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Assessment of Changes in Liver Fibrosis and Stiffness, Lipid Profile and Insulin Resistance in Patients with Chronic Hepatitis C Viral Infection Who Received Direct Acting Antiviral Therapy

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ABSTRACT

Background: With introduction of direct acting antivirals (DAAs) in the management of chronic hepatitis C viral (HCV) infection, this leads to high frequency of sustained viral response (SVR). Effect of these agents on liver stiffness and lipid isn't well studied.

Objective: We tried to assess changes in liver stiffness, insulin resistance (IR) and lipid profile after achievement of SVR with DAAs.

Patients and methods: A total of 80 patients with chronic HCV infection were recruited in the study. All patients received dual therapy of sofosbuvir and daclatasvir either without ribavirin (in case of chronic hepatitis) or with ribavirin (in case of liver cirrhosis). Liver stiffness, lipid profile and IR were assessed at baseline and at the end of therapy.

Results: All patients achieved SVR. Majority (58.8%) of patients were males. There was significant improvement in liver transaminases after therapy. There was significant reduction in frequency of IR after therapy (42.5% vs. 68.7%; p= 0.04) with percentage of decrease was 16.11%. Also, there was significant decrease in degree of fibrosis as assessed by fibroScan with percentage of decrease was 48.2%. Predictors for persistence IR after DAAs therapy were only body mass index and advanced fibrosis. Cholesterol, low density lipoproteins and triglycerides showed significant increase after therapy.

Conclusion: Sofosbuvir and daclatasvir with or without ribavirin are effective and tolerable agents in management of chronic HCV infection. Degree of liver fibrosis and insulin resistance would be reduced after DAAs therapy. Future multi centers are warranted to confirm these findings.

Keywords: Insulin resistance, FibroScan, Sofosbuvir, Daclatasvir, Sustained virological response.

INTRODUCTION

Globally, up to 71 million people were infected with hepatitis C virus (HCV) infection. Out of those infected people, 55–85% will have chronic liver disease [(1)].

HCV can disrupt glucose homeostasis in a variety of ways, the majority of which involve insulin signaling. Multiple and synergistic mechanisms are suggested, including insulin receptor substrate-1 (IRS-1) degradation, insulin activity inhibition, decreased cellular glucose uptake, increased glucose synthesis and release from hepatocytes [(2-4)].

HCV infection has a significant impact on the host's lipid and lipoprotein metabolism. In chronic hepatitis C (CHC) patients, the consequences of this alternation are frequently observed as hypolipidemia and hepatic steatosis. The clinical significance of these changes reflects the fact that lipids and lipoproteins play an important role in all stages of the HCV life cycle [(5)].

The introduction of oral direct-acting antiviral (DAA) drugs, which specifically target virus-specific proteins, has fundamentally changed the treatment of chronic HCV. Numerous studies have shown that DAA can not only effectively and safely remove HCV, but also achieve some unexpected benefits when compared to interferon-based therapy, such as repairing liver function damage, recovery of metabolic impairment, and restoration of immunity dysfunction caused by HCV infection [(6)].

To our knowledge in our locality, there is paucity in the studies that assessed effects of DAAs on degree of fibrosis, lipid and glucose metabolism after HCV clearance. In the current work, we tried to study the effects of DAAs on liver fibrosis, lipogram and insulin resistance.

PATIENTS AND METHODS

The enrolled 80 patients with known chronic HCV infection attending at Al-Rajhi University Hospital for receiving treatment of HCV with DAAs in period between September 2018 to January 2020.

Inclusion criteria: Age > 18 years' old, both sexes, and HCV infection either chronic hepatitis or developed cirrhosis.

Exclusion criteria: Known diabetic patients, HCV co-infection with hepatitis B virus, presence of other causes of chronic liver disease (alcohol consumption more than 80 g/day, hepatotoxic drugs, autoimmune hepatitis, primary biliary cholangitis, hemochromatosis and Wilson's disease), patients with hepatocellular carcinoma, and patient's refusal.

All subjects were evaluated as regard the following:

Through history with clinical assessment and calculation of body mass index (calculated as weight

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divided by the square of the height (kg/m^2)). Laboratory investigations were done before therapy and 12-weeks after therapy.

