RESEARCH ARTICLE

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Improvement of glycemic state among responders to Sofosbuvir-based treatment regimens: Single center experience

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Chronic HCV infection has emerged as a complex multifaceted disease with manifestations extending beyond the liver. HCV plays a direct role in glucose metabolism leading to both insulin resistance and type 2 diabetes. To evaluate the changes in the glycemic state following Sofosbuvir-based treatment regimens in diabetic HCV patients. Four hundred chronic hepatitis C patients who underwent Sofosbuvir-based treatment regimens were retrospectively screened. Sixty-five diabetic HCV patients only enrolled in our analysis. Baseline demographic and laboratory data were recorded. Pretreatment Transient elastography was performed. At 24-week post EOT (SVR24), Fasting Plasma glucose, and Hemoglobin A1c were re-evaluated and compared with baseline. All enrolled diabetic patients were responders. They showed statistically significant decline in Fasting Plasma glucose and Hemoglobin A1c values at SVR24. Whatever the degree of hepatic fibrosis, the level of Fasting Plasma glucose and Hemoglobin A1c decreased at SVR24 in comparison to baseline level. Fifty-one patients showed improvement in their Hemoglobin A1c values at SVR24 and this improvement was more likely to occur among patients with low Body mass index. The reduction in Fasting Plasma glucose >20 mg/dL (>1.1 mmol/L) and Hemoglobin A1c ≥0.5% was not associated with age, gender or hepatic fibrosis stage. Sofosbuvir-based regimens are a highly efficient antiviral therapy for diabetic chronic HCV patients resulted in improvement in Fasting Plasma glucose and Hemoglobin A1c.

KEYWORDS
chronic hepatitis C virus, diabetes mellitus, fasting plasma glucose, Hemoglobin A1c

1 | INTRODUCTION

Diabetes mellitus (DM) is a global public health threat. In 2014, more than 387 million cases reported worldwide and expected to rise up to 592 million by 2035.[1]

Hepatitis C virus (HCV) infection is another substantial global health burden chronically infecting 130-150 million people[2] and HCV patients are at risk of developing liver cirrhosis and HCC. Moreover, HCV infection is a risk factor for the development of glucose metabolism disorder as chronic hepatitis C (CHC) patients were

more prone to diabetes with type 2 (T2DM) mainly compared to healthy people.[3] T2DM in CHC patients is associated with worsening insulin sensitivity and an impaired first phase insulin response.[4]

Egypt is the country with the highest HCV prevalence in the world[5] with almost all infections due to genotype 4.[6] The prevalence of T2DM among Chronic HCV Egyptian patients is 13-33%.[7]

The previously used standard of care treatment of chronic HCV infection with Pegylated-interferon (Peg-IFN) and ribavirin combination therapy had a limited efficacy and many side effects when used in our genotype four infected patients.[8]

Moreover, Diabetes has been reported as one of host-related factors that is associated with poor treatment response to interferon (IFN) and ribavirin treatment.[9–10]

In 2014, many direct antiviral agents (DAAs) have been approved in treatment of HCV infection and they showed a promising future for HCV treatment with higher SVR rates, shortened and simplified regimens and minimal treatment-related side effects in HCV infected patients.[11]

Little is known about the impact of direct acting antiviral agents (DAAs) on glycemic state of diabetic HCV patients.

The aim of our study is to evaluate the changes in the glycemic state following Sofosbuvir-based treatment regimens in diabetic HCV patients.

2 | MATERIALS AND METHODS

2.1 | Patient population

This is a retrospective study including 400 Egyptian CHC patients who were seropositive for HCV antibodies and HCV RNA positive. They were recruited from Kasr Al-Ainy Viral Hepatitis Center; Cairo University and aged 18-75 years. They received HCV antiviral treatment according to inclusion criteria approved by the national committee for control of viral hepatitis (NCCVH) in Egypt and EASL guidelines, 2014.[12] Treatment-naïve or Treatment experienced patients with any Body mass index (BMI) was calculated as (weight in kilograms/squared height in meters), and with any stage of hepatic fibrosis were included. Patients with hepatitis B virus co-infection, human immunodeficiency virus infection, decompensated liver disease, hepatocellular carcinoma or extra-hepatic malignancies were excluded from the study. Diabetes was found among 65 patients (16.25%) out of the 400 included subjects and they were enrolled in our final analysis.

