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Effect of eradication of HCV infection by direct-acting antivirals in diabetic HCV-infected patients as regards glycemic control

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Abstract

Background: A burden of data suggests that insulin signaling could be impaired with hepatitis C virus infection, and this boost the onset of type 2 diabetes mellitus beyond and in addition to the histological effect on the associated liver disease. We aimed to evaluate the hemoglobin A1c (HbA1c) levels before and after therapy with direct-acting antivirals (DAAs) in HCV-diabetic patients who achieved sustained virological response (SVR) at Aswan Fever Hospital. This prospective study was conducted at the Viral Hepatitis Treatment Center, Aswan Fever Hospital, Aswan, Egypt, between November 2017 and May 2018. A total of 85 randomly selected diabetic patients (type 2 diabetes mellitus) with chronic HCV infection were received sofosbuvir and daclatasvir as a dual therapy for 3 months, then followed up for week 12 after the end of DAA therapy, Changes in the levels of hemoglobin A1c (HbA1c) were measured at baseline then 12 weeks after the end of treatment with DAAs.

Results: Thirty-two patients (37.6%) showed a significant glycemic improvement after receiving DAAs therapy; in the form of > 1% reduction in HbA1c level (p value < 0.001). Their baseline mean HbA1c level was 7.98 ± 0.62% which was significantly improved 12 weeks after the end of therapy (SVR) to reach a level of 6.88 ± 0.81%. Meanwhile, 53 patients (62.4%) had a baseline mean HbA1c of 8.24 ± 0.64% and a post-treatment mean HbA1c level of 8.34 ± 0.61% (p value = 0.083).

Conclusion: DAAs-based eradication of HCV is associated with improved glycemic control in 37.6% of patients with diabetes as evidenced by a significant reduction of mean HbA1c.

Keywords: Direct-acting antiviral drugs (DAAs), HCV, Glycated hemoglobin (HA1C), Glycemic control, Eradication, Diabetic

Background

Hepatitis C virus (HCV) affects over 185 million people, with an estimated 2.8% increase globally over the last decade. It has been estimated that HCV is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) cases worldwide. Global- and region-specific estimates of HCV prevalence vary greatly [1, 2], but the highest prevalence has been reported in China, Pakistan, Nigeria, Egypt, India, and Russia which together accounted for more than half of the total infections [3].

In Egypt, HCV was estimated to affect 14.7% of the population; over 90% of the infections have been reported to be HCV genotype 4. The spread of chronic HCV infection in Egypt is thought to be largely due to needle re-use during mass-treatment programs for schistosomiasis during the late 1950s through the early 1980s. Unfortunately, transmission continues to occur,

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primarily through iatrogenic sources, such as blood transfusions, injections, and dental care [4].

It is widely recognized that there is a link between infection with HCV and type 2 diabetes mellitus (T2DM). Patients chronically infected with HCV are 4 times more likely to have T2DM than HCV negative subjects. Several studies focused on the treatment of HCV with pegylated interferon (peg)/ribavirin (RBV) based therapy prior to the widespread use of the new direct-acting antiviral drugs (DAAs) [5].

With recent advances, many DAAs developed and led to a more promising future for HCV infected patients. Excellent advantages were related to their high potency, pangenotypic coverage and intermediate to high barrier to resistance. They paved the way to the possible application of oral interferon-free regimens. In addition, these regimens can be taken once daily and may result in global HCV eradication in the near future [6].

