Impact of sustained virologic response on glycemic control among diabetic patients with hepatitis C virus-related liver disease

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Background
Previous studies have revealed contradictory results regarding the effect of interferon and direct-acting antivirals treatment for hepatitis C virus on the glycemic control of patients with type-2 diabetes mellitus. Our study explored the effect of one of the most commonly used regimens for the treatment of chronic hepatitis C virus infection in Egypt (sofosbuvir and daclatasvir, with or without ribavirin) on the glycemic control of patients with concomitant type-2 diabetes mellitus.

Patients and methods
This prospective, cross-sectional study was conducted at the Department of Tropical Medicine and Gastroenterology, Assiut University during the period between January 2019 and December 2019.

Results
The absolute values and mean changes of glycosylated hemoglobin and fasting plasma glucose among patients with sustained virologic response compared with those with therapeutic failure did not show significant differences when compared between patients with sustained virologic response and those without.

Conclusion
A significant improvement in glycemic control was observed in diabetic patients with chronic hepatitis C.

Keywords:
sustained virologic response, glycemic control, chronic hepatitis C virus

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Introduction

The 11-fold higher prevalence of diabetes mellitus (DM) among patients with chronic hepatitis C virus (HCV) infection (one-third of patients have type-2 DM) reflects the association between HCV infection and DM. DM is 11-fold higher among patients with HCV infection compared with those without [1]. Not only patients with chronic HCV infection who demonstrate such association but also those with HCV-related cirrhosis type-2 DM among patients with liver cirrhosis due to HCV infection when compared with patients with cirrhosis due to causes other than HCV infection [2].

Two different mechanisms can explain the development of DM among patients with chronic HCV infection. The first one is the development of an autoimmune reaction, among those who are genetically susceptible, against pancreatic β-cells, with subsequent destruction of such cells. Insulin resistance (IR) caused by increased serine and threonine phosphorylation of insulin receptor substrate-1 is the second suggested mechanism [3].

Patients and methods

This prospective, cross-sectional study was conducted at the Department of Tropical Medicine and Gastroenterology, Assiut University during the period between January 2019 and December 2019. This work was conducted by the Code of GP rather than the guidelines of Declaration of Helsinki, 7th revision, 2013, and after being approved by the Medical Ethics Committee of the Faculty of Medicine at Assiut University. Assiut Faculty of Medicine approved the study under IRB number 17100567 and all patients signed an informed consent before being enrolled in the study (registration number at clinical trials is NCT03591783).

Patients with concomitant chronic HCV infection and type-2 DM were enrolling in the studies. Chronic HCV infection was diagnosed based on positive testing for both serum HCV RNA and antibody for

HCV (anti-HCV Ab), while fasting blood glucose of more than 126 mg/dl and/or fasting serum level of glycosylated hemoglobin (HbA1c) more than 6.5% were used to establish the diagnosis of type-2 DM.

Any patient with coinfection with hepatitis B virus infection, hepatocellular carcinoma, Child C class of cirrhosis, type-1 DM, and those receiving corticosteroids were excluded from the study.

All the studied patients were evaluated using history taking and physical examination, including determination of BMI. At baseline, the following laboratory investigations were done: liver chemistry panel, prothrombin time, complete blood count, fasting plasma glucose (FPG) level, HbA1c level, anti-HCV Ab, hepatitis B surface antigen, qualitative HCV RNA by PCR, lipid profile (total cholesterol, HDL, LDL cholesterol, and triglycerides), and alpha-fetoprotein. All the laboratory investigations were repeated at the end of treatment and 24 weeks after therapy.

All patients were evaluated by abdominal ultrasound before therapy. Based on laboratory data and abdominal ultrasound, the model for end-stage liver disease score, Child score, aspartate aminotransferase to platelets ratio index (APRI), and fibrosis-4 (FIB-4) were calculated.

