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Clinical Impact of Direct-Acting Antivirals on Glucose Metabolism in Chronic HCV Patients

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Abstract

Background:

Chronic HCV infection affects host glucose metabolism. The virus induces insulin resistance (IR), diabetes, atherosclerosis, and steatosis.

Aim:

To determine the effect of treatment with DAAs on the glycemic profile in chronic HCV patients.

Methods:

The enrolled 423 patients were 347 naïve and 76 experienced patients. All patients received a single oral dose of Sofosbuvir (400 mg) and daclatasvir (150 mg) for 12 weeks ineligible for DAAs treatment. For all the included patients, History and clinical examination were done at baseline. Routine investigations were done at weeks 4, 8, 12, and 12 weeks after treatment (SVR12). Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin level, Homeostatic Model Assessment of Insulin Resistance HOMA–IR was assessed for all the included patients at baseline and after the end of DDAs therapy.

Results:

The overall percentage of SVR was 98.8% (418/423 patients). In the experienced patients, the SVR was 98.7% (75/76), while 98.8 % (343/347) in naïve patients with no statistical difference. There were statistically significant improvement in FBG (135+23 vs. 103+ 6 mg/dl, p<0.001), HB A1C (7.6 + 0.6 vs. 5.4 + 0.5 p<0.001), and HOMA-IR (5.3 ± 1.06 vs. 3.1 ± 0.45 p<0.001) after DAAs treatment, with no statistically significant change regarding fasting insulin level.

Conclusion:

DAAs treatment for chronic HCV has a possible role in decreasing insulin resistance and improving the glycemic profile.

Keywords: HCV; Hepatitis C virus; Lipid metabolism; Glucose metabolism.

1. Introduction

Hepatitis C virus (HCV) is a major public health problem and is considered a major leading cause of chronic liver disease, including cirrhosis and liver cancer. According to the World Health Organization, about 170 million people are chronically infected with HCV worldwide [1]. Egypt carries the highest prevalence of HCV (15%) where 90% of HCV infection is genotype 4 [2]. Chronic HCV patients have a significant increase in type 2 diabetes mellitus (T2DM) prevalence, regardless of underlying liver disease. When compared to healthy controls or hepatitis B virus (HBV)-infected patients. T2DM is common comorbidity present in approximately one-third of chronic HCV patients [3]. The exact mechanism of such relation between chronic HCV and DM is not clear, however, it may be explained by the capability of HCV to trigger autoimmune reactions against pancreatic β-cells in genetically susceptible subjects leading to direct destruction of β-cells; thereby, by causing type 1 diabetes [4]; or the mechanism may be related to increased insulin resistance (IR) [5]. An estimated 47 million patients have type 2 diabetes mellitus (T2DM) secondary to chronic HCV infection worldwide [6].

The most accepted theory in such patients is the presence of Insulin resistance (IR) which is a pathophysiological state that is commonly associated with chronic HCV infection and moreover, associated with increased disease severity, extrahepatic manifestations, and decreased response to antiviral therapy. Insulin resistance (IR) is observed in approximately 30% :70% of chronic HCV patients as compared to only 10% :25% of general population [6]. This association has been studied in both cirrhotic and non-cirrhotic patients secondary to chronic HCV infection [7]. The clinical impact of successful eradication of HCV infection using direct-acting antiviral agents (DAAs) on the long-term outcome of T2DM in diabetic patients remains an issue of controversy. This is mostly due to the inadequate prospective studies that sufficiently describe this important issue [8]. The aim of this study was to predict the effect of HCV eradication using DDAs on glycemic control and IR in T2DM.

2. Patients and Methods

2.1. Study Design

This prospective cohort study was performed in accordance with the Helsinki Declaration and approval of the local ethical committee was

taken. Written informed consent was obtained from all patients before the beginning of the treatment. A total of 488 Type2 diabetes mellitus. Chronic HCV patients were recruited from the Virology clinic of Tropical Medicine Department- Minia University Hospitals. We excluded 65 patients from the study)

1. Child C liver cirrhosis (N=16).
2. Inadequately controlled DM (HbA1c > 9) (N=16).
3. Patients coinfected with hepatitis B virus (N=6).
4. HCC (N=4) or Extra-hepatic malignancy (N=1).
5. Patients with chronic renal impairment (creatinine > 1.5mg/dl) (N=5).
6. BMI > 25(N=8).
7. Patients who refused to be included in the study (N=9).

The enrolled 423 patients were 347 naïve and 76 experienced patients. All patients received a single oral dose of Sofosbuvir (400 mg) and daclatasvir (150 mg) for 12 weeks ineligible for DAAs treatment according to (National committee for control of viral Hepatitis (NCCVH) treatment protocol 2015).

