

Impact of Direct Acting Antivirals for Treatment of Chronic Hepatitis C Virus Infection on Glycemic Control in Egyptian Patients with Type 2 Diabetes Mellitus

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Abstract: Background: hepatitis C virus (HCV) infection looks to increase the probability of incidental type 2 diabetes mellitus in predisposed subjects, unrelated to the stage of liver disease. The processes through which hepatitis C triggers T2DM include direct effects of HCV, insulin resistance, proinflammatory cytokines and other immune-induced mechanisms. The aim of this study was to evaluate the impact of direct acting antiviral agents for treatment of chronic HCV infection on insulin resistance and glycemic control in Egyptian patients with type 2 diabetes mellitus. Methods: This study was conducted on 230 type 2 DM patients with genotype 4 chronic HCV. 200 patients received DAAs in the form of sofosbuvir plus daclatasvir with or without ribavirin for 12 weeks, while the remaining 30 patients did not receive DAAs and served as a control group (group C). Patients who reached the SVR 12 weeks after DAAs (190 patients, 95%) were subdivided into three groups according to the end-point of glycemic control; that is, the achieved glycemic control (AGC) group with chronic hepatitis (group A), which comprised 80 patients (42.1%), the achieved glycemic control (NAGC) group with liver cirrhosis child A (group B), which included 62 patients (32.6%) and the non-achieved glycemic control (NAGC) group with liver cirrhosis child B (group C) which comprised of 48 patients (25.3 %). Results: In group A (chronic hepatitis with AGC), 30 patients (36.1%), and group B (liver cirrhosis Child-Pugh A class with ACG) necessitated to decrease the dose of antidiabetic treatment. There were no statistically significant differences between our groups as regard to age, sex, and body mass index (BMI). Our patients in group C (Liver cirrhosis Child-Pugh classification B with non-achieved glycemic control) had positive family history of type 2 DM and longer duration of DM if compared to group A, and group B. Conclusion: In Egyptian type 2 diabetic patients with CHC, the administration of direct acting antiviral agents led to a dramatic advance in blood sugar control and should be closely observed for antidiabetic drug reduction to prevent hypoglycemic events. Clearance of HCV improves insulin resistance as evidenced by a reduction of plasma insulin, HbA1c, and HOMA-IR. Achievement of glycemic control in Egyptian HCV patients treated with direct acting antiviral agents is appreciated in patients with mild liver disease (Child-Pugh class A), with short duration of diabetes, and without family history of T2DM, but is not related to body mass index, age, and sex.

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1. Introduction:

Chronic hepatitis C (HCV) virus infects an approximate 170 million individuals worldwide and is a major cause of chronic liver disease, including cirrhosis and liver cancer (1). Egypt constitute the highest prevalent area catching HCV infection all over the worldwide (15%) with genotype 4 (90%) is the most prevalent one (2). The treatment of hepatitis C virus (HCV) has dramatically changed since the recent introduction of direct-acting antiviral agents (DAAs). DAAs have increased the sustained viral response (SVR) rate to over 90% with minimal adverse effects and short treatment duration. The short treatment duration allows for a clear comparison of the changes in the body before and after the eradication of HCV.

HCV infection is closely associated with metabolic complications, including glucose intolerance, hepatic steatosis, and dysregulated lipid metabolism (3, 4). It is widely recognized that HCV infection is associated with several metabolic derangements including hypolipidemia, hepatic steatosis and metabolic syndrome (5, 6, and 7). Different studies have also confirmed an increase in the prevalence of blood sugar abnormalities in HCV patients as compared to controls (8, 9). As such, the virus has been implicated in the development of insulin resistance (IR) by modulating cellular gene expression and interfering with insulin signaling pathways.

