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Insulin Resistance and Related Glycemic Parameters in Type 2 Diabetes Mellitus after Successful Treatment of HCV

Amira M. Elsayed, Medhat M. Elamawy, Walaa M. Ibrahim
Internal Medicine Department, Benha Faculty of Medicine, Benha University, Egypt
Corresponding author: Medhat M. Elamawy,Email: m.elamawy@fmed.bu.edu.eg,
Mobile Phone: 01024443810, Orcid ID: 0000-0003-4072-0697

ABSTRACT

Background: Chronic hepatitis C virus infection is a worldwide health problem that could cause complications such as cirrhosis or even hepatocellular carcinoma. Hepatitis C virus (HCV) infection has increased preponderance of diabetes mellitus (DM) type 2 and insulin resistance.

Objectives: Our goal is to determine whether the most recent direct acting antiviral (DAA) medications for the HCV treatment are linked to improvements in insulin resistance and other related glycemic parameters in type 2 DM patients.

Patients and Methods: This prospective, observational study was conducted on 40 diabetic patients aged >18 years treated from HCV by DAA. Baselines HCV PCR and liver function tests were obtained before DAA. Pre-and post-treatment change of the glycemic profile including calculated homeostatic model assessment of insulin resistance **(**HOMA-IR**)** lab results were taken.

Results: Impact of DDA drugs on our subjects' glycemic profile showed improvements of all glycemic indices (Fasting plasma glucose (FPG), fasting insulin, HBA1c and HOMA-IR with p-value < 0.001. HCV PCR changes after treatment was positivity correlated significantly especially with FPG and HOMA-IR (r value 0.501 and 0.478 respectively) with p-value < 0.05.

Conclusion: We concluded that DAAs improved insulin resistance and related glycemic control parameters after eradication of HCV. Our results suggest that HCV take a part in glucose homeostasis. Liver function before treatment could be a predictor of improvement of insulin resistance.

Keywords: HCV, HOMA-IR, Diabetes Mellites, Direct Acting Antiviral DAA

INTRODUCTION

Around 170 million people worldwide had hepatitis C virus (HCV) infection, and its other later consequences such as cirrhosis and liver malignancy, which are linked to increased mortality, are significantly increased by chronic hepatitis C (CHC) infection [(1)].

According to epidemiological studies, hepatitis C virus (HCV) infection may be related to increased preponderance of diabetes mellitus (DM) type 2 [(2)]. Moreover, having persistent HCV infection raises the likelihood of developing type 2 DM in patients with metabolic syndrome risk factors by an additional 11 times [(3)].

Molecular mechanisms explain how HCV infection might raise the chance of developing type 2 DM or decrease glycemic control in people who already have condition [(4)].

One study demonstrated that insulin resistance (IR) was linked to decreased sustained virological response (SVR) rates in patients undergoing interferon (IFN)-based therapy, independent of viral genotype [(5)]. IFN-based therapy is being replaced by direct-acting antivirals (DAAs), which have SVR rates above 90% [(1)].

Hum *et al.* and Wong *et al*. discovered that individuals with type 2 DM had better glycemic control when HCV was eradicated with direct acting antiviral (DAA) medications [(3,6)].

Our goal is to determine whether the most recent DAA medications for the treatment of HCV infection improve insulin resistance and other related glycemic parameters in type 2 DM patients.

SUBJECTS AND METHODS

This prospective, observational study was conducted on patients treated from HCV by DAA who were attending medical clinics at Benha University Hospital for follow up. Data were recruited from patient with HCV that had positive serum real time HCV PCR and type 2 DM. Diagnosis of DM was according to American Diabetes Association (ADA) 2022 [(7)].

40 patients, aged >18 years old, received sofosbuvir, simeprevir, peg-interferon, and daclatasvir with or without ribavirin as a dual or triple therapy for 3 months according to the recommendations of The Egyptian National Committee for Control of Viral Hepatitis.

The following are our exclusion criteria; age < 18, HBV and/or HIV co-infection; pregnancy; liver malignancy; chronic kidney disease stage 4-5 (GFR less than 30 ml / minute); and liver or kidney transplanted patients.

Age, sex, duration of diabetes, anti-diabetic treatments, thorough clinical examination, and body mass index (BMI) were registered.

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Laboratory data in the form of complete blood picture (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin, prothrombin time and international normalized ratio (INR), serum creatinine and alpha fetoprotein (AFP) were obtained. Fasting plasma glucose level (FPG) and hemoglobin A1c (HbA1c), fasting insulin level, serum PCR for HCV were measured before and at 12 weeks after stopping the treatment by DAA.

