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# Assessment of Hepatitis C management on glycemic control among Type 2 Diabetes Mellitus patients

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**Abstract**

**Background:** HCV and DM are chronic diseases of high global prevalence. Many studies proved the association between Hepatitis C and DM in the last three decades and this consists of an interrelated association; moreover, HCV infection triggers Diabetes Mellitus, most probably type 2.

**Objective:** To assess the possibility of the improvement of T2DM in patients with HCV when applying the new DAA HCV treatment in Egypt.

**Patients and Methods:** The current study is a prospective cohort hospital-based study that aims to describe the association between T2DM on one hand and chronic HCV on the other hand after successful management of HCV through the DAAs according to the protocol of the Ministry of Health. SVR was defined as undetectable HCV RNA levels at 12 weeks after the end of treatment (EOT). Fasting plasma glucose (FPG) levels between 100–125 mg/dL were defined as prediabetes and FPG ≥ 126 mg/dL was defined as diabetes. We have found positive correlation between management of HCV using DAAs in general and improvement of HbA1c and FPG. Moreover, we reported stronger correlation between achieving SVR and the HbA1c level and FPG.

**Results:** After 12 weeks of follow-up, 82% of the patients maintained negative SVR, hemoglobin reduction was -0.6±0.4 %, 3 months after HCV treatment with a P value <0.001*. FPG reduction was -24.6±25.4 after 3 months of treatment with a P value of <0.001*. HbA1c reduction in patients with SVR was -0.8±0.2 % with a P value of <0.001*. No significant change in treatment choice was found during the period of study.

**Conclusion:** Successful HCV eradication will result in a statistically significant reduction in fasting plasma glucose and HbA1c in patients with type 2 diabetes which is an indirect indicator of improvement of insulin sensitivity in patients with type 2 DM.

Diabetes Mellitus, HCV, HbA1C, FPG, glycemic control, HCV eradication, Egyptian patients, DAA, SVR

## 1. Introduction

Hepatitis C virus infection is characterized by an inflammation in the hepatocytes caused by hepatitis C virus transmitted to the host mainly by blood borne infection which would yield to either acute or chronic hepatitis. The severity of HCV infection ranges from a mild disease for few weeks to a debilitating fatal disease. Acute infection can be in the form of subclinical, mild or may present as symptoms like jaundice, dark yellow discoloration of the urine, anorexia, nausea, fatigue, and abdominal discomfort. Most of the patients who get infected will develop chronic infection ***(WHO, 2021).***

Nearly 58 million persons worldwide are infected with HCV and 1.5 million persons get infected each year. In 2019, approximately 290 000 patients died from Hepatitis C-related liver disease, although the new antiviral treatment cures 95% of HCV patients ***(WHO, 2021).***

In Egypt, liver disease is one of the leading causes of death. In 2015, Egypt had one of the highest prevalence of HCV infection in the world (7%), which represented 7.6% of its all-cause mortality and approximately 90% of HCV infection is genotype 4 ***(Hassanin et al., 2021).***

Chronic HCV infection is considered as a systemic disease that affects most of the body systems. More than 75% of HCV patients present with extra-hepatic

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affection, which can manifest before the diagnosis of chronic HCV infection. Diabetes mellitus type 2 (T2DM) is one of the extrahepatic manifestations of chronic HCV infection ***(Ambachew et al., 2019).***

The main objective of chronic HCV infection management is to achieve sustained viral response (SVR), characterized by the complete eradication of hepatitis C virus from patient's body ***(Asselah et al., 2018).***

It is hypothesized that the hepatocytes infected by HCV secrete chemical mediators, which result in increased insulin resistance at extrahepatic sites. On the other hand, Insulin resistance increases the risk of progression to hepatocellular carcinoma and cardiovascular events in the HCV patients ***(Fabiani et al., 2018).***