Patients with chronic hepatitis C virus (Chronic HCV) infection have significantly a higher prevalence

of type 2 diabetes mellitus (T2DM), regardless of liver disease stage compared with controls or hepatitis B virus (HBV)-infected patients. T2DM is a common comorbid condition present in about one-third of individuals with chronic HCV infection (10, 11, and 12). Growing evidence shows that HCV increases the risk of incidental type 2 diabetes mellitus (T2DM) in susceptible individuals (13, 14, and 15). The mechanism whereby HCV triggers T2DM is insulin resistance (IR) (15, 16). HCV was shown to impair the hepatocyte insulin signaling pathway by several mechanisms (17), including the stimulus for the production of tumour necrosis factor- α (TNF- α), the serine phosphorylation of the insulin receptors (IRS), the over-expression of the suppressor of cytokines (SOC-3) (18, 19) and the induction of SOC-7 (20). However, in spite of HCV infects mainly the liver, the whole body insulin sensitivity is also impaired in chronic HCV patients without the metabolic syndrome, as shown by recent studies (21, 22). This suggests that the infected liver cells might produce mediators that trigger endocrine effects at extrahepatic sites, such as the skeletal muscle. The virus-influenced metabolic derangements may react with host-related genetic and environmental factors, exacerbating insulin resistance and possibly leading to the development of T2DM. The aim of this study was to evaluate the impact of direct acting antiviral agents for treatment of chronic HCV infection on insulin resistance and glycemic control in Egyptian patients with type 2 diabetes mellitus.

2. Patients and Methods:

This study was conducted on 230 type 2 DM patients with genotype 4 chronic HCV from among the outpatients of the Departments of Internal Medicine and Tropical Medicine of Al-Azhar University Hospitals between October 2014 and August 2015. All patients with chronic HCV genotype 4 infection, more than or equal 18 years were included in this study. The study protocol was approved by the Ethics Committee of the Al-Azhar University Faculty of Medicine, and the selected subjects gave prior consent to participate in the study.

Two hundred patients received DAAs in the form of sofosbuvir plus daclatasvir with or without ribavirin for 12 weeks, while the remaining 30 patients did not receive DAAs and served as a control group. Baseline demographics (age, gender, weight, height, body mass index (BMI), ascites, encephalopathy, duration and family history of type 2 DM and DM treatment medications), laboratory values (liver associated enzymes, total bilirubin, albumin, prothrombin time, international normalized ratio (INR), Child-Pugh score, alphafetoprotein (AFP), creatinine, glycated hemoglobin (HbA1c), Fasting plasma glucose (FPG),

insulin, homeostatic model assessment insulin resistance (HOMA-IR), quantitative HCV-RNA by polymerase chain reaction test, total cholesterol, high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were reviewed. Post-treatment clinical (weight, height, and body mass index) and laboratory values (alpha fetoprotein, quantitative HCV-RNA by PCR, fasting plasma glucose, plasma insulin level, HbA1c, and HOMA-IR) were obtained at the time that sustained virologic response at 12 weeks (SVR12) was examined. The severity of liver disease was determined by using the Child-Pugh classification. None of our patients develop ascites nor encephalopathy. Only CTP class A and class B patients were included. During the study period, all patients were advised to maintain their usual diet regimen and physical activity. Diabetes was confirmed by a hemoglobin A1c > 6.5%, treatment with anti-hyperglycemic medications including insulin or a fasting plasma glucose > 200 mg/dL. For better assessment of improvement in glycemic control, we used a composite end-point given by the reduction of fasting plasma glucose (FPG) (of at least 20 mg/dL) or HbA1c (of at least 0.5%).

According to the post-treatment achieved SVR after 12 weeks (190 patients, 95%), patients were subdivided into three groups according to the end-point of glycemic control; that is, the achieved glycemic control (AGC) group with chronic hepatitis (group A), which comprised 80 patients (42.1%), the achieved glycemic control (NAGC) group with liver cirrhosis child A (group B), which included 62 patients (32.6%) and the non-achieved glycemic control with liver cirrhosis child B (group C) which comprised of 48 patients (25.3 %).