HOMA-IR was calculated according to the formula: fasting insulin level x blood fasting blood glucose/22.5 [8] (pre and after post - treatment, at 12 weeks). The primary outcome of the study was to compare insulin resistance and HbA1c levels before and after treatment among those who reached SVR.

Ethical approval

The present study was approved by Medical Ethics Committee of Faculty of Medicine, Benha University, Egypt. It is consistent with the declaration of Helsinki principles. Written consent was taken from all patients before starting the study. The study no. was RC 36-10-2022.

Statistical methods

Quantitative data were presented with mean ± SD while categorical data were tabulated with number and percentage. Logistic regression and correlation analysis tests were exploited to predict the effect of certain variables on specific parameters confirming the cause effect relationships between these studied variables. Pearson correlation coefficient (r) test was used to evaluate different independent variables. Chi square test (x^2 value) was used to compare different variables of categorical data IBM SPSS (version 23, 2015; Chicago, USA) for windows package. A significant p-value is considered when <0.05.

RESULTS

In our prospective observation study, 40 patients were recruited, and baseline characteristics (Age, gender, BMI, and disease duration) were obtained as shown in table 1. Male constitutes 60 % of selected populations with 13.4 years was the mean diabetic mellitus duration. 52.5 % of the patients were treated with oral hypoglycemic drugs while 47.5 % were on insulin therapy.

Table (1): Baseline characteristics of study participants

Age mean ± S.D.	56.6 (8.6)
Female/male No. (%)	16 (40)/24 (60)
BMI, mean ± S.D.	27.03 (2.9)
Disease duration, mean ± S.D. in years	13.4 (7.1)
Laboratory data	
FPG (mg/dl), mean ± S.D.	287.6 (74.2)
HB (gm/dl), mean ± S.D.	10.2 (2.1)
Platelets (10^3/µl), mean ± S.D.	270.3 (97.01)
TLC (10^3/µl), mean ± S.D.	7.1 (1.7)
ALT(U/L), mean ± S.D.	180.5 (228.5)
AST(U/L), mean ± S.D.	190.4 (245.7)
Albumin(g/dl), mean ± S.D.	3.5 (0.6)
Bilirubin(mg/dl), mean ± S.D.	3.5 (1.6)
Creatinine(mg/dl), mean ± S.D.	1.4 (0.7)
AFP (ng/ml), mean ± S.D.	197.1 (233.9)
INR, mean ± S.D.	1.4 (0.6)
PCR(IU/ml) mean ± S.D.	2330645.6 (1199591.8)
DM Treatment No. (%)	
Premixed insulin	13 (32)
Insulin glargine + actrapid	2 (5)
SU, Insulin glargine	4 (10)
SU, DPP4	5 (12.5)
SU, DPP4, MET	12 (30)
SU, MET	4 (10)
HCV Treatment No. (%)	
SOF+DAC+RIB	15 (37.5)
SOF+LED	8 (20)
SOF+LED+RIB	4 (10)
SOF+PEG INT+RIB	2 (5)
SOF+SIM	11 (27.5)

BMI: Body Mass Index, FPG: Fasting Plasma Glucose, HB: haemoglobin, TLC: Total Leucocytic Count. ALT: alanine transaminase. AST; aspartate transaminase, AFP: Alfa Fetoprotein, INR: International Normalised Ratio. PCR: Polymerase Chain Reaction, SU: Sulfonylureas, DPP4: Dipeptidyl peptidase 4, MET: Metformin, SOF: sofosbuvir, DAC: daclatasvir, RIB: ribavirin, LED: Ledipasvir, Sim: Simeprevir

Impact of DDA drugs on our subjects' glycemic profile was achieved by paired t test that significantly showed improvements of all glycemic indices (FPG, fasting insulin, HBA1c and HOMA-IR) as shown in table (2).

Table (2): Impact of HCV treatment with direct acting antiviral drugs on the parameters of glycemic control

	Before treatment (40 Patients)		After treatment (40 patients)		Paired t test	p-value
	Mean	±SD	Mean	±SD		
FPG (mg/dl)	204.48	29.17	170.53	26.87	20.03	<0.001*
Fasting Insulin (mIU/**ml)**	17.21	1.86	15.13	2.51	9.9	<0.001*
HbA1c %	8.73	1.41	7.81	1.15	12.01	<0.001*
HOMA-IR	8.67	1.35	6.35	1.31	16.2	<0.001*

*: Significant, FPG: Fasting Plasma Glucose, HbA1c: hemoglobin A1c, HOMA-IR: homeostatic model assessment of insulin resistance

When a linger regression and correlation analysis was applied to evaluate the effect of each variable to the glycaemic profile, we found that HCV PCR changes after treatment was positivity correlated significantly especially with FPG and HOMA-IR, which denotes the effect of HCV DAA on glycemic control as shown in table (3a).
Also, our study showed that better baseline liver function tests could be a predictor of improvements in glycemic control (tables 3b and 5).