DAAs is considered a significant recent breakthrough in the management of chronic HCV infection. The use of a combination of at least two of DAAs, especially NS5A inhibitor, NS5B inhibitor, or NS3/4a protease inhibitor, results in a high response rate. Currently, DAAs are considered the standard of care of HCV management in all the recent guidelines. DAAs are tolerable, effective and achieve a SVR in 90–98% of cases ***(Asselah et al., 2018).***

More than 20% of the chronic HCV patients could have T2DM. most of the studies performed in the past used interferon as a main treatment of chronic hepatitis C infection and pointed out that a significant decrease in the fasting glucose and glycated hemoglobin (HbA1c) levels when the HCV patients achieved SVR. Meanwhile, this improvement in T2D was not observed in the patients who had a relapse from HCV. A better compensation of diabetes mellitus in patients with HCV infection who are treated with DAA is assumed, hence reducing antidiabetic therapy in a certain part of patients is possible ***(Gilad et al., 2019).***

The present study was designed to evaluate the possible effect of the new DAAs drugs, used for treatment of HCV, on insulin resistance and glycemic control at the end of treatment and 3 months after end of treatment of HCV infection in patients with T2DM in Egypt.

## Experimental: Study design

### Study design

The current study is a prospective cohort hospital-based study that aims to describe the association between T2DM on one hand and chronic HCV on the other hand after successful management of HCV through the DAAs according to the protocol of the Ministry of Health.

### Sample size

The study was conducted on 50 patients with T2DM and chronic HCV infection who were recruited from the outpatient clinics of the Health care facilities in El-Demerdash hospital and the National Research Center, depending on ***(Hashim et al., 2017)*** who found that the Mean±SD of HbA1c before and after HCV treatment were 7.11±0.88 and 6.77±0.98 respectively. And assuming the correlation between before and after levels was 0.500, power= 0.96 and α=0.05, and by using G*Power 3.1.9.4 release ***(Faul et al., 2009)*** the minimal sample size for a single group cohort study to detect a significant statistical change in HbA1c was found to be 49. We recruited 50 cases for possible attrition.

### Study duration

From September 2019 to December 2020, during which the full study population was collected.

### Study population

All HCV infected patients with liver fibrosis eligible for DAA treatments and diagnosed as diabetics were enrolled in this study after being checked in the outpatient clinic according to the below inclusion and exclusion criteria:

**Inclusion criteria:** Both gender. Age: more than 18 years old (T2DM). All subjects should exert moderate strenuous work (increases strenuous work, improvse DM and aggravates hepatitis).

**Exclusion criteria:** Co-infection with hepatitis B virus or human immunodeficiency virus (HIV). History of alcohol intake. History of previous DAA intake. Patients who are not candidates for HCV treatment according to the guidelines of national committee for control of viral hepatitis established by the Egyptian Ministry Of Health and Population and were patients with:

- Child C cirrhosis (score ≥9).
- Platelets count less than 50 000/mm.
- Had hepatocellular carcinoma, except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (computed tomography or MRI).
- Extra hepatic malignancy except after 2 years of disease-free interval, except in case of lymphomas and chronic lymphocytic leukemia.
- Pregnancy or inability to use effective contraception.
- Inadequately controlled diabetic mellitus (HBA1c>9).

**Methods**

Selected subjects should pass through the following investigations before and after the study: A structured self-administrated questionnaire was constructed to collect data about personal history which includes name, age, sex, residence and education, and present history which includes onset, course and duration of HCV and Diabetes. Clinical assessment: The studied participants were subjected to thorough clinical examination. Laboratory investigations:

- Liver function tests and renal function tests.
- Complete blood count.
- Serum fasting blood glucose.
- HbAlc: HbA1c levels of all patients were measured within 3 hours of sample collection Patients were divided into three groups according to the level of HbA1c with cut-off 6.5% as a diagnostic criteria of diabetes mellitus according to ***ADA Diagnosis and Classification of Diabetes Mellitus (2021).***
- Hepatitis C virus RNA levels were evaluated by real-time polymerase chain reaction (PCR) assay.