Statistical Analysis:

The data were analyzed using the statistical package for the Social Sciences Software (version 23.0; SPSS Inc., Chicago, IL) package. Independent Student's *t*-test was used to test the differences in the mean values for the continuous variables. Chi-square test was used to test the differences in the proportion of the categorical variables. The Pearson correlation coefficient (*r*) was used to determine the correlation between variables. Statistical significance was set at $P < 0.05$.

3. Results:

Two hundred thirty consecutive adult patients, 134 females (58.3%) and 96 males (41.7%) with mean age 40.5 ± 12.6 years were treated for chronic HCV and were enrolled in this study. Mean body mass index was 26.51 ± 2.57 kg/m², with normal BMI in one (0.4%) patient, overweight in 155 (67.4%) patients and obesity in 74 (32.2%) patients. Sustained

virologic response (SVR) after 3 months of direct acting antiviral agents (DAAs) was occurred in 190 patients (95%). According to the improvement in fasting plasma glucose more than or equal 20 mg/dl, and/or glycated hemoglobin more than or equal 0.5% (improved glycemic control) after 3 months of DAAs, we classify our patients into three groups: group A which include 80 patients with chronic hepatitis C and achieved glycemic control, group B which include 62 cirrhotic Child-Pugh A patients and achieved glycemic control, group C which include 48 cirrhotic Child-Pugh B patients with non-achieved glycemic control. The remaining 30 controls (group D) also included in this study. In group A, 30 patients (37.5%) needed to decrease the dose of antidiabetic treatment; 6 of 14 patients needed to decrease the insulin dose and 24 of

69 patients needed to decrease the gliclazide dose. In group B, 20 patients (32.3%) needed to decrease the dose of antidiabetic treatment; 5 out of 16 patients needed to decrease the insulin dose and 15 of 46 patients needed to decrease the gliclazide dose. None of the achieved glycemic control patients (group A and B) needed to decrease the dose of dipeptidyl peptidase-4 (DPP4) inhibitor or metformin. There were no statistically significant differences between our groups as regard to age, sex, and body mass index (BMI). Our patients in group C (Liver cirrhosis Child-Pugh classification B with Non-achieved glycemic control) had positive family history of type 2 DM and longer duration of DM if compared to group A, and group B as shown in table 1.

Table 1: Baseline demographic and clinical values of our patients

Variable	Group A (Chronic hepatitis with AGC)	Group B (Liver cirrhosis CP- A with AGC)	Group C (Liver cirrhosis CP- B with NAGC)	Group D (Controls)
Age, years (Mean±SD)	41.650±12.73	37.56±12.36	40.61±11.35	43.50±14.46*
Gender:				
• Male, n (%)	36 (43.4%)	26 (41.9%)	22 (40%)	12 (40%)*
• Female, n (%)	47 (56.6%)	36 (58.1%)	33 (60%)	18 (60%)
Family history of DM:				
• Positive, n (%)	0 (0%)	0 (0%)	38 (69.1%)	30 (100%) **
• Negative, n (%)	83 (100%)	62 (100%)	17 (30.9%)	0 (0%)
Type of therapy for DM:				
• Insulin, n (%)	14 (16.9%)	16 (25.8%)	45 (81.8%)	0 (0%)
• Oral hypoglycemic drugs, n (%)	69 (83.1%)	46 (74.2%)	10 (18.2%)	0 (0%)
• No medications, n (%)	0 (0%)	0 (0%)	0 (0%)	30 (100%)
DAAs regimen for HCV:				
• Sofosbuvir + Dalatasvir, n (%)	83 (100%)	62 (100%)	0 (0%)	-
• Sofosbuvir+Daclatasvir+Ribavirin, n (%)	0 (0%)	0 (0%)	55 (100%)	-
Liver disease:				
• Chronic hepatitis, n (%)	83 (100%)	0 (0%)	0 (0%)	30 (100%)
• Liver cirrhosis Child-A, n (%)	0 (0%)	62 (100%)	0 (0%)	0 (0%)
• Liver cirrhosis Child-B, n (%)	0 (0%)	0 (0%)	55 (100%)	0 (0%)
Weight, Kg (Mean ± SD)	73.87 ± 5.32	72.24 ± 3.63	77.50 ± 7.90	70.20±4.09*
Height, Cm (Mean ± SD)	168.03 ± 2.94	167.43 ± 3.03	168.34 ± 3.69	169.76±4.01*
BMI, Kg/m ² (Mean ± SD)	26.28±2.9	26.53±2.05	26.72±2.78	26.69±3.10*
Duration of type 2 DM, years				
• Range	1-3	1-6	7-17	1.2-3
• Mean±SD	1.90±0.71	4.47±1.3	13.25±2.34	2.24±0.54**

