:** 20 diabetic, non-obese patients.

**Group 3:** 20 obese, non-diabetic patients.

**Group 4:** 20 diabetic, obese patients.

(obese BMI value >30) (non diabetic HbA1C <6.5%-diabetic>6.5% according to American Diabetes Association recommendations).

**I. Inclusion criteria:** -All inclusion criteria were abided according to the Egyptian National HCV Control Program. The ages range was between 18 and 75 years old. All patients tested positive for serum Real Time HCV RNA PCR.

**II. Exclusion criteria:-** Application of exclusion criteria was taking in consideration The Egyptian National HCV Control Program guidelines. These criteria included the following: Patients who are co-infected with HIV or HBV. patients who <18 or >75 years old. Pregnant female. Hepatocellular carcinoma or other extrahepatic malignancy. Total serum bilirubin more than 3mg/dl. Serum albumin less than 2.8 g/dl. INR more than 1.7. Platelet count less than 50,000/mm. Renal impairment with GFR less than 30 ml / minute. Non-compliant patients.

### III. Clinical Examination:-

**All patients were subjected to:** Written consent before therapy. Complete history taking, which included history of other comorbid conditions such as DM, cardiac disease and renal

failure. History of previous treatment with anti-HCV medicines (e.g. peg interferon plus ribavirin, sofosbuvir plus ribavirin, or other combination regimens) was also evaluated. Sensitivity to any other drug had to be checked out.

**Full clinical examination:** which included manifestations of chronic liver disease (such as jaundice, flapping tremors, lower limb edema, organomegaly, ascites) and obesity (BMI). All patients were submitted to ECG (Electric cardiography) at study entry (baseline).

### IV. Laboratory Investigations:

**Blood samples were collected from patients and submitted to the following:** Complete blood picture (CBC): hemoglobin concentration (Hb %), red blood cells (RBCs), white blood cells (WBCs) and platelet count. Liver profile: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, direct bilirubin, prothrombin time and INR. Renal function tests: serum creatinin. Pregnancy test (for females). Alpha Feto protein (AFP). Fasting blood glucose level & hemoglobin A1c (pre and at end of treatment and 12 weeks after the end of the treatment). Fasting insulin level (pre and at end of treatment and 12 weeks after the end of the treatment). HBsAg (Hepatitis B surface antigen). Serum PCR (pre and at end of treatment and 12 weeks after the end of the treatment). Insulin resistance calculation: HOMA test calculation by the following equation (fasting insulin level x fasting blood glucose/22.5).

**V. Imaging:-** Study patients were submitted to screening with the following procedures: Abdominal Ultrasonography: which included liver size (diameter), liver echogenicity, portal and splenic vein diameters, splenic size and amount of ascites if present.

**The Expected study Outcomes:** Treatment of chronic HCV infections with regimens containing DAAs alone or with regimens that add ribavirin to DAAs have shown decrease insulin resistance (HOMA test)

### Obstacles, Disadvantages, and Solutions:

**I. Safety of the collected personal and clinical information:** To keep personal information and clinical data of study safe, the following procedures were followed: Personal identification information like name, phone numbers or email were eliminated from spread sheet at end of follow up. Patients having a new ID serial number as soon as included in study. All personal information and

clinical data were stored in a secured computer with appropriate password.

**II. Study subjects withdrawn during follow up - the following actions were required to cover the withdrawn subject's situation:** Data of the lost study subject were segregated and moved to a separate file. Trying to contact the withdrawn subjects to clarify the actual cause of leaving the study and working on any merging issues to avoid repeating the same problems during conduction of other study.

**III. Coasts of HCV PCR:-** This problem was solved by taking the following actions: Patient who could not afford the prices of both screening, got help from various Government Add Programs to perform both screening either free of charge or at a markedly discounted prices.

Patients who could afford the prices of both screening were guided to specific centers that are certified by Ministry of Health and were qualified to perform both investigations.

**IV. Data handling by Biostaticain:** The availability of biostaticain was crucial for appropriate and sound data analysis according to international standard. Data were handed to a consultant office on a regular base. The meeting of working team with the biostaticain was done as much as required to establish the appropriate scheme for analysis. The analyzed data (figures and tables) for thesis and publication would be available through the biostaticain office.

**Ethical Aspects:**

**I. Approving protocol:-** Current protocol was approved by Committee of Tropical Medicine Department and Committee of Faculty of Medicine at Al-Azhar University, and then by the Ethical Committee of Al-Azhar University.