**Data analysis**

Data are expressed as mean ± standard deviation. Significant differences between pre-treatment and post-treatment were evaluated by paired t-test for quantitative values and Chi-square test to identify significant differences in the prevalence.

**Ethical consideration**

The study was carried out in accordance with the Declaration of Helsinki. Written consent was obtained from all participants. The protocol was approved by the ethical committee of Ain Shams University and the National Research Center.

**Results and Discussion**

T2D is one of the main reported extrahepatic manifestations of chronic HCV. There has been reported a possible correlation between T2D and HCV because of the interrelated pathologies between HCV and insulin resistance ***(Safi et al., 2015). Allison et al. (1994)*** hypothesized the possible correlation between both diseases by being the first who reported an increased risk of T2D in chronic HCV patients.

In Egypt, the burden of HCV disease is more than 14% of the total Egyptian citizens. Moreover, the HCV incidence rate exceeds 3 per 1000 every year. Many studies reported that there is a predominance of HCV infection as a main cause of liver cirrhosis, end-stage liver disease, HCC, and liver-related mortality in Egypt. Whilst the inclusion of DAAs in the Egyptian HCV management guidelines and official campaigns yielded to a notable decrease in HCV disease prevalence in Egypt ***(Badry et al., 2020).***

A plenty of studies pointed out that the estimated prevalence of T2D among HCV patients exceeds 30% and many studies reported a lot of pathways that resulted in the high prevalence of T2D in chronic HCV patients. These mechanisms include pro-inflammatory cytokines, chemokines, direct HCV effects, insulin resistance, and other immune-mediated mechanisms ***(Thrift et al., 2017).***

An increase in T2DM before the advancement of liver cirrhosis was reported by ***Ndako et al. (2020)***. Previous studies reported that higher fibrotic stages in liver histology, family history of T2D and impaired FPG were strongly correlated to the development of T2D in HCV patients and this was noticed after excluding HCV patients with previous history of interferon therapy.

In the last few years, the emergence of DAAs is considered a breakthrough that dramatically changed the management of HCV and yielded to a hypothesized cure for HCV infected patients. The high efficacy, the wide genotypes coverage and low probability of development of viral resistance paved the way to an interferon-free regimens era. Additionally, this class can be taken once daily and is expected to result in the HCV global eradication ***(Omran et al., 2018).***

Recently, body of research confirmed the possible correlation between achieving SVR and the glycemic control in HCV patients treated with DAAs ***(Yuan et al., 2020).***

In our study, selected subjects should pass through the following: liver function tests, CBC, FPG, HbA1c, HCV-RNA with PMS of SVR group and non-SVR group.

In this study, 82% of the patients who received DAAs achieved a negative PCR at end of treatment and 78% achieved SVR after 3 months period with no significant differences in SVR and non-SVR group regarding age, sex, laboratory findings and this is comparable to what was reported by *Kamp et al. (2019)* who found out that 67.4% of the HCV patients achieved a SVR after receiving DAAs and to what was reported by *Yuan et al. (2020)* who found out that among 1090 patients, 990 had an SVR, and the

remaining 100 had a non-SVR. The ALB, Hb and WBCs levels in the SVR group were significantly higher than those in the non-SVR group. There were no significant differences in the distribution of sex, age, genotype, HCV RNA, FPG, diabetes status, ALT, AST, ALP, GGT, Platelets between the SVR and non-SVR groups in this study.