* = Non-significant

** = Significant

There were statistically significant differences between the 4 groups of our patients as regard to alanine aminotransferase (ALT), aspartate

aminotransferase (AST), total bilirubin, serum albumin, Child- Pugh classification of liver cirrhosis, total cholesterol, high-density lipoprotein-C (HDL-C),

and low-density lipoprotein-C (LDL-C), for all the P value < 0.05 as shown in table 2.

Three months following DAAs therapy, the main value of reduction in fasting plasma glucose in group A was 22.79 mg/dl with a maximum reduction of 50 mg/dl observed in most of our patients. The main reduction in HbA1c was 0.9% with a maximum reduction of 1.03 %. There were statistically significant difference as regard to Homeostatic model

assessment (HOMA) insulin resistance (HOMA-IR), alpha fetoprotein, and HCV-RNA by PCR between groups A, B, and C (P < 0.001). There were statistically significant reduction in plasma insulin level, fasting plasma glucose, and glycated hemoglobin in group A, B, but no statistically significant difference between these parameters in group C (P > 0.05) as shown in table 3.

Table 2: Baseline laboratory characteristics of our patients

Variable		Group A (Chronic hepatitis with AGC)	Group B (Liver cirrhosis Child A with AGC)	Group C (Liver cirrhosis Child B with NAGC)	Group D (Controls)	F	P
ALT (U/L)	Mean ± SD	45.6±11.1	40.9±8.9	47.03±10.7	34.8±3.9	12.872	0.001
AST (U/L)	Mean ± SD	48.5±8.5	4.4±7.6	56.3±2.6	31.1±4.3	71.377	0.001
Total bilirubin (mg/dL)	Mean ± SD	1.1±0.1	1.5±0.24	2.6±0.3	1.5±0.2	571.196	0.001
Albumin (gm/dL)	Mean ± SD	3.98±0.1	3.74±0.2	3.17±0.2	3.74±0.2	301.323	0.001
INR	Mean ± SD	1.2±0.1	1.4±0.2	1.9±0.2	1.37±0.1	380.280	0.001
CTP Score	Mean ± SD	1.0 ± 0.1	1.5±0.24	2.6±0.3	1.01±0.1	4.075	0.018
Total Cholesterol (mg/dL)	Mean ± SD	175.9±12.9	170.8±15.2	176.5±15.4	155.9±3.2	18.970	0.001
HDL-C (mg/dL)	Mean ± SD	57.9±4.6	57.5±5.5	58.6±5.2	60.7±5.8	2.906	0.036
LDL-C (mg/dL)	Mean ± SD	101.7±16.5	90.8±5.8	91.7±11.03	86.0±2.9	18.531	0.001
α fetoprotein (ng/mL)	Mean ± SD	5.7 ± 1.5	5.2 ± 1.5	5.3 ± 1.8	3.7 ± 0.5	12.661	0.001
Plasma insulin (mIU/mL)	Mean ± SD	14.1 ± 4.1	5.7 ± 1.1	9.8 ± 6.9	5.6 ± 1.4	59.015	0.001
Fasting blood sugar (mg/mL)	Mean ± SD	187.6±10.6	130.6 ± 12.8	147.2 ± 32.4	128.6 ± 16.7	133.757	0.001
HbA1c (%)	Mean ± SD	8.0 ± 0.6	7.5 ± 0.4	7.9 ± 0.8	7.2 ± 0.2	24.557	0.001
HOMA-IR	Mean ± SD	6.5 ± 1.9	1.8 ± 0.2	4.0 ± 3.6	1.7 ± 0.3	71.942	0.001
HCV-RNA by PCR (IU/mL)	Mean ± SD	537120.5 ± 347823.4	449338.7 ± 56951.1	782727.3 ± 292868.7	78666.7 ± 197000.04	33.594	0.001