Diabetes was defined in our study according to the American Diabetes Association criteria that stated briefly that patient with previously established diagnosis of DM, currently taking any form of oral hypoglycemic/ insulin or twice-fasting glucose level equal to or greater than 126 mg/dL (7 mmol/L) of previous medical records.[13]

Liver cirrhosis was diagnosed on clinical basis involving laboratory tests and ultrasonographic findings of liver cirrhosis and/or liver stiffness measurement using Fibroscan ≥12.5 kPa.[14]

Enrolled diabetic patients were subjected to detailed medical history, clinical examination with special emphasis on diabetes onset,

disease duration, type of received anti-diabetic agents, and routine laboratory work up. All patients underwent a pretreatment Transient elastography examination within 2 weeks before treatment initiation.

The following Sofosbuvir-based treatment regimens were prescribed according to the approved treatment recommendation (EASL 2014) [12] and the protocol approved by the National Committee for Control of Viral Hepatitis (NCCVH) in Egypt. These regimens included sofosbuvir (SOF)/simeprevir (SMV), sofosbuvir (SOF)/ledipasvir and sofosbuvir (SOF)/daclatasvir (Daklinza) with or without ribavirin (RBV) for 12 weeks.

Patients were assessed for HCV RNA at week 0 (baseline), at end of treatment (EOT), at 12-week post-treatment follow-up (SVR12) and at 24-week post-treatment follow-up (SVR24). Undetectable HCV RNA by quantitative polymerase chain reaction assay (Cobas Amplicor, HCV Roche, Branchburg, NJ, v 2.0, detection limit 15 IU/mL) at 12-week (SVR12) or 24-week (SVR24) post-treatment follow-up. Both SVR12 and SVR24 have been widely accepted and recognized as indicative of therapeutic success.[15]

Pre-treatment Fasting Plasma glucose (FPG) and Hemoglobin A1c (HbA1c) were assessed at week 0 (baseline) and at 24-week of follow up after the EOT (SVR24).

Written informed consent was obtained from each patient before receiving treatment. The study was conducted according to the principles of the Declaration of Helsinki and was approved by Institutional Review Board (IRB) of faculty of medicine, Cairo University.

2.2 | Laboratory tests

Baseline laboratory investigations were done in form of hemogram, liver function tests; kidney function test, AFP and FPG as well as HbA1c in addition to HCV PCR. HCV PCR was done again at end of treatment (EOT), 12 weeks of follow up after EOT (SVR12) and 24 weeks of follow up after EOT (SVR24) while FPG and HbA1c were re-assessed at SVR24. Improvement of the glycemic state was considered with a decrease of FPG at least 20 mg/dL (1.1 mmol/L) and HbA1c 0.5% when compared to baseline values or reduction of hypoglycemic drugs dosing during anti-HCV treatment [16]

2.3 | Transient elastography

Liver stiffness measurements were done for all patients with Transient elastography (Echosense, Fibroscan 502, Paris, France). At least ten valid measurements were performed, and median of liver stiffness expressed in kilopascals (kPa) was reported.[17] Only examinations with success rate >60% and interquartile range (IQR, reflecting the variability of measurement) <30% were included in this study and were considered reliable. TE results were correlated to different stages of liver fibrosis according to the histological staging system of METAVIR which demonstrated different stages of fibrosis (F0-F4) by means of validated cut-off values.[18] Patients were further grouped

TABLE 1 Baseline feature of studied diabetic patients

	(Mean ± SD, n %)
Demographics	
Age (years)	56.7 ± 9.27
Sex, n (%)	
Male	45 (69.2 %)
Female	20 (30.8%)
BMI (Kg/m^2)	30.12 ± 4.19
Treatment status, n (%)	
Treatment naïve	46 (70.8%)
Prior Peg IFN/RBV treatment	19 (29.2%)
Presence or absence of baseline cirrhosis, n (%)	
Non-cirrhotic.	34 (52.3%)
Cirrhotic.	31 (47.7%)
Stage of hepatic fibrosis by liver stiffness measurement, n (%)	
Mild to significant fibrosis (F0, F1, and F2)	25 (38.5%)
Advanced fibrosis and cirrhosis (F3-F4).	40 (61.5 %)
Laboratory tests	
ALT (U/L)	52.5 ± 27.7
AST (U/L)	56.5 ± 48.5
FPG (mg/dL) (mmol/L)	122.8 ± 35.7 (6.8 ± 2)
HbA1c (%)	6.8 ± 0.99
Type of anti-diabetic treatment, n (%)	
OHG	36 (55.4%)
Insulin	18 (27.7%)
Both insulin & OHG	10 (15.4%)
Not on specific treatment	1 (1.5%)
Type of HCV treatment, n (%)	
Sofosbuvir-based treatment without ribavirin	60 (92.3%)
Sofosbuvir-based treatment with ribavirin	5 (7.7%)

SD, standard deviation; BMI, body mass index; Peg IFN/RBV, pegylated-interferon/ribavirin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c.

according to the stage of hepatic fibrosis into two groups: (i) mild to significant fibrosis (F0, F1, and F2); (ii) advanced fibrosis to cirrhosis (F3-F4) in accordance with Castera et al[14] cut-off values for staging of hepatic fibrosis.