Table (1): Baseline characteristics among the studied cases

| Demographic characteristics | | Mean±SD | Range |
|---|---|---|---|
| Age (years) | | 50.3±6.1 | 41.0–65.0 |
| BMI (kg/m$^2$) | | 28.6±3.7 | 21.0–36.0 |
| | | N | % |
| Sex | Male | 36 | 72.0 |
| | Female | 14 | 28.0 |
| Laboratory findings | | Mean±SD | Range |
| HCV RNA (x10$^3$/mL) | | 886.3±529.0 | 209.9–3100.1 |
| Platelets (x10$^3$/mL) | | 234.8±83.1 | 90.0–351.0 |
| AST (IU/L) | | 32.9±23.3 | 11.0–130.0 |
| ALT (IU/L) | | 36.6±27.7 | 11.0–153.0 |
| Total bilirubin (mg/dL) | | 1.2±0.8 | 0.1–3.0 |
| Albumin (gm/dL) | | 4.0±0.5 | 2.9–4.8 |
| INR | | 1.1±0.2 | 0.9–2.5 |
| Creatinine (mg/dL) | | 0.9±0.3 | 0.2–2.0 |
| Liver condition | | Mean±SD | Range |
| Liver size (mm) | | 10.5±1.7 | 7.9–15.3 |
| Spleen size (mm) | | 12.4±3.2 | 7.9–20.7 |
| | | N | % |
| Ascites | | 5 | 10.0 |
| Child Pough grade | A | 40 | 80.0 |
| | B | 10 | 20.0 |
| DM and HCV treatments | | N | % |
| DM | Oral | 29 | 58.0 |
| | Insulin | 14 | 28.0 |
| | Mixed | 7 | 14.0 |
| HCV | Sofosbuvir | 30 | 60.0 |
| | Ledipasavir | 20 | 40.0 |

Total=50. BMI: Body mass index.

Table (2): Follow-up HCV PCR among the studied cases

| Variables | | N | % |
|---|---|---|---|
| End of treatment | Negative | 41 | 82.0 |
| | Positive | 9 | 18.0 |
| Month-3 after treatment end | Negative | 39 | 78.0 |
| | Positive | 11 | 22.0 |
| Relapse (total=41) | Negative | 39 | 95.1 |
| | Positive | 2 | 4.9 |

Total=50.

Table (2) shows that: More than three quarters of cases had negative HCV PCR at the end of treatment. Relapse occurred in less than 5.0% of end of treatment responders.

*Ciancio et al. (2018)* studied the effect of achieving SVR on T2D in HCV patients through a prospective case-control study of 122 patients and reported that achieving SVR by using DAAs Improved FPG and HbA1c and this was not achieved in untreated patients, additionally more than 20% of the study patients could decrease or stop their oral antidiabetic treatment. However, many of the forementioned studies were characterized by their limitations in the short period of follow-up and it is recommended to conduct more studies to verify whether the consistency of these results (*Yuan et al., 2020).*

Meanwhile, *Badry et al. (2020)* conducted a study to search whether this possible improvement is occurring in the Egyptian patients who received DAAs or not *(Badry et al., 2020).*

In a study to investigate the correlation between SVR and DAA treatment of HCV. SVR is defined as HCV RNA results below the lower limit of quantification at least 12 weeks or more after the EOT. Patients were categorized as No SVR if they had an HCV RNA above the limit of quantification 12 weeks or more after the EOT or at any time after the EOT and no subsequent test ≥12 weeks after the EOT. Patients who lacked definitive laboratory information, for example, patients with HCV RNA below the limit of quantification on their last HCV viral load test but no tests ≥12 weeks after the EOT, were excluded from the analysis. On-treatment HCV RNA was used as a surrogate marker for adherence, and No SVR patients were characterized as having a result either below the lower limit of quantification, a ≥2-log decrease from baseline, or a <2-log decrease from baseline at least 4 weeks after treatment start. VA guidance recommends that providers obtain a 4-week on-treatment HCV RNA for all patients receiving DAA therapy *(Badry et al., 2020).*

While **Hum et al. (2017)** reported that there was no significant difference in baseline pretreatment Hemoglobin A1c level in patients who achieved sustained viral response and who did not, the patients who achieved SVR attained significant drop in HbA1c (0.37 ± 1.2%) than those who did not achieve SVR (0.19 ± 1.3%) with the difference (0.37% minus 0.19%) of −0.18% (P = 0.03). Moreover, **Morales et al. (2016)** who assessed the effect of sofosbuvir (SOF) based regimens on glycemic control in a retrospective analysis of hepatitis C virus (HCV)-infected patients treated and cured with SOF regimen. HbA1c obtained before and after treatment, and HbA1c was significantly decreased with treatment of HCV (pretreatment 6.66% ± 0.95% vs post-treatment 6.14% ± 0.65%, P < 0.005).