The effect of sustained virological response (SVR) on various clinical outcomes provides another line of evidence linking HCV infection with Insulin resistance (IR). Sustained virological response (SVR) is associated with a reduction in HCC incidence, liver-related mortality, and overall mortality. A number of clinical trials demonstrate that SVR was associated also with improved IR. For instance, a longitudinal study of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis Trial found that SVR was associated with an improvement in IR [7]. Another study based on the Milan Safety Tolerability study cohort found a reduction of de novo IR development in SVR patients compared to non-SVR patients although the mean baseline and post-treatment Homeostatic Model Assessment for Insulin Resistance (HOMA) values were similar in SVR patients [8]. Gilad et al. (2019) reported that HCV eradication leads to a decrease in HbA1c ≥ 0.5% with no increase in diabetes medications or a decrease in diabetes medications with a stable HbA1c. Thus, the association between HCV eradication and glycemic improvement has been widely postulated. However, a little is known about the exact percent of glycemic improvement within SVR patients. Therefore, the aim of this study is to evaluate the HbA1c levels before and after therapy with DAAs in HCV-diabetic patients who achieved SVR [9].

Methods

This prospective observational study was done in the Viral Hepatitis Treatment Center, Aswan Fever Hospital, Egypt, which is one of the centers affiliated to the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) in the period between November 2017 and May 2018. Preliminary, 100 randomly selected diabetic patients with chronic HCV infection who intended to receive DAAs were participated, then followed up for week 12 after the end of DAAs therapy, only 85 patients continued till the end of the study. The remaining fifteen patients were excluded due to loss of follow-up, also those who demonstrated a viremic relapse 4 weeks after the end of therapy and remained HCV-RNA positive at week 12 were excluded.

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from the Institutional Review Board (IRB) for human subject research at the National Hepatology and Tropical Medicine Research Institute. Written informed consents were obtained from all enrolled participants before enrolment to the study. Diabetes was defined according to American Diabetes Association (ADA) guidelines and confirmed by a hemoglobin Alc > 6.5% [10]. The SVR was defined as undetectable HCV-RNA at week 12 after the end of therapy. The stated glycemic improvement in our study was defined as a ≥ 1% reduction of baseline HbA1c levels. Other previous studies involving DAAs therapy reported a decline of HbA1C by 0.5–1.95% [9, 11].

Patients were included in the study according to the standardized protocol for HCV management issued by NCCVH. Key exclusion criteria were Child–Turcotte–Pugh (CTP) class C, hemoglobin level < 10 g/dL, platelet count < 50,000/mm3, hepatocellular carcinoma (HCC) except 6 months following a successful intervention and cure with no proof of recurrence by dynamic imaging (CT, MRI), extra-hepatic malignancy except after 2 years of cure, co-infection with hepatitis B or HIV, and hypersensitivity to any of study medications. All patients included in this study were subjected to full history taking and thorough clinical examination. Baseline demographics (age, gender, and treatment medications) were recorded. Baseline laboratory investigations were done, including complete blood count (CBC), prothrombin time (PT), international normalized ratio (INR), hemoglobin A1c (HbA1c), renal function tests (BUN, creatinine), hepatitis B virus surface antigen (Hbs Ag), alpha fetoprotein (AFP), and liver function tests including AST and ALT. Patients were followed up for 12 weeks after the end of DAAs therapy and post-treatment laboratory values were obtained at the time of SVR response (HCV-RNA clearance 12 weeks after the end of therapy).The analysis of CBC was done using Coulter LH 750 Cell Counter, measurement of PT was performed using Stago Compact Autoanalyzer using Neoplastine CI Plus supplied by Diagnostica Stago and serum chemistry was performed using Beckman Coulter AU480 Autoanalyzer, HCV (RNA) PCR using the COBAS® TaqMan® HCV Test v2.0. The HbA1c measurement is based on a turbidimetric inhibition immunoassay (TINIA) principle and was performed using Roche Diagnostics Cobas c 311 Autoanalyzer.

Statistical analysis

Statistical analysis was done using IBM SPSS software version 20. The values for the biochemical markers were expressed as mean and standard deviation in case of parametric data, and as median and interquartile ranges in case of skewed data, while categorical variables were summarized using frequency measures. Independent *t* test was used in the comparison between two groups with quantitative data and parametric distribution and Mann-Whitney test was used in the comparison between two groups with quantitative data and non-parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the chi-square test when the expected count in any cell found to be less than 5. Univariate analysis was performed using paired *t* test for continuous variables. In all statistical analyses, $p < 0.05$ was considered significant.