The studied patients were classified into a group with chronic HCV infection (APRI >1.45 and/or FIB-4 >3.25) and another group with HCV-related cirrhosis (APRI <1.45 and/or FIB-4 <3.25, and/or ultrasonographic signs of cirrhosis).

Sofosbuvir (400 mg/day, in a single dose) and daclatasvir (60 mg/day, in a single dose) for 12 weeks were used for patients with chronic HCV infection. For those with cirrhosis, weight-based ribavirin was added to sofosbuvir and daclatasvir (<75 kg received 1000 mg/day, on three divided doses; >75 kg received 1200 mg/day, on three divided doses). Dose adjustment of ribavirin during therapy was done based on the level of hemoglobin.

Sample size justification and statistical analysis

Based on the prevalence of HCV in Egypt (12–15%) [4], a minimum of 139 patients were enrolled in the student with a probability of 0.05 and 95% power on a two-tailed test. The sample size was calculated using OpenEpi, Version 3 (Developed in Javascript and hypertext markup language [HTML]), and another open-source calculator.

Data were collected and analyzed using SPSS (the Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA).

Multivariate regression analysis was used to determine the predictors of sustained virologic response (SVR) among the study population. The level of confidence was kept at 95% and then the ice value was significant if less than 0.05.

Results

In all, 139 HCV patients were included in the study. All the patients achieved SVR, except for 15 (10.8%); they did not receive another regimen during the study period.

Baseline demographic data is shown n Table 1. The mean age was 46.53 ± 11.66 years. Out of the 139 patients, 76 (54.7%) were males. Tobacco smoking was reported by 53 (38.1%) patients. The mean duration of DM was ~5 years. All the patients received direct-acting antiviral (DAAs) for 12 weeks.

Table 2 shows the clinical data of the study population. The mean BMI was 28.54 ± 6.15 kg/m^2. The most common abnormality of BMI was obesity (35.3%).

Table 3 shows the laboratory data of the study population at baseline, at end of the therapy, and 24 weeks after the end of therapy.

Table 4 fasting levels of plasma glucose and HbA1c of the study population at baseline, at the end of therapy,

Table 1 Demographic data of the study population (*n*=139)

Items	*n*=139
Age (years)	
Age group	46.53±11.66
<40	40 (28.8)
≥40	99 (71.2)
Sex	
Male	76 (54.7)
Female	63 (45.3)
Residence	
Rural	86 (61.9)
Urban	53 (38.1)
Tobacco smoking	53 (38.1)
Occupation	
Farmer	66 (47.5)
Not employed	73 (52.5)
Duration of DM (years)	4.62±1.94 (1.40-8.56)
Type of therapy for DM	
Oral hypoglycemic agents	80 (57.5)
Insulin	35 (25.2)
Both	24 (17.3)
Systemic hypertension	31 (22.3)
Ischemic heart disease	11 (7.9)
Method of HCV detection	
Accidental	102 (73.4)
Fatigue	37 (26.6)

Data are expressed as frequency (percentage) and mean (SD).
DM, diabetes mellitus; HCV, hepatitis C virus.

and 24 weeks posttherapy. There was no significant change at the end of therapy or 24 weeks posttherapy compared with baseline data, except for alanine aminotransferase, aspartate aminotransferase, APRI, FIB-4, F, and HbA1c, which were significantly lower.

Table 5 shows radiological data and Child class of the study population. Abdominal ultrasound revealed that 59 (42.4%) patients had hyperechoic liver, while signs of liver cirrhosis were present in 38 (27.3%). Out of 139 patients, 64 (46%) patients had mild splenomegaly. Regarding patients with cirrhosis, 27 (71%) out of 38 had Child class A, while only 11 (7.9%) had Child class B. Radiological data did not demonstrate significant difference both at the end of therapy and 24 weeks posttherapy when compared with the baseline before starting treatment.