Table (3 a): Correlations between change of glycemic control parameters and different patients' characteristics

	HOMA-IR Change 40 patients		A1C Change 40 patients		Fasting Insulin Change 40 patients		FBS Change 40 patients	
	r	p-value	r	p-value	r	p-value	r	p-value
age	-0.231	0.152	-0.203	0.209	-0.241	0.134	-0.141	0.387
BMI	-0.228	0.158	-0.115	0.480	-0.254	0.114	-0.142	0.381
Duration of DM	-0.031	0.848	-0.290	0.070	0.006	0.972	-0.065	0.692
HCV PCR change	0.478	0.002*	0.350	0.027*	0.368	0.019*	0.501	0.001*

*: Significant, BMI: Body Mass Index, DM: Diabetes Mellitus, HCV PCR: HCV Polymerase Chain Reaction, HOMA-IR: homeostatic model assessment of insulin resistance.

Table (3b): Correlations between the change of glycemic control parameters and baseline liver function tests.

	HOMA-IR Change		A1C Change		Fasting Insulin Change		FPG Change	
	r	p-value	r	p-value	r	p-value	r	p-value
HB	-0.183	0.258	-0.094	0.564	-0.205	0.204	-0.097	0.553
Platelets	0.049	0.765	0.007	0.965	0.074	0.652	0.019	0.908
TLC	-0.223	0.166	-0.111	0.495	-0.216	0.180	-0.178	0.270
ALT	-0.609	<0.001*	-0.464	0.003*	-0.503	<0.001*	-0.593	<0.001*
AST	-0.645	<0.001*	-0.475	0.002*	-0.540	<0.001*	-0.611	<0.001*
Albumin	0.374	0.018*	0.391	0.012*	0.264	0.100	0.439	0.005*
Bilirubin	-0.552	<0.001*	-0.433	0.005*	-0.396	0.012*	-0.637	<0.001*
Creatinine	-0.003	0.987	-0.046	0.776	0.015	0.929	-0.028	0.864
AFP	-0.633	<0.001*	-0.535	<0.001*	-0.505	<0.001*	-0.644	<0.001*
INR	-0.439	0.005*	-0.358	0.023*	-0.394	0.012*	-0.368	0.019*

*: Significant, HB: haemoglobin, TLC: Total Leucocytic Count, FPG: Fasting Plasma Glucose, ALT: alanine transaminase. AST; aspartate transaminase, AFP: Alfa Fetoprotein, INR: International Normalised Ratio, HOMA-IR: homeostatic model assessment of insulin resistance

Furthermore, univariate, and multivariate regression analysis revealed that HCV PCR level was significant predictor for all glycemic profile as shown in table (4 and 5).

Table (4): Univariate regression analyses of various variables for prediction of glycemic profile change

	HOMA-IR Change 40 patients		A1C Change40 patients		Fasting Insulin Change 40 patients		FBS Change 40 patients	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	0.23	0.15	0.2	0.2	0.24	0.13	0.14	0.39
Sex	0.22	0.86	0.1	0.6	0.1	0.8	0.1	0.9
BMI	0.81	0.16	0.2	0.5	0.3	0.1	0.1	0.9
Duration of DM	0.1	0.19	0.3	0.07	0.1	0.9	0.07	0.7
HCV PCR	0.48	0.002*	0.35	0.02*	0.37	0.02*	0.5	0.001*

*: Significant, FPG: Fasting Plasma Glucose, DM: Diabetes Mellitus , HCV PCR: hepatitis C virus Polymerase Chain Reaction, BMI: Body Mass Index.

Table (5): Univariate and multivariate regression analyses of various variables for prediction of HOMA-IR change.