Results

This study included 85 adult diabetic patients with chronic HCV infection, 5 patients (5.8%) of them were cirrhotic (child A) and 14 patients (16.4%) were hypertensive; by history and clinical examinations, there were no any associated diabetic microvascular or macrovascular complications. All included patients were HCV genotype 4. The mean (SD) diabetic duration of the enrolled patients was 11 (5.3). The baseline demographic and clinical characteristics of all included patients are summarized in Table 1. Table 2 demonstrates the statistical comparison of the post-treatment parameters in glycemic improved patients versus glycemic non-improved patients.

Statistical comparison between pre-treatment and post-treatment parameters in both glycemic improved and glycemic non-improved patients are shown in Tables 3 and 4, respectively. At the end of therapy, there was a significant decrease in hemoglobin, bilirubin, AST, ALT levels, AFP, and FIB-4 scores, in both studied groups (p value < 0.001) (Table 4).

At the end of treatment, 32 patients (37.6%) showed a significant improvement in the form of > 1% reduction in HbA1c level (p value < 0.001). Their baseline mean HbA1c level was 7.98 ± 0.62% which was significantly improved at the end of therapy to reach a level of 6.88 ± 0.81%. Meanwhile, 53 patients (62.4%) had a baseline mean HbA1c of 8.24 ± 0.64% and a post-treatment mean HbA1c level of 8.34 ± 0.61% (p value = 0.083).

Discussion

Chronic HCV infection is a major health-related burden in Egypt which affects 14.7% of the Egyptian population. Moreover, the incidence rate of HCV infection was reported to range between 2 and 6 per 1000 every year; this leads to an estimated 170,000 new cases every year to add to the 11.5 million patients suffering from the disease. Chronic infection with HCV is the leading cause of end-stage liver disease, HCC, and liver-related death in Egypt [12]. However, with a recent introduction of genotype 4 effective DAAs to the treatment protocol, there was a revolutionary reduction HCV epidemic in Egypt; DAAs combinations were reported to show high rates of SVR and pan-genotypic clinical efficacy in HCV genotypes 1–6 [13].

On the other hand, the current body of evidence shows a higher prevalence of T2DM among patients with chronic HCV infection, it was proposed that HCV proteins increase serine and threonine phosphorylation of insulin receptor substrate-1, which contributes to insulin resistance. In addition, HCV proteins enhance the release of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which then upregulate gluconeogenesis and enhance lipid accumulation in the liver [14].

Therefore, it is presumed that effective HCV management would result in improved glycemic control in diabetic patients. A growing body of evidence has shown a promising role of effective HCV eradication on glycemic control of diabetic patients; previous reports showed that the change in HbA1c was greater in those who achieved SVR (0.98%) with DAAs than in those who sustained treatment failure. Also, the use of anti-diabetic medications decreased more in patients who achieved SVR than in those who failed to achieve SVR [15].

This was further confirmed by recent studies focusing on the association of SVR achievement and the glycemic improvement in HCV patients who received DAAs regimen [15, 16]. Meanwhile, we conducted our study only on patients who achieved SVR, in order to verify whether this suggested improvement is occurring to all patients who achieved SVR with DAAs or not.

The drop in average HbA1c level after treatment was greater in 37.6% of our included patients, from 7.98 to 6.88% (yielding a mean HA1C difference more than 1%), than in those for whom glycemic control failed (from 8.24 to 8.34%). Moreover, our results revealed that those who achieved a significant glycemic improvement were less likely to have hepatic fibrosis as presented by the FIB-4 score. In agreement with our findings, Abdel Alem and his colleagues reviewed the clinical records of 65 diabetic HCV patients; there were statistically significant declines in fasting plasma glucose and HbA1c values at SVR24. Notably, whatever the degree of hepatic fibrosis, the level of fasting plasma glucose and HbA1c decreased at SVR24 in comparison to the baseline level. The improvement rate of HbA1c was as high as 78% of the included patients [17].