The laboratory data included complete blood picture, international normalized ratio, liver function tests (alanine transaminase, aspartate transaminase, albumin and bilirubin), kidney function tests (serum creatinine and blood urea nitrogen), fasting blood sugar and lipogram.

Specific investigations:

Fasting insulin level, the level of fasting insulin in the serum was measured by the Sandwich enzyme-linked immunosorbent assay (ELISA) technique using Enzyme Immunoassay Test Kit Catalog Number: 10801.

- Insulin resistance index {IR} (Normal index is ≤ 2.5).

Fasting Insulin level was used to estimate IR according to equation of homeostasis model: IR= Insulin fasting level in μIU/ml x Glucose fasting level in mmol/L / 22.5.

Non-invasive fibrosis markers:

- FIB- 4 index= Age (years) × AST (IU/L)/platelet count (109/L) × √ALT (IU/L) [(7)].
- AST/platelet ratio score (APRI) = [AST (IU/L)/AST upper limit of normal (IU/L)] / platelet count (109/L) × 100 [(8)].

Abdominal imaging:

- Abdominal ultrasonography and fibroScan were done at baseline and end of treatment (12 weeks).
- FibroScan (Transient elastography).

  (FibroScan® 502 Touch, Echosens, Paris, France) were performed by a single experienced operator. Liver stiffness measurements (LSMs) were performed after 3 hours of fasting in the right lobe of the liver through the intercostal spaces with the patient in the supine position and the right arm at maximal abduction, and it was expressed in kilopascals (kPsc) according to the usual standard procedure. The cutoff value for limited fibrosis (≥F2) is 7.1 kPa whereas the cutoff value for cirrhosis (F4) is 12.5 kPa) [(9)].

Treatment protocol:

Patients were received sofosbuvir and daclatasvir with or without ribavirin as a dual or triple therapy for 12 weeks according to the recommendations of The Egyptian National Committee for Control of Viral Hepatitis.

Ethical consent:

The study protocol was approved by the Medical Ethics Committee of the Institutional Review Board of the Faculty of Medicine, Assiut University, Egypt. Informed written consent was obtained from all participants according to the declaration of Helsinki. The study protocol was registered at Clinicaltrails.gov ID: NCT03612973

Statistical analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Sciences, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean ± standard deviation (SD) while nominal data were expressed in form of frequency and percentage.

Continuous data were compared with paired t test. Logistic regression analysis was used to determine the independent risk factors for prediction of IR after therapy with DDAs. Pearson correlation was used to determine the correlation between HOMA with each other and other variables. Level of confidence was kept at 95% and hence, P value was considered significant if < 0.05.

RESULTS

Baseline data of enrolled group (Table 1):

Mean age of all enrolled patients was 56.20 ± 6.15 years and majority of them were males. Eleven patients were smokers.

Table (1): Baseline data of enrolled group

	All patients (n= 80)
Age (year)	56.20 ± 6.15
Sex	
Male	47 (58.8%)
Female	33 (41.3%)
Smoking	11 (13.75%)
Body mass index (kg/m2)	23.50 ± 1.67

Data expressed as frequency (percentage), mean ± SD

Baseline and follow up laboratory data among enrolled group (Table 2):

Follow up of those patients after therapy revealed that there was significant decrease in alanine transmarine and aspartate transmarine. Also it was found that there was significant improvement of albumin level.

It was noticed that there was significant rise in levels of cholesterol, TG, and LDL. Among all enrolled patients, it was found that there was significant reduction in HOMA and significant decrease in insulin resistance. Percentage of improvement in HOMA was 16.11%.