We reported in this study that after the end of treatment, all the patients achieved drop in HbA1c (-0.3±0.3) with a P value=<0.001 and the drop after 3 months of treatment increased to (-0.6±0.4) also with

a P value=<0.001 and this means that HbA1c significantly decreased only in negative HCV PCR at treatment end and month-3 after treatment end. HbA1c at treatment end and month-3 after treatment end were significantly lower in cases with negative HCV PCR. HbA1c reductions at treatment end and month-3 after treatment end were significantly highest in cases with negative HCV PCR at treatment end, followed by cases with negative HCV PCR at moth-3 after treatment end and least in positive HCV PCR cases.; however, HbA1c at treatment end and month-3 after treatment end were significantly lower in cases with negative HCV PCR and sustained SVR after 3 months (-0.4±0.3) vs those who did not achieve HCV PCR and sustained SVR after 3 months (-0.7±0.3) with P value= <0.001. HbA1c reductions at treatment end and month-3 after treatment end were significantly higher in cases with negative HCV PCR.

Table (3): Baseline and follow ups HbA1c (%) and FPG (mg/dL) among the studied cases

| Time | Mean ± SD | Range | ^p-value (from baseline) |
|---|---|---|---|
| HbA1c levels | | | |
| Baseline | 7.7±0.7 | 6.4–9.0 | |
| Treatment end | 7.3±0.7 | 5.8–9.0 | <0.001* |
| Month-3 after treatment end | 7.1±0.7 | 5.6–9.0 | <0.001* |
| # HbA1c Changes from baseline (time-baseline) | | | |
| Treatment end | -0.3±0.3 | -0.9–0.4 | |
| Month-3 after treatment end | -0.6±0.4 | -1.2–0.3 | |
| FPG levels | | | |
| Baseline | 171.1±41.7 | 102.0–289.0 | |
| Treatment end | 155.0±41.6 | 90.0–270.0 | <0.001* |
| Month-3 after end | 146.7±44.2 | 84.0–276.0 | <0.001* |
| # FPG Changes from baseline (time-baseline) | | | |
| Treatment end | -15.9±17.8 | -60.0–41.0 | |
| Month-3 after end | -24.6±25.4 | -86.0–58.0 | |

Total=50. #Negative values indicate reduction. ^Paired t-test. *Significant

HbA1c significantly decreased after HCV treatment. FBG significantly decreased after HCV treatment.

Table (4) shows that: No significant differences according to HCV PCR at treatment end regarding demographic characteristics. HCV PCR and total bilirubin were significantly lower in cases with negative HCV PCR. No significant differences according to HCV PCR at treatment end regarding baseline liver condition. No significant differences according to HCV PCR at treatment end regarding DM and HCV treatments.

Table (4): Comparison according to HCV PCR at treatment end regarding baseline characteristics