Based on laboratory investigations (APRI and FIB-4) and radiological evaluation (abdominal ultrasound), the study population was classified into patients with chronic HCV infection (91, 65.5%) and patients with cirrhosis (48, 34.5%). All patients received DAAs for 12 weeks, sofosbuvir plus daclatasvir for patients with chronic HCV infection, and sofosbuvir plus daclatasvir with ribavirin for those with cirrhosis. Both regimens were safe and tolerable, with the absence of adverse effects in 112 (80.6%) patients.

Table 6 shows adverse effects of the used DAAs among the study population. The most frequent adverse effect was diarrhea (9.4%). More than one adverse effect was reported by five (4%) patients; diarrhea with itching in two patients and itching with skin rash. Adverse effects did not lead to the discontinuation of therapy. Anemia among patients who received ribavirin was corrected using dose adjustment. There was no significant difference in adverse effects between patients who

Table 2 Clinical data of the study population (*n*=139)

Items	*n*=139
Height (m)	1.65±0.06
Weight (kg)	77.69±4.04
BMI (kg/m^2)	28.54±6.15
Normal	66 (47.5%) (18.5-25)
Overweight	24 (17.3%) (25-30)
Obesity	49 (35.3%) (>30)
Systolic blood pressure (mmHg)	123.56±10.34
Diastolic blood pressure (mmHg)	78.34±5.55

Data are expressed as frequency (percentage) and mean (SD).

Table 3 Laboratory data of the study population (*n*=139)

	Baseline	End of therapy	24 weeks posttherapy	*P*1	*P*2	*P*3
ALT (U/l)	42.29±27.44	31.92±18.36	26.94±18.35	0.04	0.01	0.57
AST (U/l)	34.39±24.98	24.26±8.84	19.28±8.84	0.04	0.03	0.45
Bilirubin (mg/dl)	0.74±0.40	0.82±0.30	0.78±0.28	0.10	0.09	0.09
Albumin (g/dl)	3.87±0.47	4.26±0.49	4.25±0.27	0.53	0.76	0.33
Protein (g/dl)	8.34±0.45	8.59±0.49	8.27±0.49	0.09	0.53	0.21
Hemoglobin (g/dl)	13.85±1.38	12.61±1.87	13.51±1.87	0.11	0.51	0.98
Platelets (×10^6/ml)	236.21±67.17	216.60±57.18	217.16±57.18	0.76	0.07	0.12
Leukocytes (×10^6/ml)	6.23±2.01	6.24±1.89	3.94±1.87	0.11	0.18	0.08
Creatinine (mg/dl)	1.01±8.92	0.99±0.23	0.89±0.22	0.06	0.39	0.43
INR	1.12±0.08	1.05±0.09	0.98±0.09	0.44	0.09	0.42
Cholesterol (mg/dl)	156.45±44.56	159.11±23.45	153.01±30.45	0.42	0.21	0.18
LDL cholesterol (mg/dl)	101.34±25.56	99.34±33.98	101.11±30.30	0.18	0.22	0.16
HDL cholesterol (mg/dl)	45.56±5.35	47.65±3.89	46.66±6.70	0.09	0.07	0.94
Triglycerides (mg/dl)	130.45±45.50	128.09±34.05	133.54±32.89	0.33	0.19	0.06
APRI	0.75±0.33	0.30±0.18	0.29±0.18	<0.001	<0.001	0.33
FIB-4	2.57±1.17	1.03±0.52	1.03±0.44	<0.001	<0.001	0.77
MELD	8.64±2.33	8.34±1.90	8.29±0.98	0.09	0.18	0.08
Positive HCV RNA	139 (100)	15 (10.8)	15 (10.8)	<0.001	<0.001	–

Data are expressed as mean (SD). ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelets ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCV, hepatitis C virus; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MELD, model for end-stage liver disease. *P* value was significant if less than 0.05. *P*1: compared between baseline data and data at the end of therapy. *P*2: compared between baseline data and data 24 weeks posttherapy. *P*3: compared between data at end of therapy and 24 weeks posttherapy.