Table (2): Baseline and follow up laboratory data of enrolled patients

	Baseline (n= 80)	Follow up (n= 80)	*P* value
Hemoglobin (mg/dl)	12.98 ± 1.50	12.24 ± 1.60	0.34
Leukocytes (10^3/ul)	7.71 ± 1.73	6.91 ± 1.56	0.56
Platelets (10^3/ul)	160.64 ± 38.61	176.18 ± 40.31	0.45
INR	1.18 ± 0.28	1.11 ± 0.24	0.22
Creatinine (mg/dl)	0.78 ± 0.19	0.73 ± 0.19	0.30
Bilirubin (mg/dl)	1.07 ± 0.26	0.95 ± 0.21	0.11
ALT (u/l)	59.38 ± 13.49	35.71 ± 7.33	< 0.001
AST (u/l)	56.41 ± 11.61	32.48 ± 7.78	< 0.001
Albumin (g/dl)	3.43 ± 0.64	3.54 ± 0.55	0.03
Cholesterol (mg/dl)	155.31 ± 18.87	200.49 ± 21.19	< 0.001
LDL (mg/dl)	73.41 ± 15.32	108.50 ± 13.21	0.02
Triglycerides (mg/dl)	110.26 ± 15.73	134 ± 15.89	0.04
HDL (mg/dl)	48.72 ± 8.92	51.12 ± 7.83	0.34
HOMA	4.56 ± 1.34	3.88 ± 1.23	0.01
Insulin resistance	55 (68.7%)	35 (42.5%)	0.04
Percentage of improvement in HOMA	16.11%		

Data expressed as mean ± SD. ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; LDL: low density lipoprotein; HDL: high density lipoprotein; HOMA: homeostasis model assessment index

Baseline and follow up fibrosis indices of enrolled patients (Table 3):

Indices of fibrosis were significantly decreased as FIB-4 index and APRI score. Percentage of improvement in the degree of fibrosis are shown in the table.

Table (3): Baseline and follow up fibrosis indices of enrolled patients

	Baseline (n= 80)	Follow up (n= 80)	*P* value
Fibrosis degree by fibroScan (Kpa)	16.67 ± 3.85	10.20 ± 2.31	< 0.001
FIB-4 index	2.98 ± 0.61	1.73 ± 0.36	< 0.001
APRI score	1.02 ± 0.16	0.47 ± 0.11	< 0.001
Percentage of decrease in fibr			
Based on fibroScan	48.2%		
Based on FIB-4 index	53.1%		
Based on APRI score	73.8%		

Data expressed as mean ± SD. ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; FIB-4: fibrosis-4

Safety and efficacy among enrolled patients (Table 4):

All patients achieved SVR. Generally, majority of patients had no adverse events while the most frequent adverse events were headache and diarrhea. All these adverse events were symptomatically managed and none of those patients discontinued therapy.

Table (4): Safety of drug therapy among enrolled patients

	All patients (n= 80)
Adverse events	
Headache	10 (12.5%)
Diarrhea	5 (6.3%)
Abdominal pain	4 (5%)
Joint pain	2 (2.5%)

Data expressed as frequency (percentage).

Correlation between degree of HOMA and other variables in the study (Table 5):

It was found that HOMA had positive correlation with age, fibrosis degree by fibroScan, FIB-4 and APRI and body mass index. Other correlations were statistically insignificant.

Table (5): Correlation between HOMA and other variables in the study

	HOMA
Age (years)	**0.48 (0.02)**
HCV PCR level (u/l)	0.10 (0.34)
BMI (kg/m2)	0.19 (0.45)
Hemoglobin (mg/dl)	0.18 (0.34)
Leukocyte (103/ul)	0.11 (0.56)
Platelets (103/ul)	0.10 (0.32)
INR	0.19 (0.20)
Creatinine (mg/dl)	0.10 (0.10)
Bilirubin (mg/dl)	0.14 (0.18)
ALT (u/l)	0.24 (0.09)
AST (u/l)	0.10 (0.53)
Albumin (g/dl)	0.14 (0.18)
Fibrosis degree (Kpa)	**0.79 (< 0.001)**
FIB-4 index	**0.60 (< 0.001)**
APRI score	**0.58 (< 0.001)**
Cholesterol (mg/dl)	0.18 (0.06)
LDL (mg/dl)	0.01 (0.11)
Triglycerides (mg/dl)	0.17 (0.06)
HDL (mg/dl)	0.31 (0.11)

Data expressed as r (Correlation coefficient), *P* (significance of correlation), HOMA: homeostasis model assessment index; ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; FIB-4: fibrosis-4; LDL: low density lipoprotein; HDL: high density lipoprotein; BMI: Body mass index.

Predictors of persistence of IR after DAAs therapy (Table 6):

Based on the current study predictors for persistence IR after DAAs therapy were only body mass

index and advanced fibrosis based on either fibroScan, APRI and/or FIB-4.