2.4 | Statistical analysis

Data analysis was done using Statistics/Data Analysis (STATA) version 13.1 software. Continuous variables were tested for normality by the Shapiro-Wilk normality test. Values are presented as mean ± standard deviation, or in the case of non-normally distributed data as median and inter-quartile range.

The Chi-squared test was used to compare percentages between different groups of patients. Normally distributed data were analyzed using independent samples t-test. Data found to be non-normally distributed were analyzed using the Mann-Whitney U test. Non-normally distributed paired samples were analyzed using the Wilcoxon signed-rank test. Logistic regression analysis was done to determine factors associated with a significant reduction in FPG and HBA1c.

3 | RESULTS

Out of 400 chronic HCV patients enrolled for treatment, 65 patients with type 2 diabetes mellitus (T2DM) were reported and included in the statistical analysis. The baseline characteristics of patients are shown in Table 1. The mean age is 56.7 ± 9.27 years with male predominance (69.2%), their BMI was 30.12 ± 4.19 Kg/m^2. About 47.7% were cirrhotic; the majority of patients were Treatment-naïve (70.8%). According to the results of liver stiffness measurement, 38.5% had mild to significant fibrosis (F0, F1, and F2) while 61.5% of the studied population had advanced fibrosis and cirrhosis (F3-F4). The baseline mean value of FPG was 122.8 ± 35.7 mg/dL (6.8 ± 2 mmol/L) while mean value of HbA1c was 6.8 ± 0.99%. Anti-diabetic treatment was based on oral hypoglycemic agents in 36 patients and on insulin in 18 patients; 10 patients assumed both insulin and oral hypoglycemic agents while one patients was not under treatment. All diabetic patients were responders to HCV treatment at EOT and achieved SVR12 as well as SVR24.

There was a statistically significant decline in ALT and AST levels at SVR24 compared to baseline as shown in Table 2.

FPG value showed a significant reduction (P = 0.005) with a reduction mean value of −11.51 mg/dL (−0.6 mmol/L). The maximum reduction of 160 mg/dL (8.9 mmol/L) was observed in one patient (FPG declined from 250 mg/dL (13.9 mmol/L) at baseline to 90 mg/dL (5 mmol/L) at SVR24). HbA1c value also showed a significant reduction (P = < 0.001) with a reduction mean value of −0.5%. The maximum reduction of 3.4% points was observed in one patient

TABLE 2 Changes of Laboratory tests at baseline and SVR24

	Baseline (median (IQR))	SVR24 (median (IQR))	P-value
ALT (U/L)	49 (26)	18 (13)	<0.001
AST (U/L)	44 (26)	25.5 (12.5)	<0.001
FPG (mg/dL)	113 (41)	103 (24)	0.005
HbA1c (%)	6.9 (1.4)	6.4 (1.3)	<0.001

IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; OHG, oral hypoglycemic.

TABLE 3 Changes of glycemic control among different groups at baseline and SVR24

		Baseline (median (IQR))	SVR24 (median (IQR))	*P*-value
Type of anti-diabetic treatment				
Both insulin and OHG (*n* = 10)	FPG (mg/dL)	106 (21)	105 (30)	0.7
	HbA1c (%)	6.4 (1.6)	6 (1.3)	0.15
Insulin (*n* = 18)	FPG (mg/dL)	107.5 (41)	105 (22)	0.2
	HbA1c (%)	6.7 (1.26)	6.2 (1)	0.007
OHG (*n* = 36)	FPG (mg/dL)	116.5 (55.5)	100 (24.5)	0.008
	HbA1c (%)	7 (1.2)	6.5 (0.9)	0.001
Stage of hepatic fibrosis				
Advanced fibrosis/cirrhosis (*n* = 40)	FPG (mg/dL)	111.5 (49.5)	104 (26)	0.02
	HbA1c (%)	6.9 (1.5)	6.4 (1.4)	0.001
Mild/significant fibrosis (*n* = 25)	FPG (mg/dL)	115 (43)	101 (18)	0.09
	HbA1c (%)	6.9 (1.1)	6.4 (1)	0.001

IQR, interquartile range; OHG, oral hypoglycemic; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c.