Table 4 Fasting plasma glucose and glycosylated hemoglobin of the study population (*n*=139)

	Baseline	12 weeks end of therapy	24 weeks posttherapy	*P*1	*P*2	*P*3
FPG (mg/dl)	152.75±36.19	118.84±35.52	112.13±35.65	<0.001	<0.001	0.33
HbA1c (%)	7.33±0.82	5.46±0.82	5.44±0.81	<0.001	<0.001	0.07

Data are expressed as mean (SD). FPG, fasting plasma glucose; HBA1c, glycosylated hemoglobin. *P* value was significant if less than 0.05. *P*1: compared between baseline data and data at the end of therapy. *P*2: compared between baseline data and data 24 weeks posttherapy. *P*3: compared between data at the end of therapy and 24 weeks posttherapy.

received sofosbuvir plus daclatasvir and those received sofosbuvir plus daclatasvir with ribavirin.

Table 7 shows the mean changes in HbA1c and FPG of the study population after treatment and 24 weeks after treatment compared with before treatment. It was found that HbA1c was lower at the end of therapy compared with before therapy (−1.86 ± 0.18%), while the decrease was (−1.90 ± 0.10%) when the pretreatment levels were compared with those 24 weeks posttherapy. Regarding the change of FPG level, it decreased at the end of therapy compared with before treatment (−33.90 ± 6.58 mg/dl) and it was lower 24 weeks posttherapy compared with pretreatment (−40.03 ± 5.56 mg/dl).

Table 8 shows HbA1c and FPG among patients with SVR compared with those with therapeutic failure. The absolute values and mean changes of both did not show significant differences when compared between patients with SVR and those without.

Table 5 Radiological data and Child class of the study population (*n*=139)

Items	*n*=139
Liver	
Normal findings	42 (30.2)
Hyperechoic liver	59 (42.4)
Liver cirrhosis	38 (27.3)
Splenomegaly	64 (46)
Child class (for patients with cirrhosis)	
A	27 (71)
B	11 (29)
C	0

Data are expressed as frequency (percentage).

Table 6 Adverse effects of direct-acting antivirals used by the study population (*n*=139)

	n=139	Chronic HCV infection (*n*=91)	Liver cirrhosis (*n*=48)	*P*
Adverse effects	13 (9.4)	8 (8.8)	5 (10.4)	0.98
Diarrhea	4 (2.8)	3 (3.3)	1 (2)	
Itching	5 (3.5)	3 (3.3)	2 (4.1)	
Skin rash	5 (3.5)	3 (3.3)	2 (4.1)	
Anemia	112 (80.6)	74 (81.3)	38 (79.2)	

Data are expressed as frequency (percentage). HCV, hepatitis C virus. Patients with chronic HCV infection received sofosbuvir plus daclatasvir. Patients with liver cirrhosis received sofosbuvir plus daclatasvir with ribavirin. *P* value was significant if less than 0.05.

Table 7 Percentage of reduction in glycosylated hemoglobin and fasting plasma glucose compared with before treatment among the study population

	At end of therapy	24 weeks posttherapy
Mean change of HbA1c (%)	−1.86±0.18	−1.90±0.10
Mean change of FPG (mg/dl)	−33.90±6.58	−40.03±5.56

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.

Table 8 Glycosylated hemoglobin and fasting plasma glucose among the study patients with sustained virologic response compared with those with therapeutic failure

	SVR (*n*=124)	No SVR (*n*=15)	*P*
Before therapy			
HbA1c	7.19±0.75	8.49±0.36	0.12
FPG	151.09±35.15	166.46±40.04	0.06
At the end of therapy			
HbA1c	5.33±0.73	6.22±0.36	0.15
FPG	117.12±34.72	133.11±40.04	0.07
Mean change of HbA1c	(−) 1.86±0.19	(−) 1.88±0.13	0.72
Mean change of FPG	(−) 33.97±6.97	(−) 33.35±6.89	0.99
6 months posttherapy			
HbA1c	5.31±0.73	6.18±0.36	0.16
FPG	110.39±34.85	126.43±40.04	0.11
Mean change of HbA1c	(−) 1.90±0.13	(−) 1.89±0.12	0.09
Mean change of FPG	(−) 40.03±2.34	(−) 39.11±5.11	0.33

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SVR, sustained virologic response.