	Univariate analysis		Multivariate analysis	
	β	p-value	β	p-value
Age	0.23	0.15		
Sex	0.22	0.86		
BMI	0.81	0.16		
Duration of DM	0.1	0.19		
PCR	0.48	0.002*	-0.096	0.68
HB	-0.89	0.26		
Platelets	0.1	0.77		
TLC	-1.3	0.16		
ALT	-0.03	<0.001*	-1.095	0.155
AST	-0.03	<0.001*	1.117	0.044*
Albumin	5.8	0.02*	0.026	0.879
Bilirubin	-3.5	<0.001*	0.192	0.323
Creatinine	-0.04	0.9		
b.AFP	-0.03	<0.001*	0.662	0.158
b.INR	-7.2	0.005*	-0.059	0.784

*: Significant

HB: haemoglobin, TLC: Total Leucocytic Count, FPG: Fasting Plasma Glucose, ALT: alanine transaminase. AST; aspartate transaminase, HOMA-IR: homeostatic model assessment of insulin resistance, b.AFP : basal Alfa Fetoprotein, b.INR : basal International Normalised Ratio.

DISCUSSION

Although, metabolic derangements and diabetes mellites have been studied and explored in different publications even with heterogenous ethnicity including Egyptian chronic HCV patients [9-11], reciprocal relation between type 2 DM and HCV treatment still needs more convincing arguments [12]

Several cohort and meta-analysis studies confirmed the observation that HCV is more prevalent in type 2 DM patients and on the contrary the rates of DM development and uncontrolled glucose profile in chronic HCV patients is much higher. More than 10 percent of chronic HCV patients had type 2 diabetes that was one of most common extrahepatic features of chronic HCV [13,14]. To note, a meta-analysis of more than 30 studies ascertained that the odd ratios for new diabetes development in HCV patients were 1.58 (95%CI: 1.30-1.8) [15].

10 years earlier, it seems the first evolving concepts about the association between chronic hepatitis and insulin resistance. It was coherent to accept this because the liver has a fundamental role in glucose regulation [16].

In our study, with all enrolled oral antiviral treatment modalities, sustained virological response was obtained in all studied patients after 12 weeks in addition to improvement of the glycemic profile. These results are consistent with other studies including HCV genotype 4. Oxidated stress was the fundamental pathway that explains how chronic HCV can deteriorate glycemic profile so its treatment can ameliorate that effect [17,18]. In the contrary, some studies found that although IR was decreased after HCV eradication, superoxide dismutase SOD activity was non significantly elevated, whether with the use of peg interferon or sofosbuvir based treatment [19].

Our study is consistent with other studies' results that explored the benefits gained from HCV treatment on insulin resistance whether to use in a diabetic or nondiabetic participants [20]. **Yosef *et al.*** showed that DAA can significantly decrease HOMA-IR in non-diabetic patients after achieving SVR [21]. This could be explained because the effect of insulin resistance is much related to virological response irrespective of the antiviral treatment used. On the contrary, **Brandman *et al***. found that virological response was not a surrogate marker to predict substantial decrements in insulin resistance as the participants showed a decrease in IR even without reaching SVR. These findings were related to peg-interferon era that might give these results [22].

Also, another study explored both HOMA-S (insulin sensitivity) and HOMA-β (pancreatic β function) changes after achieving sustained virological response. The delta change was not related to treatment response [23].

In our study, although there was significant decrease of HOMA-IR with direct acting antiviral treatment, we cannot confirm whether HOMA-IR would be used as forecaster for SVR or a directly proportional to viral load. Large meta-analysis consists of 8 studies with nearly thousand patients contemplated the impact of treatment of chronic HCV infection on insulin resistance and found that there is not much statistically important difference of HOMA-IR changes between the HCV treatment response and non-response groups [1].

Study of HOMA-IR in chronic HCV patients is of paramount benefit as some authors evaluated the effect of metformin as a treatment for insulin resistance in HCV patients and found that it could improve overall morbidity associated with chronic HCV [24].

In our study, most baseline liver function tests were inversely related to change of HOMA-IR, A1C, fasting insulin and fasting blood sugar which may indicate a severity of the liver condition that could complicate insulin resistance normalization, so early treatment of chronic HCV especially with direct acting antiviral might be warranted to achieve a good response in insulin resistance.

Some studies with large participants number explored the relation of liver enzymes and HOMA-IR and find a positive association between them [25] but to our

knowledge our article might be the first to evaluate the base line of liver enzymes and the change of HOMA-IR that could be a predictor of insulin resistance response to treatment.

CONCLUSION

We concluded that DAAs improved insulin resistance and related glycemic control parameters after eradication of HCV. These findings suggest that HCV plays a role in glucose homeostasis. Liver function before treatment could be a predictor of improvement of insulin resistance. Some limitations hampered our study; small study populations, individual antiviral regimens need to be assessed in detail, evaluation of insulin resistance according to the functional status of the HCV patients such as Child Pugh classification and subgroup analysis of HCV genotype for identification of which of them is associated with better glycemic improvements.

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