Table (6): Multivariate regression analysis for persistence of IR after DAAs therapy

	Odds ratio	95% confidence interval	*P* value
Age (years)	1.34	1.23-2.35	0.43
BMI (kg/m2)	**2.64**	**1.45-4.56**	**< 0.001**
Advanced fibrosis*	**3.15**	**1.36-5.56**	**< 0.001**
Delta cholesterol	0.45	0.34-1.78	0.32
Delta LDL	1.95	1.12-2.90	0.98
Delta triglycerides	0.57	0.34-1.87	0.19
Delta HDL	0.61	0.33-1.03	0.10

BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; IR: insulin resistance; DAAs: direct acting antivirals

*****based on either fibroScan, APRI and/or FIB-4

DISCUSSION

There is paucity in the literature about effect of DAAs on lipid profile and insulin resistance among patients received these agents for chronic hepatitis C infection (CHC) and its relation to the presence of liver cirrhosis. So, this work was designed to evaluate that issue. This study examined the changes in degree of fibrosis, lipid profile and IR.

We found that mean age of all enrolled patients was 56.20 ± 6.15 years and majority (58.8%) of them were males. In accordance with the current study **Russo *et al.*** [3] studied 138 with hepatitis C infection. Mean of the patients was 58 ± 10 years and majority (61.5%) of those patients were males. In contrast, previous studies reported female predominance among their patients [10-11]. These discrepancies in sex predominance in different studies may be attributed to selection bias, sample size, different genotypes and race.

The current study revealed that there was improvement of liver enzymes (AST and ALT) from baseline to end of treatment. This was consistent with recently published study that concluded increase in serum albumin with decrease liver enzymes, bilirubin and INR after DAAs therapy [12]. In consistent with the current study, **Reddy *et al.*** [13] concluded that the recent antiviral agents were found to improve hepatic functions during short term follow up in particular increase in serum albumin. Such observations have been made during short-term follow-up in many studies as well [14-17].

In the current study, degrees of fibrosis by fibroScan in addition to FIB-4 and APRI score were significantly decreased after therapy in all patients. The percentage of improvement in the degree of fibrosis was 48.2%, 53.1% and 73.8% based on fibroScan, FIB-4 and APRI score, respectively in all study patients. This was in agreement with **Fouad *et al.*** [18] who concluded that there was a significant improvement of the LS after 12 weeks of the end of HCV antiviral therapy. Also **Elsharkawy *et al.*** [16] reported the improvement rate in fibrosis degree by fibroScan was 22% in different fibrosis stages, while it was 81.5 and 93% in FIB4 and APRI scores respectively. The data in the current study were also concordant with **Laursen *et al.*** [19] who investigated DAAs therapy effects on liver inflammation and fibrosis in patients with advanced liver disease before, during, and after successful management. Their study showed a significant decrease in liver stiffness by 20% at the end of treatment and early resolution of liver inflammation had been suggested.

Concurrently, the present results indicate that non-invasive measurements of liver fibrosis, APRI index, and FIB-4 score were gradually reduced when patients achieved SVR12 after DAA therapy, suggesting that eradication of HCV may be responsible for decreased APRI and FIB-4 score. These scores were improved significantly upon laboratory investigation owing to normalization of liver enzymes after treatment. We found that the serum level of ALT and AST were lowed at 12 weeks, but platelets count did not change significantly. Thus, long-term follow-up evaluation of liver fibrosis is still needed [19].

Thus, the post-treatment stiffness decrease can be the result of the attenuated inflammation, and/or of a decrease in fibrosis severity. Hence, this may explain the marked improvement of the APRI and FIB4 scores, which were impacted by the marked improvement of the ALT and AST after end of therapy as reported by current study and which is agreed by **Fouad *et al.*** [18].

In the current study, we found that cholesterol, triglycerides and low density lipoproteins were significantly higher after therapy. These changes were noticed among all patients. These results were also consistent with previous reports of other authors [11,15,20-21]. The direct link between HCV and host lipoproteins explicates the significant interrelationship between HCV and host lipid metabolism, as proved both in vitro and in clinical studies [22]. The rapid and sustained changes in cholesterol, LDL and TG are most likely a result from the increased delivery of lipids from the liver to blood circulation after viral eradication by DAA treatment [11]. This effect may be attributed to a reversal of the impact of HCV replication on hepatic lipid metabolism [23].