**II. Permission from Ministry of Health:-** Permission was obtained from Gastroenterology and Hepatology Unit, Police Authority Hospitals from the Outpatient HCV management Clinics.

**III. Patient Consent:-** All patients that were included in the current study signed an approved consent from Al-Azhar University Ethical Committee.

**Statistical Analysis:**

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Chi-square test (X<sup>2</sup>): was used for comparing non-parametric data. A one-way analysis of variance (ANOVA): when comparing between more than two means. Post Hoc test (LSD Least significance difference): was used for multiple comparisons between different variables. Probability (P-value). P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

**RESULTS**

**Table (1):** Comparison between FBS. Fasting insulin and HOMA-IR before and after therapy in group I (nob-diabetic non-obese individuals).

Variables		Groups			ANOVA (p-value)		
		At start	EOT	12weeks post treatment	0 vs 12 (weeks)	0 vs 24 (weeks)	12 vs 24 (weeks)
FBS (mg/dl)	Mean	90.9	88.5	88.7	0.6	0.6	0.9
	± SD	8.5	10.7	21.9			
FBS (mmol/L)	Mean	5.0	4.9	4.9	0.6	0.6	0.9
	± SD	0.5	0.6	1.2			
HbA1C (%)	Mean	5.1	4.9	4.8	0.3	0.05	0.4
	± SD	0.3	0.3	0.4			
F.Insulin (uU/L)	Mean	14.3	11.2	11.1	<0.001**	<0.001**	0.9
	± SD	2.5	2.3	2.8			
HOMA-IR	Mean	3.2	2.5	2.5	0.002*	0.003*	0.9
	± SD	0.7	0.7	0.8			

\*: p-value < 0.05 is considered significant.

\*\* : p-value < 0.001 is considered highly significant.

**This table showed:** Highly statistical significant decrease (p-value < 0.001) before and after therapy as regard fasting insulin in group I. Statistical significant decrease (p-value < 0.05) before and after therapy as regard HOMA-IR in group I.

**Table (2):** Comparison between FBS. Fasting insulin and HOMA-IR before and after therapy in group II (diabetic, non-obese patients).

Variables		Groups			ANOVA (p-value)		
		At start	EOT	12 weeks post treatment	0 vs 12 (weeks)	0 vs 24 (weeks)	12 vs 24 (weeks)
FBS (mg/dl)	Mean	143.3	142.4	150.1	0.9	0.4	0.3
	± SD	27.8	26.8	28.0			
FBS (mmol/L)	Mean	8.0	7.9	8.3	0.9	0.4	0.3
	± SD	1.5	1.5	1.6			
HbA1C (%)	Mean	7.1	6.1	6.1	< 0.001**	<0.001**	1
	± SD	0.7	0.5	0.5			
F.Insulin (uU/L)	Mean	15.4	11.3	10.8	< 0.001**	<0.001**	0.6
	± SD	4.2	2.5	2.3			
HOMA-IR	Mean	5.4	4.1	4.1	0.01*	0.01*	0.9
	± SD	1.7	1.6	1.5			

\*: p-value < 0.05 is considered significant.

\*\* : p-value < 0.001 is considered highly significant.

**This table showed:** Highly statistical significant decrease (p-value < 0.001) before and after therapy as regard fasting insulin and HbA1C in group II. Statistical significant decrease (p-value < 0.05) before and after therapy as regard HOMA-IR in group II.

**Table (3):** Comparison between FBS, Fasting insulin and HOMA-IR before and after therapy in group III (obese, non-diabetic patients).

Variables	Groups	At start	EOT	12weeks post treatment	ANOVA (p-value)		
					0 vs 12 (weeks)	0 vs 24 (weeks)	12 vs 24 (weeks)
FBS (mg/dl)	Mean ± SD	90.1 6.7	88.8 11.0	88.2 10.8	0.6	0.5	0.8
FBS (nmol/L)	Mean ± SD	5.0 0.4	4.9 0.6	4.9 0.6	0.6	0.5	0.8
HbA1C (%)	Mean ± SD	5.4 0.6	5.3 0.5	5.2 0.7	0.5	0.3	0.8
F.Insulin (uU/L)	Mean ± SD	14.4 3.7	11.5 2.9	11.8 2.7	0.005*	0.01*	0.7
HOMA-IR	Mean ± SD	3.2 0.9	2.5 0.8	2.6 0.7	0.01*	0.02*	0.9

\*: p-value < 0.05 is considered significant.