Table 3: Changes in plasma insulin, fasting plasma glucose, HbA1c, and HOMA-IR before DAAs, and three months after therapy

Variable		Group A		Group B		Group C		F	P
		Before DAAs	After DAAs	Before DAAs	After DAAs	Before DAAs	After DAAs		
Plasma Insulin (mIU/mL)	Range	9 – 25	8.7-25	3-10	3-9	3-25	3-24	56.690	0.001
	Mean±SD	14.09±4.09	13.89±4.15	5.56±1.12	5.46±1.54	9.78±6.84	9.69±6.83		
	P < 0.001		P < 0.001		P = 0.335				
FPG (mg/dL)	Range	170-205	120-185	80-160	65-120	80-205	70-200	80.778	0.001
	Mean±SD	187.56±10.64	155.4±12.15	130.56±12.77	102.62±9.14	147.21±32.41	136.40±35.35		
	P < 0.001		P < 0.001		P = 0.525				
HbA1c (%)	Range	6.9-8.7	6.4-7.7	6.9-8.1	6.4-7.6	6.8-8.8	6.5-8.7	16.759	0.001
	Mean±SD	8.0±0.55	7.37±0.43	7.47±0.36	6.97±0.36	7.86±0.76	7.59±0.73		
	P < 0.001		P < 0.003		P = 0.093				
HOMA-IR	Range	4.2-12.1	2.8-11.9	1.1-2.2	1-2	1.1-12.7	1.0-12.3	50.260	0.001
	Mean±SD	6.53±1.96	5.52±2.03	1.78±0.23	1.45±0.23	4.01±3.63	3.77±3.58		
	P < 0.001		P < 0.001		P < 0.001				
AFP (ng/dL)	Range	3.2-8.0	2.3-7.9	3.0-8.0	2.2-7.5	3.0-9.5	2.2- 8.9	6.974	0.001
	Mean±SD	5.65±1.53	5.18±1.61	5.23±1.48	4.75±1.53	5.29±1.79	4.91±1.77		
	P < 0.001		P < 0.001		P < 0.001				
HCV-RNA by PCR (IU/mL)	Range	59000-1200000	0 -450000	59000-1200000	0 -0	200000-1200000	0 - 650000	9.787	0.001
	Mean±SD	537120.5±347823.5	9156.6±54776.8	449338.7±356951.1	0.0±0.0	782727.3±292868.7	53396.2±150664.5		
	P < 0.001		P < 0.001		P < 0.001				

There were statistically significant correlations between the sustained virologic response (SVR) with fasting plasma glucose, glycosylated hemoglobin, plasma

insulin, and Homeostatic model assessment-insulin resistance (HOMA-IR) in our patients before and after DAAs as shown in table 4.

Table 4: Correlation between FPG, Hb1c, plasma insulin and HOMA-IR before and after DAAs as regard to the sustained virologic response

Variable		Before DAAs	After DAAs	r	P value
FPG (mg/dL)	Mean ± SD	158.80 ± 31.81	133.65 ± 30.29	0.929	0.001
HbA1c (%)	Mean ± SD	7.80 ± 0.62	7.30 ± 0.56	0.886	0.001
Insulin (mIU/mL)	Mean ± SD	10.27 ± 5.75	10.13 ± 5.74	0.999	0.001
HOMA-IR	Mean ± SD	4.34 ± 3.04	3.77 ± 0.22	0.990	0.001

Multivariate logistic regression analysis was performed for adjustment of confounding factors, and the results showed that glycemic control was improved by the presence of the following factors: female

gender, Child-Pugh class A, negative family history of type 2 DM, and shorter duration of type 2 DM as shown in table 5.