| Variables | | Treatment-end HCV PCR | | p-value |
|---|---|---|---|---|
| | | Negative (N=41) | Positive (N=9) | |
| Age (years) | | 50.1±5.6 | 51.4±8.2 | ^0.544 |
| BMI (kg/m$^2$) | | 28.4±3.7 | 29.7±3.6 | ^0.348 |
| Sex | Male | 29 (70.7%) | 7 (77.8%) | §0.999 |
| | Female | 12 (29.3%) | 2 (22.2%) | |
| HCV PCR (x10$^3$/mL) | | 768.2±369.0 | 1423.9±798.1 | ^<0.001* |
| Platelets (x10$^3$/mL) | | 239.3±82.9 | 214.3±85.3 | ^0.420 |
| AST (IU/L) | | 31.0±22.9 | 41.6±24.3 | ^0.222 |
| ALT (IU/L) | | 35.4±27.7 | 42.0±28.2 | ^0.522 |
| Total bilirubin (mg/dL) | | 1.0±0.7 | 1.9±0.8 | ^0.004* |
| Albumin (gm/dL) | | 4.0±0.4 | 3.9±0.7 | ^0.366 |
| INR | | 1.1±0.2 | 1.1±0.1 | ^0.717 |
| Creatinine (mg/dL) | | 0.9±0.3 | 1.0±0.2 | ^0.159 |
| Liver size (mm) | | 10.4±1.6 | 10.9±2.1 | ^0.472 |
| Spleen size (mm) | | 12.3±3.0 | 13.1±3.9 | ^0.507 |
| Ascites | | 3 (7.3%) | 2 (22.2%) | §0.216 |
| Child Pough grade | A | 35 (85.4%) | 5 (55.6%) | §0.065 |
| | B | 6 (14.6%) | 4 (44.4%) | |
| DM | Oral | 24 (58.5%) | 5 (55.6%) | §0.758 |
| | Insulin | 12 (29.3%) | 2 (22.2%) | |
| | Mixes | 5 (12.2%) | 2 (22.2%) | |
| HCV | Sofosbuvir | 24 (58.5%) | 6 (66.7%) | §0.724 |
| | Ledipasavir | 17 (41.5%) | 3 (33.3%) | |

BMI: Body mass index. ^Independent t-test. §Fisher's Exact test

Table (5): Comparison according to HCV PCR at treatment end regarding Baseline and follow ups FBG (mg/dL) and HbA1c (%)

| Time | Treatment-end HCV PCR | | ^p-value (between PCR) |
|---|---|---|---|
| | Negative (N=41) | Positive (N=9) | |
| FBG levels | | | |
| Baseline | 170.0±42.3 | 176.3±41.2 | 0.682 |
| Treatment end | 150.0±40.0 | 177.7±43.6 | 0.070 |
| Month-3 after end | 137.9±38.9 | 186.9±46.8 | 0.002* |
| # FBG Changes from baseline (time-baseline) | | | |
| Treatment end | -19.7±14.3 | 1.3±22.4 | 0.001* |
| Month-3 after end | -32.3±18.3 | 10.6±24.2 | <0.001* |
| §p-value (FBG between times and baseline) | | | |
| Treatment end | <0.001* | 0.862 | |
| Month-3 after end | <0.001* | 0.227 | |
| HbA1c levels | | | |
| Baseline | 7.6±0.6 | 7.8±1.0 | 0.449 |
| Treatment end | 7.2±0.6 | 7.8±1.0 | 0.021* |
| Month-3 after end | 7.0±0.5 | 7.7±1.1 | 0.003* |
| # HbA1c Changes from baseline (time-baseline) | | | |
| Treatment end | -0.4±0.3 | 0.0±0.3 | <0.001* |
| Month-3 after end | -0.7±0.3 | -0.1±0.3 | <0.001* |
| §p-value (HbA1c between times and baseline) | | | |
| Treatment end | <0.001* | 0.822 | |
| Month-3 after end | <0.001* | 0.254 | |

#Negative values indicate reduction. ^Independent t-test. §Paired t-test. *Significant

Table (5) show that: No significant differences according to HCV PCR at treatment end regarding baseline FBG. FBG significantly decreased in negative and positive HCV PCR at treatment end and treatment end. FBG at treatment end and treatment end were significantly lower in cases with negative HCV PCR. FBG reductions at treatment end and treatment end were significantly higher in cases with negative HCV PCR. No significant differences according to HCV PCR at treatment end regarding baseline HbA1c. HbA1c significantly decreased in negative and positive HCV PCR at treatment end and treatment end. HbA1c at treatment end and treatment end were significantly lower in cases with negative HCV PCR. HbA1c reductions at treatment end and treatment end were significantly higher in cases with negative HCV PCR.