**This table showed:** Statistical significant decrease (p-value < 0.05) before and after therapy as regard fasting insulin and HOMA-IR in group III.

**Table (4):** Comparison between FBS, Fasting insulin and HOMA-IR before and after therapy in group IV (diabetic, obese patients).

Variables	Groups	At start	EOT	12 weeks post treatment	ANOVA (p-value)		
					0 vs 12 (weeks)	0 vs 24 (weeks)	12 vs 24 (weeks)
FBS (mg/dl)	Mean ± SD	166.6 31.8	161.3 37.6	162.3 38.0	0.6	0.7	0.9
FBS (nmol/L)	Mean ± SD	9.3 1.8	9.0 2.1	9.0 2.1	0.6	0.7	0.9
HbA1C (%)	Mean ± SD	7.8 1.01	6.7 0.8	6.4 0.7	< 0.001**	< 0.001**	0.2
F.Insulin (uU/L)	Mean ± SD	16.2 4.7	10.5 3.0	12.1 2.5	< 0.001**	< 0.001**	0.1
HOMA-IR	Mean ± SD	6.8 2.7	4.4 2.2	4.9 2.0	0.002*	0.01*	0.4

\*: p-value < 0.05 is considered significant.

\*\* : p-value < 0.001 is considered highly significant.

**This table showed:** Highly statistical significant decrease (p-value < 0.001) before and after therapy as regard fasting insulin and HbA1C in group IV. Statistical significant decrease (p-value < 0.05) before and after therapy as regard HOMA-IR in group IV.

**Table (5):** Comparison between studied groups as regard the response of cases to DAAs by measuring HCV RNA PCR before, at end of treatment and 12 weeks post treatment.

Variables	Groups	Group I (N = 20)	Group II (N = 20)	Group III (N = 20)	Group IV (N = 20)
		Before therapy	Positive Negative	20 (100%) 0 (0%)	20 (100%) 0 (0%)
EOT	Positive Negative	0 (0%) 20 (100%)	0 (0%) 20 (100%)	0 (0%) 20 (100%)	0 (0%) 20 (100%)
12 weeks post treatment	Positive Negative	0 (0%) 20 (100%)	0 (0%) 20 (100%)	0 (0%) 20 (100%)	0 (0%) 20 (100%)

**This table showed:** All cases achieved sustained virological response at 12 weeks post-treatment (negative PCR) with success rate 100%.

## DISCUSSION

HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and hepatocellular carcinoma and is causally associated with impaired glucose homeostasis. Globally, it is estimated that up to 185 million people have been infected with HCV <sup>(1)</sup>, and among these, according to the World Health Organization, ~ 130–150 millions are chronically infected <sup>(2)</sup>. Epidemiological surveys have consistently revealed a higher prevalence of insulin resistance in HCV infected patients than in the general population or in those with other chronic liver diseases <sup>(10)</sup>.

Many studies evaluated the association between HCV chronic infection and IR, yet, the results were conflicting. With the development of the DAA therapies, HCV can be successfully eradicated; with high safety and efficacy <sup>(11)</sup>.

The relationship between IR & HCV genotype is still debatable. *Hui et al.* <sup>(12)</sup> reported that patients with genotype 3 had significantly lower HOMA-IR than other genotypes even after the adjustment of other variables. Despite similarity in the genotype 4, in a cohort of Egyptian patients with CHC, IR was reported in only 31% of nondiabetic patients <sup>(13)</sup>.

Generally, it is well known that males poses a higher risk for IR and diabetes, but the protective effect of female decreases with age, particularly in women above the age of 50, considered an average age for menopause <sup>(14)</sup>.

HCV infection is also associated with several extra-hepatic manifestations, which add to the morbidity and mortality burden of HCV. The pathogenesis of the extra-hepatic features of HCV is not always clear and may involve endocrine effects, direct toxic effects due to HCV replication in extra-hepatic tissues, or disproportionate immune reactions with systemic effects <sup>(15)</sup>.

Insulin resistance is associated with a higher risk for worse outcomes of HCV infection, including progression to fibrosis and cirrhosis, and higher risk for development of hepatocellular carcinoma (HCC) <sup>(16)</sup>.

The aim of this study was to evaluate the effect of direct acting antivirals (DAAs) on insulin resistance in chronic HCV patients.