In our study, the changes in lipid profile after DAAs were atherogenic, which might represent a predictor for cardiovascular risk. This may justify long-term monitoring of lipid parameters. It was reported that central arterial stiffness and lipid profiles in patients with chronic HCV worsen immediately after viral eradication by DAA treatment and persist at one year. Worsening of lipid profiles after DAA treatment

contributes to central arterial stiffness in this patient population and persists long term [11].

Notably, the negative effect on the lipid profile may be at least partially compensated by the decrease of IR, which itself should reduce the cardiovascular (CV) risk [11]. Markedly, our data are not enough to establish any possible impact of DAA on the CV global risk. However, evaluating the whole lipid profile at baseline and after the end of DAA treatment would be informative. Patients who have one or more classical CV risk factors and are treated with DAA might be monitored for an accurate stratification of CV risk [24].

The HCV infection showed a complex relationship with IR. IR appears in the early stages of HCV infection and increases the rate and the progression of hepatic fibrosis through compensatory hyperinsulinemia, hepatic stellate cells increment, and type 1 collagen proliferation [25].

In our study, baseline analysis confirmed the association between IR and HCV, with almost two-thirds (68.7%) of the entire cohort having IR. As expected, in accordance with a recent study by **Adinolfi *et al.*** [26] baseline IR did not affect efficacy of DAAs based antiviral therapy, with almost all the patients achieving SVR.

During follow up we found that percentage of reduction of HOMA was 16.1%. Also, we found that there was insignificant difference between both groups as regard percentage of improvement in the HOMA (49% vs. 34%).

This finding has been also confirmed by the positive correlation between HOMA and all the fibrosis indices used in the current study. We found that not only was the degree of fibrosis, but also HOMA positively correlated with BMI. With multivariate regression analysis; degree of fibrosis and high BMI were predictors for IR after DAAs therapy. In line with the study, **Gaggini *et al.*** [27] reported that IR was associated with more severe liver disease and higher degrees of fibrosis. They focused on the associations between degree of liver fibrosis (as an index of severity of chronic liver disease) and IR indexes, i.e., HOMA, which reflects impaired insulin action in glucose metabolism. While **Russo *et al.*** [3] found that obesity and degree of fibrosis were predictors for IR at baseline but they also concluded that the degree of fibrosis had no significant effect on persistence of IR after therapy as the presence of baseline cirrhosis was not associated with a lower probability of IR reversibility. In accordance with the findings of **Adinolfi *et al.*** [26] high BMI significantly reduced the probability of IR improvement. Elevated peripheral resistance to insulin activity is one of the primary causes of IR in HCV patients, and it is induced by the pro-inflammatory cytokine milieu induced by chronic hepatic injury.

In the current study, all patients achieved SVR. Generally, majority of patients had no adverse events while the most frequent adverse events were headache (12.5%), and diarrhea (6.3%). All these adverse events were symptomatically managed and none of those patients discontinued therapy. These results were consistent with many reported studies about efficacy and safety of DAAs in therapy of HCV infection as they have excellent tolerability and high efficacy for HCV therapy in clinical practice, resulting in higher SVR rates, fewer side effects and shorter treatment courses than interferon-based combination therapy [3,15,28].

The present study has some limitations. Firstly, relative small sample size. Secondly, the follow-up was relatively short, and a longer observation time is probably needed to properly assess the effect of HCV eradication on degree of fibrosis. Thirdly; this short term follow up isn't sufficient to assess long term follow up of IR and lipid profile in such patients. Finally, our data should be interpreted with caution in more advanced patients that were not adequately represented in the present study.

CONCLUSION

Hepatitis C virus eradication following DAAs treatments is safe and effective in viral eradication. Also, viral eradication with DAAs is associated with a progressive reduction of insulin resistance, and also in patients with advanced liver disease.

Nevertheless, IR can persist after the achievement of sustained virological response, especially in patients with high body mass index. The lipid changes in this study were interesting to the extent that long-term follow-up is strongly warranted for a better clarification of the possible role of chronic HCV infection as a potential risk for cardiovascular risk.

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Author contribution: Authors contributed equally in the study.

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