2.2. Baseline Assessment

For all the included patients, History and clinical examination were done at baseline. Routine investigations were done at weeks 4, 8, 12, and 12 weeks after treatment (SVR12) including complete blood picture (hemoglobin, total leucocytic count, and platelet count), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, international normalization ratio (INR) and body mass index (BMI) according to the equation (weight /height^2).

2.3. Virological Monitoring

Quantitative HCV RNA PCR test using the COBAS Ampli Prep/COBAS TaqMan HCV Quantitative Test (version 2.0, Roche, Pleasanton, California, USA, with a lower limit of quantification of 20IU/ml) were also done at weeks 4, 8, 12 (EOT) and 12 (SVR12) weeks after treatment.

2.4. Glycemic Profile Assessment

Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin level, Homeostatic Model Assessment of Insulin Resistance HOMA–IR (glucose in mmol/L x insulin in mIU/mL/22.5) were assessed for all the included patients at baseline and after the end of DDAs therapy.

2.5. Treatment Follow-up

Treatment monitoring was undertaken by clinical evaluation including extreme and basic adverse effects, drug compliance, and hematological and biochemical review at weeks 4, 8, 12, and 12 weeks after diagnosis.

2.6. Statistical Analysis

Data were analyzed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented in mean± standard deviation. Qualitative data were presented in frequency and percentage. To compare between groups, we used the student *t*-test and the chi-square test. The significance level for $P \leq 0.05$.

3. Results

3.1. Characteristics of Study Population

This prospective cohort study included 423 Type 2 diabetes mellitus chronic HCV patients (mean age 58±5, 59% males, and BMI 21±4). All patients received SOF / DAC combination treatment for 12 weeks. As to the root of transmission of the HCV infection; 137 (32.4%) patients had a history of household contact; 33(7.8%) patients had a history of dental procedure; 18 (4.3%) patients had a history of operations with or without blood transfusion and and the rest of patients had no unknown source of infection. There were 76 (18%) patients who were treatment-experienced, this was due to relapse and breakthrough in 48(63%) patients and discontinuation of treatment due to non-compliance and serious adverse effects in 28 (37%) **(Table: 1).**

Demographic Characteristics	Patient Data
Age (years); Mean ± SD	58+5
Sex	
Male	59%
Female	41%
BMI; Mean ± SD	21 + 4
Route of transmission	137(32.4%) household contact
	33(7.8%) dental procedures
	18(4.3%) operations with or without blood transfusion
	235(55.5%) unknown

#BMI: body mass index, #SD: standard deviations

Table 1: Demographics of the study patients.

Data	Before Treatment	After Treatment	P-Value
Hemoglobin (g/dl)	13.7 ± 0.4	13.5 ± 0.5	0.06
Total Leukocytic Count /mm3)	8.3×103± 1.2×103	8.5 ×103 ± 1.3 ×103	0. 7
Platelets Count (/mm3)	245×103 ± 3×103	242×103 ± 4×103	0.66
AST (mg/dl)	65 ± 9	31 ± 12	<0.001*
ALT (mg/dl)	74+12	28+8	<0.001*
Creatinine (mg/dl)	0.96 ± 0.15	0.92 ± 0.15	0.7
Albumin	3.9 ± 0.29	4.1 ± 0.35	0.65
INR	0.9 ± 0.07	1 ± 0.08	0.6
Total Bilirubin	0.9 ±0.11	0.98 ± 0.12	0.07

#INR, international normalization ratio; AST, #Aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2: Basic laboratory data of study groups.

3.2. Hematological Marker, Liver function, and Renal function Changes

Apart from the decrease of both ALT and AST after the end of treatment (74±12 vs. 28±8 and 65±9 vs. 31±12 respectively p≤o. ooo1), there were no significant changes in all parameters before and after treatment

3.3. Response to DAAs Treatment

The overall percentage of SVR was 98.8% (418/423 patients). In the experienced patients, the SVR was 98.7% (75/76), while 98.8 % (343/347) in naïve patients with no statistical difference. Three patients out of the 5 patients who failed to achieve the SVR lost follow-up after week 12 and non-compliance to treatment was observed in the other 2 patients **(Figure:1).**

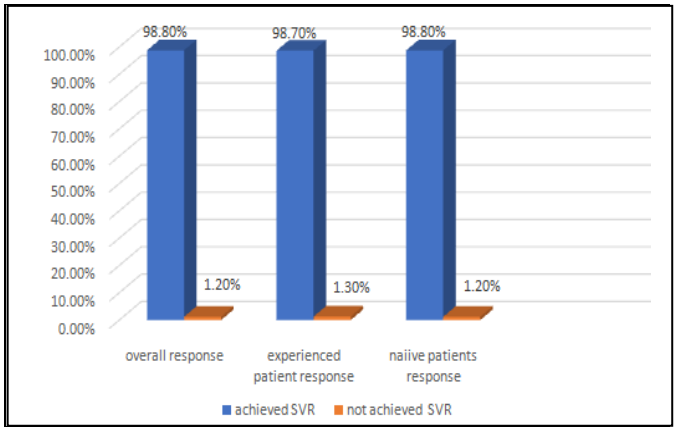

Figure 1: Treatment response in studied patients.