This prospective study was conducted on 80 patients from the outpatient clinics of Gastroenterology and Hepatology Unit, Police Authority Hospitals. All patients were chronically infected with HCV and received sofosbuvir & daclatasvir with or without ribavirin for 12 weeks.

All patients were subjected to detailed history taking including age, sex, body mass index (BMI).

The patients of all groups received DAAs. 80 patients received DAAs in the form of sofosbuvir + daclatasvir with or without ribavirin for 12 weeks. Before starting DAAs therapy, laboratory tests were carried out that included fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), quantitative HCV RNA polymerase chain reaction test, liver enzymes, serum bilirubin, serum albumin, the international normalized ratio, CBC, AFP, fasting insulin level and serum creatinine.

FPG, fasting insulin level, CBC, liver enzymes, AFP and HCV RNA PCR were repeated after ending of treatment and 12 weeks post treatment.

### SVR

SVR was defined as a serum viral load below the lower limit of quantification 12 weeks after the end of treatment.

Among 80 chronic HCV patients were treated with sofosbuvir & daclatasvir ± ribavirin, the following baseline characteristics were found: Improvement in insulin resistance after 12 weeks of treatment where HOMA-IR changed significantly during the antiviral therapy overall. These findings are in agreement with *Pavone et al.*<sup>(17)</sup> who found that HCV suppression with DAA therapy produced a significant improvement in insulin resistance<sup>(17)</sup>. In addition, they are in agreement with *Hum et al.*<sup>(18)</sup> who reported that eradication of HCV with DAA therapy led to improved insulin resistance<sup>(18)</sup>. In addition, these finding are in agreement with *Cheng-Hao et al.*<sup>(19)</sup> who found that viral eradication implicated clinical effectiveness in extra hepatic outcomes.

Consistent with our results, several studies from western countries where they reported the

efficacy of anti-HCV therapy (DAAs) in improving insulin resistance<sup>(20)</sup>. Similar results were reported from the Virahep-c study, which exclusively enrolled genotype<sup>(1)</sup> infected patients with insulin resistance (HOMA-IR) >2 showed linear decrease according to virological response during the treatment<sup>(21)</sup>.

As the most prevalent genotype of HCV in Egypt is genotype 4, we did not determine the HCV genotype of our patients, and we did not determine if the insulin resistance or glyceimic improvement with DAAs was genotype-related or not. However, most genotypes of HCV increase insulin resistance<sup>(22)</sup>. These findings are in agreement with *Chehadeh et al.*<sup>(23)</sup> who found a significant correlation between genotype 4 infection and insulin resistance<sup>(23)</sup>.

The results revealed that there was a significant improvement in glyceimic control (HbA1C) after 3 months of treatment especially in diabetic patients. These findings are in agreement with *Knobler and Malnick*<sup>(24)</sup> who found improvement in glyceimic control in T2DM after DAAs treatment<sup>(24)</sup>.

The present results agreed with *Saady et al.*<sup>(25)</sup> in Egypt who showed that pretreatment of IR was an independent negative predictor of SVR. Moreover, two published meta-analyses examined the effect of IR on SVR including fourteen studies with more than 2700 patients. Some of these studies did not find an association between IR and achievement of SVR; with a baseline HOMA-IR less than 3<sup>(24)</sup>.

At the end of treatment, there was a reduction in mean value of FBG, median values of fasting insulin and HOMA-IR. These results went with the study, which elucidated the mutual impact between the treatment response and parameters of the glucose abnormalities after DAAs therapy in CHC patients. It was found that the mean IR declined at the follow up<sup>(25)</sup>.

In a retrospective study evaluating 149 HCV-positive diabetic patients who received different DAA regimens, FBG analysis revealed a significant reduction during treatment. The results were neither dependent on the DAA regimen nor HCV genotype<sup>(17)</sup>.

Results revealed highly statistically significant improvement in liver enzymes at the end of treatment and 12 weeks post treatment. In addition, combination of daclatasvir to sofosbuvir has benefit at increased the success rate of DAAs to eradicate HCV.

## CONCLUSION

Antiviral therapy (DAAs) improved insulin resistance during HCV treatment. These findings suggest that HCV plays an etiological role in the pathogenesis of impaired glucose homeostasis. Moreover, the decrease of insulin resistance through viral eradication implicates clinical benefits by readily available regimens.

## RECOMMENDATIONS

Confirmation of the current results by conduction of larger scale studies.

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