Discussion

Compared with the general population, patients with chronic HCV infection have a higher chance of developing DM, with a 30–70% prevalence of IR among [5]. The mechanisms underlying the higher prevalence of DM among patients with chronic HCV infection are not fully clear; however, several proposed theories exist. One of the suggested mechanics is the destruction of pancreatic β-cells as a result of an autoimmune reaction again in genetically susceptible patients. In addition, increased serine and threonine phosphorylation of insulin receptor substrate-1 can lead to HCV-induced IR. Also, HCV proteins may induce proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha with subsequent regulation gluconeogenesis and enhancement of lipid accumulation in the liver [3].

Based on the previous data, successful eradication of HCV infection can improve the glycemic control of patients with concomitant type-2 DM through the reversal of HCV-induced IR. It was reported that diabetic patients with chronic HCV infection treated with combination therapy (interferon and ribavirin) were protected from developing retinopathy and/or neuropathy when they achieve SVR after a follow-up for 7 years [6], implying that early treatment of HCV infection could potentially slow both onset and progression of microvascular complications among patients with DM.

Before the era of DAAs, interferon therapy for chronic HCV infection led to a significant reduction in FPG and HbA1c levels among patients who achieved SVR, which was not the case with HCV relapse [7]. After starting the use of DAAs, several studies have investigated the effect of DAAs on the glycemic control of patients with type-2 DM. A retrospective study of diabetic patients infected with HCV showed that HCV

suppression by DAAs therapy was associated with a significant decrease in FPG after as short as 4 weeks of treatment [8]. In Egypt, three studies reported a significant reduction in FPG or HbA1c during therapy and/or after the end of therapy by DAAs in patients with concomitant chronic HCV infection and type-2 DM [9–11]. In agreement with the previously mentioned studies, our results revealed a significant improvement in glycemic control of diabetic patients with HCV infection. The significant reduction of both FPG and HbA1c among our study patients was not only confined to the point at the end of therapy but also extended to 24 weeks after ending treatment.

However, the changes of FPG and HbA1c among our study population with DAAs were not significantly different when comparing the patients who achieved SVR with those who did not. This finding was consistent with the results of a previous study by Hum *et al.* [12]; it revealed that the significant decrease in HbA1c after DAAs was not related to achieving SVR. Apart from another HbA1c level, SVR plays a major role in the reduction in homeostasis model of assessment value as reported by several other studies, suggesting that HCV plays a direct role in mediating IR and contributes to the progression of DM [5,13,14].

Contradictory to our results, Stine *et al.* [15] found that the HbA1c level was not significantly reduced by treating HCV infection using DAAs regarding the presence of cirrhosis. This finding was attributed to the type of pharmacologic therapy for DM rather than SVR, to the more frequent risk factors of IR among the study patients.

Among our study population, the predictors for glycemic control were of younger age (odds ratio = 2.45, 95% confidence interval = 2.11–4.50; $P < 0.001$), absence of liver cirrhosis (odds ratio = 2.11, 95% confidence interval = 1.55–4.03; $P < 0.001$), and absence of obesity (odds ratio = 1.11, 95% confidence interval = 1.01–3.01; $P < 0.001$). The results of previous studies supported our findings; BMI more than or equal to 23 kg/m^2, homeostasis model of assessment-IR more than or equal to 2, and significant liver fibrosis by histopathologic examination was dependently associated with a lower SVR, suggesting that glycemic control was mediated by regression of liver fibrosis rather than eradication of HCV [16].

Conclusion

Based on our study results, a significant improvement in glycemic control was observed in diabetic patients with chronic hepatitis C. Furthermore, diabetes could be considered as an indication for the treatment of chronic hepatitis C patients with no apparent liver disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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