Table 5: Multivariate logistic regression analysis for factors affecting glycemic control with DAAs

Parameter	B	P value	Odds ratio	95% CI
Gender (Male gender)	1.003	0.003	2.126	1.416 – 5.246
Child-Pugh score (Child A)	0.913	0.001	3.418	0.716 – 4.305
Family History of type 2 DM (Negative)	0.915	0.001	2.497	1.997- 4.255
Duration of type 2 DM (< 6years)	0.778	0.001	2.177	1.626 – 2.914

CI, confidence interval; DM, diabetes mellitus.

4. Discussion:

The association between HCV infection and T2DM remains controversial but has been widely postulated. The prevalence of diabetes mellitus did not differ in patients with and without HCV infection in the United States population in one study (23). On the other hand, many studies aid the association between HCV infection and type 2 diabetes mellitus (T2DM). Patients with chronic HCV infection are more vulnerable to develop T2DM when compared to both healthy controls and patients with other chronic liver diseases (24). The etiology of T2DM in HCV infected individuals has been suggested to develop from either hepatogenous T2DM resulting from progression of liver disease or “classical” T2DM due to insulin resistance mediated by chronic HCV infection (1). The distinction between hepatogenous T2DM and “classical” T2DM is not trivial; in fact, according to some studies (25-27), hepatogenous T2DM is considered clinically different from the “classical” T2DM, because it is less frequently associated with microangiopathy.

In this study, 190 (95 %) patients achieved sustained virologic response (SVR), from whom 145 (76.3%) had an improvement in glycemic control after 3 months of treatment. In the achieved glycemic control groups (group A, and B), 30 patients (36.1%), and 20 patients (32.3%) needed to decrease their dose of antidiabetic treatment respectively. Our patients with normal or near normal baseline fasting plasma glucose and/or HbA1c did not develop hypoglycemia, thus we excluding the hypoglycemic effect of DAAs.

The impact of antiviral therapy on type 2 diabetes mellitus is inconsistent. One study found that HCV suppression with interferon- α or interferon- α plus ribavirin treatment produced a profound improvement in blood sugar control regardless of genotype (28). Other study suggested that danoprevir treatment for HCV infection may decrease insulin resistance in patients with genotype 1 (29). In contrast to the previous studies, a third study found that direct acting antiviral therapy with sofosbuvir and ledipasvir led to the development of new-onset T2DM (30).

Insulin resistance is presumed to underlie “classical” HCV-mediated T2DM, but the exact mechanism remains unknown. Studies show that HCV

impedes glucose metabolism directly via viral proteins and indirectly by modulating proinflammatory cytokine levels (31). The HCV core protein inhibits the insulin receptor substrate-1 (IRS-1) association with its insulin receptor by increasing IRS-1 breakdown through upregulation of serine/threonine phosphorylation or increased activity of suppressor of cytokine.

Signaling 3 (SOCS3) (1, 32, 33). These direct effects on the insulin signaling pathway impair downstream signaling and proper regulation of glucose and its metabolism. Indirectly, HCV-enhanced production of the proinflammatory cytokines IL-6 and TNF- α from sinusoidal liver cells impedes the insulin signaling pathways, enhancing gluconeogenesis (34).