(HbA1c decreased from 9.4% at baseline to 6% at SVR24) as shown in Table 2.

Subgroup analysis for the changes in FPG and HbA1c values in relation to the type of treatment received for diabetes showed significant decline in FPG in patients receiving OHG (*P* = 0.008) and significant decrease in HbA1c among patients receiving both insulin and OHG drugs (*P* = 0.007 and 0.001, respectively) as shown in Table 3.

Among patients with advanced fibrosis and cirrhosis, a statistically significant decline was observed in both HbA1c and FPG values (*P* = 0.001 and 0.02, respectively) while those with mild to significant fibrosis, only significant improvement was observed in HbA1c levels (*P* = 0.001) as shown in Table 3.

Improvement in HbA1c values occurred in 51 patients (78%) at SVR24 compared to baseline values and it was more likely to occur among patients with low BMI as shown in Table 4.

Regression Logistic analysis was done to identify factors associated with reduction in FPG>20 mg/dL (1.1 mmol/L) and HbA1c ≥0.5%. It revealed that the higher the BMI, the lower odd ratio of reduction in HbA1c ≥0.5% with (OR (95%CI) 0.86 (0.75-0.98), *P* = 0.02) as shown in Table 5.

4 | DISCUSSION

Diabetes and hepatitis C infection are among the most prevalent diseases worldwide. HCV is a multifaceted infection affecting different processes such as mitochondrial function, insulin resistance (IR), lipid metabolism, and signaling pathways.[19] Diabetes has been recognized as part of the spectrum of HCV-associated diseases[20] and it worsen hepatitis C outcomes including increasing the risk for cirrhosis, HCC

TABLE 4 Characters of patients who showed improvement in HbA1c or not

	HbA1c decreased (*n* = 51)	HbA1c did not change or increased (*n* = 14)	*P*-value
Age			
Mean (SD)	56.7 (7.80)	56.9 (13.75)	0.9
Gender (Male)	36	9	0.6
BMI			
Mean (SD)	29.56 (4.03)	32.17 (4.28)	0.04
Baseline ALT			
Median (IQR)	49 (24)	42 (29)	0.7
Baseline AST			
Median (IQR)	47 (32)	42 (22)	0.8
Stage of hepatic fibrosis			
Advanced fibrosis_to_cirrhosis N(%)	30 (58.8%)	10 (71.4%)	0.4

SD, Standard deviation; BMI, Body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HbA1c, Hemoglobin A1c.

TABLE 5 Univariate regression analysis for factors associated with reduction in FPG >20 mg/dL (1.1 mmol/L) and HbA1c ≥0.5%

	Reduction in FPG >20 mg/dL (1.1 mmol/L)		Reduction in HbA1c ≥0.5%	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age	0.98 (0.92-1.04)	0.5	1.02 (0.97-1.07)	0.5
Gender				
Female	0.41 (0.12-1.44)	0.2	0.47 (0.16-1.40)	0.2
Male	1			
BMI	0.89 (0.77-1.02)	0.09	0.86 (0.75-0.98)	0.02
Baseline ALT	1.02 (0.99-1.04)	0.06	1.02 (0.99-1.04)	0.1
Baseline AST	1.02 (0.99-1.04)	0.05	1.01 (0.99-1.02)	0.3
Ribavirin_containing regimens	3.49 (0.54-22.76)	0.2	1.71 (0.27-11.01)	0.6
Advanced fibrosis-cirrhosis	1.02 (0.35-2.98)	0.9	0.98 (0.36-2.67)	0.9
Mild−significant fibrosis	1		1	

BMI, Body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HbA1c, Hemoglobin A1c; FPG, Fasting plasma glucose.

and poor antiviral treatment response. Strict control of blood glucose levels may improve survival in HCV patients.

HbA1c is a standard biomarker of long term glycemic control and plays a critical role in the management of diabetic patients and correlates well with both micro- and macro-vascular complications.[13] Although HOMA-IR is a valid and reliable surrogate measure of insulin resistance, HbA1c may be utilized as a surrogate marker of insulin resistance.[21]

The current study aimed to elucidate the change in the glycemic state among diabetic responders HCV patients who received Sofosbuvir –based treatment regimens.