Table 1 Baseline demographic and clinical characteristics of all included patients

	Glycemic non-improved Patients (no = 53)	Glycemic improved Patients (no = 32)	*P* value
Male, *n* (%)	21(39.6%)	12(37.5%)	0.846
Age (year)[a]	55.26 ± 9.24	57.50 ± 7.37	0.248
Insulin therapy, *n* (%)	23(43.4%)	13(40.6%)	0.538
Oral hypoglycemic therapy, *n* (%)	30(56.6%)	19(59.4%)	0.538
Family history of DM, *n* (%)	29(54.7%)	15(46.9%)	0.483
Hemoglobin (g/dL)[a]	12.98 ± 1.34	13.07 ± 1.05	0.764
Leukocytes (× 103/μL cells)[a]	6.53 ± 1.67	6.53 ± 1.91	0.998
Platelets (× 103/μL cells)[a]	223.57 ± 50.09	206.56 ± 53.82	0.144
Albumin (g/dL)[a]	4.25 ± 0.42	4.30 ± 0.40	0.622
Bilirubin, total (mg/dL)[a]	0.81 ± 0.15	0.78 ± 0.22	0.436
INR[a]	1.29 ± 1.36	1.41 ± 1.75	0.722
AST (IU/L)[a]	50.65 ± 24.36	51.59 ± 28.20	0.871
ALT (IU/L)[a]	55.71 ± 27.48	64.13 ± 35.90	0.227
Creatinine (mg/dL)[a]	1.02 ± 0.86	0.87 ± 0.15	0.304
AFP (ng/mL)[a]	7.08 ± 5.01	7.41 ± 6.24	0.789
HCV RNA viral load (log10 IU/mL)[a]	6.77 ± 6.661	6.77 ± 6.640	0.847
HbA1c (%)[a]	8.17 ± 0.58	7.91 ± 0.69	0.062
FIB-4[b] score[a]	1.89 ± 0.85	1.75 ± 0.76	0.442

[a]Mean ± SD. Glycemic improved group: ≥ 1% reduction of baseline HbA1c levels at SVR. Non-glycemic improved group: < 1% reduction of baseline HbA1c levels at SVR

AFP Alpha-fetoprotein, *ALT* Alanine transaminase, *AST* Aspartate transaminase, [b]FIB-4 score = [age 3AST]/[platelets 3 ALT1/2], *INR* international normalized ratio, *HbA1c* glycated hemoglobin

Table 2 Statistical comparison of the post-treatment parameters in glycemic improved patients versus glycemic non-improved patients

	Glycemic non-improved Patients (no = 53)	Glycemic improved Patients (no = 32)	*P* value
Hemoglobin (g/dL)[a]	12.25 ± 1.44	12.57 ± 1.23	0.289
Leukocytes (× 103/μL cells)[a]	6.98 ± 1.72	6.58 ± 2.03	0.337
Platelets (× 103/μL cells)[a]	228.9 ± 51.77	217.31 ± 47.82	0.307
Albumin (g/dL)[a]	4.28 ± 0.39	4.31 ± 0.37	0.664
Bilirubin, total (mg/dL)[a]	0.67 ± 0.16	0.67 ± 0.19	0.848
INR[a]	1.07 ± 0.06	1.07 ± 0.09	0.992
AST (IU/L)[a]	22.38 ± 7.83	24.53 ± 8.27	0.232
ALT (IU/L)[a]	23.87 ± 9.43	24.22 ± 7.98	0.861
Creatinine (mg/dL)[a]	0.93 ± 0.18	0.88 ± 0.15	0.181
HbA1c (%)[a]	7.91 ± 0.79	6.50 ± 0.72	< 0.001
AFP (ng/mL)[a]	6.43 ± 4.09	6.56 ± 5.94	0.906
FIB-4[b] score[a]	1.38 ± 0.47	1.17 ± 0.44	0.039