In this study, there were statistically significant higher levels of plasma fasting glucose, HbA1c and HOMA-IR levels before DAAs therapy in our patients when compared with controls. After sustained virologic response (SVR) with DAAs, the fasting plasma glucose and HbA1c levels were significantly lower in patients who achieved glycemic control (group A, and B), but not in group C (NAGC group). On the other hand HOMA-IR were significantly improved 3 months after successful treatment with DAAs in all groups of our patients but BMI was not an important factor in improving glycemic control with use of DAAs therapy. Our results are in agreement with Kawaguchi et al who concluded that clearance of HCV improves both insulin resistance and beta-cell function (28). Other fail to establish this hypothesis (35). In this study, HOMA-IR was improved and significantly correlated with serum HCV RNA levels 3 months after eradication of HCV (SVR). In fact, non-significant changes in BMI before and after DAAs, HOMA-IR correlated significantly with serum HCV RNA levels, suggesting a direct role of viral replication on the development of IR. A recent study documents this hypothesis, showing an advancement of IR in patients who developed sustained virologic response after antiviral treatment. In addition, IR was more frequent and IR parameters higher ($P < 0.001$) in chronic HCV patients than in chronic HBV patients selected as a control group in this study and very well corresponded with chronic

HCV patients for clinical, biologic, and also histologic features (28).

Successful eradication of HCV infection can improve glucose metabolism and reduce insulin requirements. In the current study, 30 patients (36.1%) of group A needed to decrease the dose of antidiabetic treatment; 6 out of 14 patients needed to decrease the insulin dose and 24 of 69 patients needed to decrease the gliclazide dose, 20 patients (32.3%) of group B needed to decrease the dose of antidiabetic treatment; 5 out of 16 patients needed to decrease the insulin dose and 15 of 46 patients needed to decrease the gliclazide dose. A prior study demonstrated an improvement in noninsulin dependent T2DM when genotype 1 HCV patients were successfully treated with pegylated-interferon alpha and ribavirin (36). Another case report established an achieved glycemic control restricted to the treatment phase in an insulin dependent T2DM patient with HCV who did not improve to therapy with interferon and ribavirin (37). Another study reported an amelioration of hyperglycemia in type 2 diabetic patient treated with IFN- α and ribavirin for hepatitis C (28).

In our study, the percentage of patients with positive family history of T2DM was significantly lower in the AGC groups (group A, and B) compared with the NAGC control group (group C). In patients with negative family history of T2DM, the likelihood of insulin resistance is probable due to chronic hepatitis C viral infection only, so treatment of HCV infection aids in the improvement of insulin resistance and hyperglycemia, if compared to those with inherited insulin resistance. It might be useful to classify patients to familial IR or HCV-induced IR to know the effect of HCV eradication on type 2 diabetic patients with HCV infection. Thus absence of family history of T2DM may help in this differentiation. In our study, the duration of type 2 DM ranged from 1-3 years in group A (chronic HCV with achieved glycemic control), 1-6 years in group B (post-HCV liver cirrhosis Child-Pugh score A), and from 7-17 years in group C (post-HCV liver cirrhosis Child-Pugh score B), thus the longer the duration of type 2 DM, the more β -cell exhaustion and the less improvement in glycemic control.

In our study, significant improvement in diabetic control in the form of controlled FPG and HbA1c was observed after successful HCV treatment with DAA therapy. This improvement in glycemic control persisted following viral clearance during the study period despite an increase in the patient's BMI. Thus Controlling T2DM should be advised before starting HCV therapy to increase the response rates (38). However, with the future advances in DAA therapies, viral clearance not only possible despite poor glycemic

control but also may be an effective means of improving diabetic control.

In this study, 28.9% of diabetic patients with sustained virologic response (group C) did not reach glycemic control during the study period. This can be justified by the following reasons. First, patients with Child-Pugh class B were significantly higher in the NAGC group, thus the severity of liver disease may play an important role in the modulation of glycemic control state. Second, HCV infection may affect glucose level by an immune-mediated destruction of β -cells and is not related to IR. Thus, Thuluvath and John (39) provide fuel for thought as their study suggests that HCV infection is more likely to mediate diabetes in genetically susceptible individuals. However, further genetic and mechanistic studies are required to illuminate the role of HCV in disturbing glucose metabolism. Third, all patients with Child-Pugh class B with NAGC group already had normal FPG and HbA1c. Our findings were compatible with the results of Dawood et al (40) as regard to uncontrolled glycemic control in Child Pugh Class B patients (group C). The relationship between liver fibrosis and IR is difficult to assess. Because of the importance of the liver in the metabolism of carbohydrate and insulin breakdown, advanced liver fibrosis may impede insulin clearance, resulting in increased plasma insulin levels in spite of the insulin secretion status. These findings suggest that the actual link between IR and HCV infection is originated at early stages of liver disease. The principal mechanism of the advancement of fibrosis in relation to IR could be a direct stimulation of liver stellate cells by hyperinsulinism/hyperglycemia, leading to increased production of the connective tissue growth factor and ensuing cumulation of extracellular matrix (41).