Our study showed that all our enrolled diabetic patients were responders at EOT and achieved SVR12 as well as SVR24. Although previous studies reported that DM and Insulin resistance (IR) are predictors for therapeutic failure of anti-HCV therapy in IFN era in patients with different genotype infection.[10,22–23] Our results support the fact that diabetic HCV patients may benefit from the new oral DAAs – based regimens and no longer considered as a "difficult-to-treat" group.

We addressed that Sofosbuvir-based treatment regimens could effectively improve HbA1c and FPG values at SVR24 compared to baseline. The mechanism responsible for this improvement in glycemic control of HCV patients is unknown. However, a possible explanation could be that HCV promotes IR, which induces inflammatory cascades, endothelial dysfunction and causes alterations of glucose homeostasis. HCV can degrade Insulin receptor substrates 1 and 2 which are closely related to the Pi3 K/AKT pathways; these two receptors are key components in the development of IR in HCV patients.[24] Moreover, Insulin resistance (IR) is also correlated with HCV viral kinetics and improved by HCV clearance by anti- HCV therapy.[25–26] Rapid suppression of HCV replication and concurrent systemic inflammation restores glucose homeostasis and leads to improvement of IR. In the IFN/RBV era, several studies have demonstrated an improvement of IR with SVR.[27–28] Similarly, few studies evaluating the effect of DAAs – based regimens on glycemic state of HCV diabetic patients and

showed significant improvement in HbA1c and FPG values in patients with SVR.[16,29–30]

HbA1c could not be used to guide diabetes therapy during the previous era of treatment with peg-IFN plus ribavirin. Ribavirin induced hemolytic anemia was previously known to cause false reduction in HbA1c without a change in the fasting glucose levels in diabetic patients who were treated with peg-IFN plus ribavirin[31] Also the decreased lifespan of the RBC may provide an inaccurate HbA1c with falsely low values. In the current study, Sofosbuvir-based treatment regimens caused a significant decline in HbA1c values with decline in FPG levels at SVR24 and it seems that ribavirin had no role in reduction of HbA1c values.

The observed decline in FPG and HbA1c values at SVR24 among different anti-diabetic treatment regimens, further suggests the need for close monitoring of glucose levels and the potential need for dose adjustments of diabetes therapies during HCV treatment to prevent hypoglycemia. Moreover, our patients did not experience hypoglycemia during DAAs treatment, the direct hypoglycemic effect of DAAs or drug-drug interactions with insulin and OHG should be excluded.

Liver fibrosis progression was known to be responsible for the development of IR and T2DM in patients with chronic liver diseases as it causes alterations in glucose homeostasis[32] meanwhile insulin resistance (IR) was associated with fibrosis progression and cirrhosis in diabetic HCV patients.[33–34] Moreover, advanced fibrosis and cirrhosis are independent predictors of a poor response to IFN- therapy in CHC patients.[35] Our study showed that whatever the stage of hepatic fibrosis there was improvement in FPG and HbA1c values following Sofosbuvir-based treatment regimens and also a high proportion of patients with advanced fibrosis to cirrhosis had improvement in HbA1c values at SVR24. This result addressed that those diabetic HCV patients with advanced fibrosis to cirrhosis would benefit from Sofosbuvir-based regimens and no longer considered a "difficult-to-treat" group.

It is well known that higher BMI is associated with insulin resistance and hepatic steatosis that can lead to hepatic fibrosis[36] and this may explain why the higher BMI is the only variable associated with poor improvement of HbA1c in the current study. Although BMI is no longer considered as a prerequisite for HCV treatment with the new oral DAAs, our result imply that life style modification and weight reduction during HCV treatment with DAAs is still necessary for proper glycemic control.

The following variables age, gender and grade of hepatic fibrosis were not associated with reduction in FPG>20 mg/dL (1.1 mmol/L) and HbA1c ≥0.5% and this finding was in parallel with Pavone et al.[16] and Fabrizio et al.[29]

In conclusion, Sofosbuvir-based therapy is a highly effective antiviral therapy resulting in improvement of glycemic control. The effect of IR in the DAA drugs era is still unclear. Prospective studies with prolonged follow-up are needed to delineate the impact of Sofosbuvir-based therapies on insulin signaling pathways and the potential for improving glucose metabolism. This may guide therapeutic selection and improve liver and metabolic outcomes for HCV-infected patients with type 2 diabetes.

CONFLICT OF INTEREST

Gamal Esmat is a speaker, advisory board member and investigator for Gilead Science while all other authors have nothing to declared.

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