[a]Mean ± SD. Glycemic improved group: ≥ 1% reduction of baseline HbA1c levels at SVR. Non-glycemic improved group: < 1% reduction of baseline HbA1c levels at SVR

AFP Alpha-fetoprotein, *ALT* Alanine transaminase, *AST* Aspartate transaminase, [b]FIB-4 score = [age 3AST]/[platelets 3 ALT1/2], *INR* international normalized ratio, *HbA1c* glycated hemoglobin

Table 3 Statistical comparison between pre-treatment and post-treatment parameters in glycemic improved patients

	Pre-treatment (no = 32)	Post-treatment (no = 32)	*P* value
Hemoglobin (g/dL)[a]	13.07 ± 1.05	12.57 ± 1.23	0.002
Leukocytes (× 103/μL cells)[a]	6.53 ± 1.91	6.58 ± 2.03	0.876
Platelets (× 103/μL cells)[a]	206.56 ± 53.82	217.31 ± 47.82	0.130
Albumin (g/dL)[a]	4.30 ± 0.40	4.31 ± 0.37	0.501
Bilirubin, total (mg/dL)[a]	0.78 ± 0.22	0.67 ± 0.19	0.009
INR[a]	1.41 ± 1.75	1.07 ± 0.09	0.290
AST (IU/L)[a]	51.59 ± 28.20	24.53 ± 8.27	0.001
ALT (IU/L)[a]	64.13 ± 35.90	24.22 ± 7.98	0.001
Creatinine (mg/dL)[a]	0.87 ± 0.15	0.88 ± 0.15	0.525
HbA1c (%)[a]	7.91 ± 0.69	6.50 ± 0.72	0.001
AFP (ng/mL)[a]	7.41 ± 6.24	6.56 ± 5.94	0.032
FIB-4[b] score[a]	1.75 ± 0.76	1.17 ± 0.44	0.001

[a]Mean ± SD. Glycemic improved group: ≥ 1% reduction of baseline HbA1c levels at SVR. Non-glycemic improved group: < 1% reduction of baseline HbA1c levels at SVR

AFP Alpha-fetoprotein, *ALT* Alanine transaminase, *AST* Aspartate transaminase, [b]FIB-4 score = [age 3AST]/[platelets 3 ALT1/2], *INR* international normalized ratio, *HbA1c* glycated hemoglobin

Another report from Egypt by Dawood and his colleagues who included 460 T2DM patients with chronic HCV genotype 4 infection in order to evaluate the role of DAAs therapy on glycemic status. Their results showed that almost 77% of the patients achieved the improved glycemic control status after HCV-eradication by DAAs; moreover, the HbA1c and fasting blood glucose levels changed significantly 6 months following treatment [18].

In concordance with our findings, Pavone and his colleagues reported a statistically significant reduction in HbA1c, with a reduction of the mean value of 1.95%, during the DAAs treatment [11]. The impact of HCV eradication on the glycemic control was also evaluated by Gilad and his colleagues who studied the clinical characteristics of 122 diabetic patients with chronic HCV infection; the authors reported that HbA1c at the nearest time point before treatment was 8.4% ± 1.9%, compared with 7.8% ± 1.7% after treatment, a mean difference of 0.6% [9].

As regards to our patients who did not achieve the expected glycemic improvement at the end of therapy, this may be explained by two factors as proposed by Hashim et al. (2018); first, the etiology of T2DM in HCV-infected individuals has been postulated to result from either hepatogenous T2DM or classical T2DM due to

Table 4 Statistical comparison between pre-treatment and post-treatment parameters in glycemic non-improved patients