In the current study, the plasma insulin level, total cholesterol, HDL-C, and LDL-C were significantly higher in our patients than controls with a significant reduction in plasma insulin levels following DAAs therapy especially in patients with achieved glycemic control (group A, and B). These suggested that hyperlipidemia and hyperinsulinemia were contributing factors for appearance of insulin resistance in type 2 diabetes mellitus accompanying chronic HCV infection. The mechanisms by which T2DM may trigger chronic HCV infection are multifactorial. First, T2DM is a common endocrine disorder including multi-pathogenetic mechanisms including IR, aggravated hepatic glucose production, and a defect in insulin secretion, all of which contribute to the development of hyperglycemia (42, 43). It has also been suggested, based on a few in vitro studies, that HCV replication may be favored by hyperinsulinism and/or the increased plasma levels of free fatty acids observed in patients with IR and

T2DM (44,45). Additionally, T2DM is, to some extent, associated with a reduced immune state, which leads to unbalanced immune function (46). Both IR and T2DM may play a role in the modulation of the natural course of HCV infection, thus leading to augmented steatosis, steatohepatitis, and liver fibrosis (46, 47). Moreover, most patients with diabetes mellitus often extract blood and perform glycemic controls at home with the help of family members. It would be informative for diabetic patients to perform a medical record based on the eventual risk factors associated with viral hepatitis (e.g., transfusion, hospitalization, and eventual surgical operations) and other factors that may influence an eventual alteration of hepatic function (e.g., alcohol abuse and hemochromatosis).

In this study, we have observed that baseline serum alpha-fetoprotein level was significantly elevated in our patients with or without achieved glycemic control (group A, B, and C) if compared to controls. Three months after DAA therapy, the mean level of serum α -fetoprotein was significantly lower in all groups of our patients. Based on this, we put forth the notion that AFP may be used as a surrogate biomarker for likelihood of SVR. Obtaining AFP early during therapy (e.g. week 4) rather than a viral load may be useful as a biomarker to predict response to HCV therapy and should be validated with future studies. Our results as regard to alpha-feto protein were in agreement with the findings observed by Stine et al (48).

In conclusion, we demonstrated that in Egyptian type 2 diabetes mellitus patients with uncontrolled hyperglycemia, the administration of direct acting antiviral agents led to a dramatic improvement in glycemic control and those patients should be closely monitored for antidiabetic drug reduction to prevent hypoglycemic events and also to adjust the dose of these medications either insulin or insulin secretagogues before starting DAAs therapy to increase the response rates. Clearance of HCV improves.

FPG, plasma insulin level, HbA1c and HOMA-IR. These findings indicate that HCV itself is involved in the development of insulin resistance in patients with HCV infection and curing HCV results in a reduced incidence of T2DM, and an improvement of T2DM-related clinical outcomes in type 2 diabetic CHC patients who obtain SVR. However, HCV therapy appeared to improve IR. Achievement of glycemic control in Egyptian HCV patients treated with direct acting antiviral agents is appreciated in patients with mild liver disease (Child-Pugh class A), with short duration of diabetes, and without family history of T2DM, but is not related to body mass index, age, and sex. Large scale prospective studies

should be conducted to evaluate the long-term effects of direct acting antiviral agents on diabetes control, to study glycemic control and its correlation to SVR with the future advent in DAAs. In addition, studies are required to discover the effect of amelioration in liver function after DAA therapy on the long term events of T2DM, especially diabetic microangiopathic complications.

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