Table (6): Comparison according to HCV PCR at month-3 after treatment end regarding baseline characteristics

| Variables | | Month-3 HCV PCR | | p-value |
|---|---|---|---|---|
| | | Negative (N=39) | Positive (N=11) | |
| Age (years) | | 50.0±5.5 | 51.5±7.9 | ^0.488 |
| BMI (kg/m$^2$) | | 28.4±3.6 | 29.3±3.9 | ^0.508 |
| Sex | Male | 27 (69.2%) | 9 (81.8%) | §0.705 |
| | Female | 12 (30.8%) | 2 (18.2%) | |
| HCV PCR (x10$^3$/mL) | | 746.3±355.2 | 1382.6±738.0 | ^0.018* |
| Platelets (x10$^3$/mL) | | 240.1±83.6 | 215.9±82.0 | ^0.399 |
| AST (IU/L) | | 30.5±22.9 | 41.6±23.4 | ^0.162 |
| ALT (IU/L) | | 34.7±27.7 | 43.3±27.7 | ^0.369 |
| Total bilirubin (mg/dL) | | 1.0±0.7 | 1.8±0.8 | ^0.002* |
| Albumin (gm/dL) | | 4.0±0.4 | 4.0±0.7 | ^0.780 |
| INR | | 1.1±0.3 | 1.1±0.1 | ^0.819 |
| Creatinine (mg/dL) | | 0.9±0.3 | 1.0±0.2 | ^0.285 |
| Liver size (mm) | | 10.4±1.7 | 10.9±2.0 | ^0.385 |
| Spleen size (mm) | | 12.3±3.0 | 12.9±3.7 | ^0.594 |
| Ascites | | 2 (5.1%) | 3 (27.3%) | §0.064 |
| Child Pough grade | A | 34 (87.2%) | 6 (54.5%) | §0.030* |
| | B | 5 (12.8%) | 5 (45.5%) | |
| DM | Oral | 22 (56.4%) | 7 (63.6%) | §0.707 |
| | Insulin | 12 (30.8%) | 2 (18.2%) | |
| | Mixes | 5 (12.8%) | 2 (18.2%) | |
| HCV | Sofosbuvir | 22 (56.4%) | 8 (72.7%) | §0.489 |
| | Ledipasavir | 17 (43.6%) | 3 (27.3%) | |

BMI: Body mass index. ^Independent t-test.
§Fisher's Exact test

Table (6) shows that: No significant differences according to HCV PCR at month-3 after treatment end regarding demographic characteristics. HCV PCR and total bilirubin were significantly lower in cases with negative HCV PCR. Child-B was significantly more frequent in cases with positive Month-3 HCV PCR. No significant differences according to HCV PCR at month-3 after treatment end regarding DM and HCV treatments.

*Carnovale et al. (2019)* highlighted that a significant decrease in FPG levels of - 22.03 mg/dL (95% CI - 41.61 to - 2.44 mg/dL; P = 0.03), and this is consistent with *Ciancio et al. (2017)* who conducted a study to evaluate the change in FPG and HbA1c values before and after therapy with direct-acting antivirals (DAAs) in 122 HCV patients with T2D. They reported that 110 of the study patients with HCV and T2DM, were treated with DAAs and 12 remained untreated. Hence, a total of 101 patients achieved a SVR and nine did not. A significant decrease of FPG (134.3 ± 41.32 mg/dL vs 152.4 ± 56.40 mg/dL, P = 0.002) and HbA1c values were observed. Successful treatment of HCV by DAAs yielded to a significant improvement of glycemic control in HCV patients with T2D *(Ciancio et al., 2017).*

A plenty of cohort studies reported the results of treating HCV infection using DAAs on the control of T2D. *Hum et al. (2017)* conducted one of the largest studies and reported that a SVR was associated with improved glycemic control, with decreased HbA1c levels (mean decrease, 1%) and reduced insulin requirements. A significant fall in the blood HbA1c level associated with a SVR was only seen in veterans without severe hepatic fibrosis or cirrhosis. Their studies included 2,000 veterans who had T2D and were managed by an interferon-free regimen and also ribavirin-free DAA-based antiviral treatment for their HCV infection. On the other hand, *Mada et al. (2020)* pointed out that there were ~1% decrements in mean HbA1c levels in patients with or without severe hepatic fibrosis/cirrhosis.