	Pre-treatment (no = 53)	Post-treatment (no = 53)	*P* value
Hemoglobin (g/dL)[a]	12.98 ± 1.34	12.25 ± 1.44	0.001
Leukocytes (× 103/μL cells)[a]	6.53 ± 1.67	6.98 ± 1.72	0.038
Platelets (× 103/μL cells)[a]	223.57 ± 50.09	228.91 ± 51.77	0.150
Albumin (g/dL)[a]	4.25 ± 0.42	4.28 ± 0.39	0.249
Bilirubin, total (mg/dL)[a]	0.81 ± 0.15	0.67 ± 0.16	0.001
INR[a]	1.29 ± 1.36	1.07 ± 0.06	0.253
AST (IU/L)[a]	50.65 ± 24.36	22.38 ± 7.83	0.001
ALT (IU/L)[a]	55.71 ± 27.48	23.87 ± 9.43	0.001
Creatinine (mg/dL)[a]	1.02 ± 0.86	0.93 ± 0.18	0.404
HbA1c (%)[a]	8.17 ± 0.58	7.91 ± 0.79	0.001
AFP (ng/mL)[a]	7.08 ± 5.01	6.43 ± 4.09	0.012
FIB-4[b] score[a]	1.89 ± 0.85	1.38 ± 0.47	0.001

[a]Mean ± SD. Glycemic improved group: ≥ 1% reduction of baseline HbA1c levels at SVR. Non-glycemic improved group: < 1% reduction of baseline HbA1c levels at SVR

AFP Alpha-fetoprotein, *ALT* Alanine transaminase, *AST* Aspartate transaminase, [b]FIB-4 score = [age 3AST]/[platelets 3 ALT1/2], *INR* international normalized ratio, *HbA1c* glycated hemoglobin

virally mediated IR. Second explanation, HCV infection may affect glucose level by an autoimmune mechanism on β cells and is not related to IR [19].

However, it should be noted that there were limitations in the present study; the sample size and the duration of follow-up, it is well established that the micro-vascular complications of diabetes, including nephropathy, neuropathy, and retinopathy, improve with lowered HbA1c level. Therefore, early treatment of HCV could potentially slow the onset and progression of micro-vascular complications of diabetes. Given the study period, we were unable to evaluate whether improved glycemic control was durable beyond 3 months. Therefore, larger studies with a longer duration of follow-up are recommended to validate these findings.

Conclusion

In conclusion, our study reported that HCV eradication with DAAs leads to a significant reduction in HbA1c level (HbA1C improvement of more than 1%) in 37.6% of patients with diabetes. Meanwhile, 62.4% patients showed a reduction in HbA1c level less than 1% at 12 weeks after the end of therapy. These findings raise the question to whether the HCV eradication may also impact the future morbidity due to T2DM and slowing the onset and progression of micro-vascular complications of diabetes, as well as the degree of improvement of hepatic fibrosis induced by chronic HCV. For this reason, close follow-up post-HCV treatment is needed, and large prospective studies are recommended to validate these results.

Abbreviations

AFP: Alpha fetoprotein; CTP: Child–Turcotte–Pugh; CBC: Complete blood count; DAAs: Direct-acting antivirals; Hba1c: Hemoglobin A1c; Hbs Ag: Hepatitis B virus surface antigen; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; HOMA: Homeostatic model assessment; IRB: Institutional Review Board; IR: Insulin resistance; INR: International normalized ratio; NCCVH: National Committee for Control of Viral Hepatitis; Peg: Pegylated interferon; RBV: Ribavirin; PT: Prothrombin time; SVR: Sustained virological response; T2DM: Type 2 diabetes mellitus

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Authors' contributions

MME contributed in conception of the study design, clinical supervision and acceptance of the final form of the manuscript. DAA contributed in clinical examinations and collection of data. NHE contributed in statistical analysis and writing of the manuscript. MAA contributed in the laboratory investigations' design, supervision, and writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data is available upon request.

Ethics approval and consent to participate

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from Institutional Review Board (IRB) for human subject research at Aswan University Hospital (serial: 18-4-111-Aswu). An informed written consent was obtained from all enrolled participants before enrolment to the study.

Consent for publication

Non applicable.

Competing interests

The authors have no conflict of interest to declare.

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