3.4. Glycemic Profile Changes

There was statistically significant improvement in FBG (135±23 vs. 103±6 mg/dl, p<0.001), HB A1C (7.6 ± 0.6 vs. 5.4 ± 0.5 p<0.001), and HOMA-IR (5.3 ± 1.06 vs. 3.1 ± 0.45 p<0.001) after DAAs treatment, with no statistically significant change regarding fasting insulin level **(Table: 3).**

3.5. Treatment Safety

No serious adverse effects were observed in all patients which led to discontinuation of treatment, death, or hepatic decompensation. Patients only reported unspecific adverse effects; fatigue (10/423, 2.4%), headache (7/423, 1.7%), epigastric tenderness (5/423, 1.2%) and nausea (3/423, 0.7%).

4. Discussion

In the current study, we evaluated the effect of HCV eradication using DDAs on glycemic control and IR in T2DM. In all patients, adherence to treatment was closely monitored.SVR was 98.8% (98.7% experienced patients vs.98.8 % naïve patients.

Which wherein comparison with the previous studies done to evaluate the efficacy of Sof/Dacla combination for 12 w in adults,
SVR 12 was 97% [9-10].

Laboratory data	Before	After	P value
FBS (mg/dl) Mean ± SD	135+23	103+6	<0.001*
Fasting insulin level (u U/L)/ml) Mean ± SD	20.11+5	20 ± 0.13	0.78
HB A1C	7.6 + 0.6	5.4 + 0.5	<0.001*
HOMA-IR Mean ± SD	5.3 ± 1.06	3.1 ± 0.85	<0.001*

#FBS: Fasting blood sugar, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

#HBA1C, glycated hemoglobin

#HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 3: Glycemic profile of patients before and after treatment.

We observed a statistically significant decrease of serum levels of both ALT and AST which was in line with the results of a study done to evaluate the changes in liver function parameters in chronic HCV patients who received Sof/Dacla with ribavirin who found that with HCV clearance, liver function parameters, serum albumin, bilirubin, platelet count, and international normalized ratio improved significantly in the majority of patients [11].

Significant decrease in FBS FBG (135±23 vs. 103± 6 mg/dl, p<0.001), HB A1C (7.6 ± 0.6 vs. 5.4 ± 0.5 p<0.001) were observed before and after DAAS treatment in the current study, these results agree with what stated by other studies which recorded improvement of FBS and insulin resistance after DAAs treatment in both diabetic and non-diabetic patients [12-13]. Also, A significant reduction of mean FG (134.3 ± 41.32 mg/Dl vs 152.4 ± 56.40 mg/dL, P = 0.002) and HbA1c values (46.51 ± 16.15 mmoL/moL vs 52.15 ± 15.43 mmoL/moL, p <0.001) was found in patients who achieved SVR [14].

A significant reduction of mean FG (134.3 ± 41.32 mg/dLvs 152.4 ± 56.40 mg/dL, P = 0.002) and HbA1c values (46.51 ± 16.15 mmoL/moLvs 52.15 ± 15.43 mmoL/moL, P <0.001) was found. A significant reduction of mean FG (134.3 ± 41.32 mg/dLvs 152.4 ± 56.40 mg/dL, P = 0.002) and HbA1c values (46.51 ± 16.15 mmoL/moLvs 52.15 ± 15.43 mmoL/moL, P <0.001) was found.

On the other hand, in other studies, they found among the subjects who achieved SVR, the change in HbA1c was not significantly different from zero, with a mean change of −0.022 ± 0.53% (*P* = .52). When the change in HbA1c was calculated using a mean of all post-SVR values, the results were similar (−0.019 ± 0.49%, *P* = .54) [15-16].

We also recorded a statistically significant reduction of HOMA-IR (5.3 ± 1.06 vs. 3.1 ± 0.45 p<0.001) after DAAS treatment with no statistically significant change regarding fasting insulin level, which in the line with a study which found at the end of treatment, all patients cleared HCV RNA, regardless of liver fibrosis and body mass index, and a reduction in HOMA-IR at 2.42 ± 1.85 was showed (*P* < 0.001) [17].

Our study had some limitations, as relatively small sample size and selection of certain populations excluding Child C cirrhosis, the limitation of DAAs regimen including only SOF/DAC; so, our results should be confirmed by larger studies.

5. Conclusion

In conclusion, DAAs treatment for chronic HCV have a possible role in decreasing insulin resistance and improving the glycemic profile.

6. Conflicts of Interest

No conflict of interest was disclosed by any of the authors. No funding was obtained in the development and writing of this article.

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