Hence, successful eradication of HCV would improve clinical outcomes in patients with T2DM *(Gilad et al., 2019). Yuan et al. (2020)* reported a reduction in the FPG level in patients with SVR without a significant change in the non-SVR group after PSM (P = 0.027; p = 0.723).

These findings are consistent with the results of our study where FPG in PCR (-ve) patients at baseline was 171.1±41.7, at end of treatment 150.1±39.5 and 3 months after treatment it was 137.7±38.6 and this means that it was significantly reduced in these patients after 3 months with --20.5±14.2 comparing values at end of treatment to baseline and -33.4±18.1 comparing values at 3 months after end of treatment to values at end of treatment and this was highly significant with a P value= <0.001.

Table (7): Comparison according to HCV PCR at month-3 after treatment end regarding Baseline and follow ups FBG (mg/dL)

| | Month-3 HCV PCR | | ^p-value (between PCR) |
|---|---|---|---|
| | Negative (N=39) | Positive (N=11) | |
| FBG levels | | | |
| Baseline | 170.8±41.8 | 172.0±43.6 | 0.936 |
| Treatment end | 150.1±39.5 | 172.3±46.1 | 0.119 |
| Month-3 after end | 137.7±38.6 | 178.7±49.5 | 0.005* |
| # FBG Changes from baseline (time-baseline) | | | |
| Treatment end | -20.5±14.2 | 0.3±20.1 | <0.001* |
| Month-3 after end | -33.4±18.1 | 6.7±23.3 | <0.001* |
| §p-value (FBG between times and baseline) | | | |
| Treatment end | <0.001* | 0.965 | |
| Month-3 after end | <0.001* | 0.362 | |
| HbA1c levels | | | |
| Baseline | 7.6±0.5 | 7.6±0.8 | 0.979 |
| Treatment end | 7.2±0.5 | 7.6±0.8 | 0.159 |
| Month-3 after end | 7.0±0.5 | 7.5±0.9 | 0.069 |
| # HbA1c Changes from baseline (time-baseline) | | | |
| Treatment end | -0.4±0.3 | 0.0±0.3 | <0.001* |
| Month-3 after end | -0.7±0.3 | -0.1±0.2 | <0.001* |
| § HbA1c p-value (between times and baseline) | | | |
| Treatment end | <0.001* | 0.650 | |
| Month-3 after end | <0.001* | 0.167 | |

#Negative values indicate reduction. ^Independent t-test. §Paired t-test. *Significant

Table (7) show that: No significant differences according to HCV PCR at month-3 after treatment end regarding baseline FBG. FBG significantly decreased in negative and positive HCV PCR at treatment end and month-3 after treatment end. FBG at treatment end and month-3 after treatment end were significantly lower in cases with negative HCV PCR. FBG reductions at treatment end and month-3 after treatment end were significantly higher in cases with negative HCV PCR. No significant differences according to HCV PCR at month-3 after treatment end regarding baseline HbA1c. HbA1c significantly decreased in negative and positive HCV PCR at treatment end and month-3 after treatment end. HbA1c at treatment end and month-3 after treatment end were non-significantly lower in cases with negative HCV PCR. HbA1c reductions at treatment end and month-3 after treatment end were significantly higher in cases with negative HCV PCR.

## Conclusions

In this study, we concluded that successful HCV eradication will result to a statistically significant reduction in fasting plasma glucose and HbA1C in patients with type 2 diabetes which is an indirect indicator of improvement of insulin sensitivity in patients with type 2 DM. This study had some limitations including lack of control group, relatively small sample size and short follow up period.

## Conflicts of interest

"There are no conflicts to declare".

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