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Effect of achieving sustained virological response with direct-acting antiviral agents on glycemic control in diabetic patients with chronic hepatitis C infection

Mohamed El-Kassas[1*], Runia El-Folly[2], Maram Aboromia[3], Heba Aly[4], Mohamed Bahgat[2] and Mostafa Hamed[2]

Abstract

Background: Hepatitis C virus (HCV) is a significant cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma worldwide. Liver disease is not the only problem caused by chronic HCV infection; many extrahepatic complications, such as insulin resistance, can be associated with HCV infection. The aim of this study was to assess the effect of achieving a sustained virological response after treatment with directly acting antiviral drugs on insulin resistance in patients with chronic HCV infection.

Results: This prospective study was conducted on 46 HCV patients with type 2 diabetes mellitus who received directly acting antiviral drugs for HCV infections. Fasting insulin, fasting blood glucose, and lipid profiles were assessed in all patients at three time points: before treatment, at the end of treatment, and 12 weeks after the end of treatment. Despite using three different directly acting antiviral drug regimens, all patients achieved a sustained viral response, regardless of the regimen used. the Homeostatic Model Assessment for Insulin Resistance decreased significantly at the end of treatment; however, when recalculated at week 12 after end of treatment, the reduction of the Homeostatic Model Assessment for Insulin Resistance was not significant compared to the baseline levels. Total cholesterol and low-density lipoproteins increased at the end of treatment and continued to increase for 12 weeks after the end of treatment.

Conclusions: Improvements in insulin resistance and glycemic control were noted in HCV patients at the end of treatment with directly acting antiviral drugs; this effect was also apparent after 12 weeks. An increase in the levels of total cholesterol and low-density lipoprotein can be expected after treatment with directly acting antiviral drugs.

Keywords: Diabetes mellitus, Directly acting antivirals, Hepatitis C virus, Insulin resistance, HOMA-IR

Background

Infection with hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [1]. Liver disease is not the only problem caused by chronic HCV infection; many extrahepatic complications, such as insulin resistance (IR), are associated with HCV infection [2]. Some reports have suggested that chronic HCV patients have a high prevalence of metabolic disorders [3]. Modifications to these disorders can be expected after viral eradication [4]. As a result of these metabolic imbalances, HCV increases the incidence of type 2 diabetes mellitus (T2DM) in susceptible individuals, mainly through the development of IR [5]. Although HCV is primarily a hepatic infection,

*Correspondence: m_elkassas@hq.helwan.edu.eg
[1] Department of Endemic Medicine, Faculty of Medicine, Helwan University, Cairo, Egypt
Full list of author information is available at the end of the article

insulin sensitivity is compromised in chronic HCV patients in the absence of metabolic syndrome [6]. One possible explanation for this phenomenon is that infected hepatocytes might release mediators that provoke endocrine effects at extrahepatic locations, such as skeletal muscle. The interaction between the metabolic effects of HCV and host-related genetic and environmental factors can result in worsening of IR, ending in the development of T2DM [4, 7]. Once it has developed, T2DM hastens the development of liver injury, leading to an upsurge in HCC risk, and worsening the response to antiviral treatments [5]. The risk of cardiovascular disease increases because of factors including possible direct viral effects, the presence of existing systemic chronic inflammatory conditions, and possible interactions with metabolic disorders [8].

There have been significant changes in HCV management following the discovery of the oral, interferon-free, direct-acting antivirals (DAAs) that replaced the previous interferon-based standard of care therapy [9, 10]. Because of the association between HCV and the development of IR and T2DM, it was postulated that the clearance of HCV may cause a decrease in T2DM incidence. Successful HCV treatment should also improve clinical outcomes in T2DM patients [11]. Studies are needed to investigate the impact on insulin signaling pathways of treating HCV with DAAs and the possibility of improvement of glucose metabolism.

Methods

In the period between December 2017 and December 2018, 46 patients with confirmed chronic HCV infection and IR were enrolled in the study. Those patients were recruited from the New Cairo Viral Hepatitis Treatment unit, one of the specialized viral hepatitis treatment facilities affiliated to the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) [12]. They were eligible to receive HCV antiviral therapy according to the standardized protocol issued by NCCVH [13, 14]. The main criteria for inclusion were: age between 18 and 75, HCV RNA positivity, and having IR (HOMA test) > 2.5 [15]. Criteria for exclusion included total serum bilirubin > 3 mg/dl, serum albumin < 2.8 g/dl, INR $\geq$ 1.7, hemoglobin < 10 g/dl, platelets < 50,000/mm^3, HCC or extrahepatic malignancy, pregnancy, and the presence of other liver diseases such as HBV or autoimmune hepatitis.

Patients had a complete history taken, and had a thorough clinical examination and anthropometric evaluation, including measurement of weight and height, and calculation of body mass index (BMI). Laboratory investigations included fasting blood sugar (FBS), fasting insulin (FI), and the calculation of the homeostatic model assessment of IR (HOMA-IR = (FPI $\times$ FPG)/22.5) [16]. Lipid profiles, hepatitis markers (HCV antibody, HBsAg, and HCV RNA quantitative PCR), kidney function tests, and alpha-fetoprotein were also assessed. Abdominal ultrasound examinations were performed for all patients. These investigations were performed at three time points: at baseline, at the end of treatment (EOT), and 12 weeks after the EOT.

Statistical analysis

The SPSS statistical package was used for data analysis. Data were expressed as mean $\pm$ SD for parametric data, and median $\pm$ interquartile range for non-parametric data. Means were compared using paired *t* tests and repeated measure ANOVA tests, while for non-parametric values, Wilcoxon rank, and Friedman tests were used. *P* values less than 0.05 were considered to be statistically significant, and $P <= 0.01$ was considered highly significant.

Results

The mean age of the study patients was 55.89 years, and 27 of them (59%) were females. Most of the study subjects were overweight or had early obesity, however there were no significant changes in the mean BMI during the phases of the study. Ten patients (22%) were hypertensive, and two patients (0.04%) had hypothyroidism and were receiving thyroxin. Regarding DM management, most of the included patients did not use insulin (about 61%) but 39% of patient needed insulin in their DM management. Also, insulin sensitizers were not used in DM management.

Patients were assigned to groups receiving one of three different DAA regimens, according to the treatment availability and the protocol used. The combination of sofosbuvir/daclatasvir (SOF/DAC) with or without ribavirin (RBV) was the most frequently used regimen (63% of patients). The other two groups received a fixed-dose combination of ombitasvir/paritaprevir-ritonavir (OMB/PAR/RIT) with RBV (30%), or sofosbuvir/ledipasvir (SOF/LED) (7%).

An indicator of insulin resistance, HOMA-IR, was significantly decreased at the EOT compared to baseline levels [HOMA-IR: 5.25 (3.35–7.65) vs. 3.74 (2.59–5.45), $P = 0.001$]. However, when baseline HOMA-IR levels were compared to those reported 24 weeks post-treatment, there was a tendency toward a decrease, but the difference was not statistically significant [HOMA-IR: 5.25 (3.35–7.65) vs. 4.83 (3.72–6.66), $P = 0.114$]. FI levels decreased significantly directly after treatment [14.75 (9.50–22.60) vs.10.35 (8.60–16.00); $P = 0.000$]. The FI level 12 weeks after treatment was lower than the starting level, but was not statistically significant [10.35 (8.60–16.00) vs. 13.75 (9.00–18.20); $P = 0.045$]. When

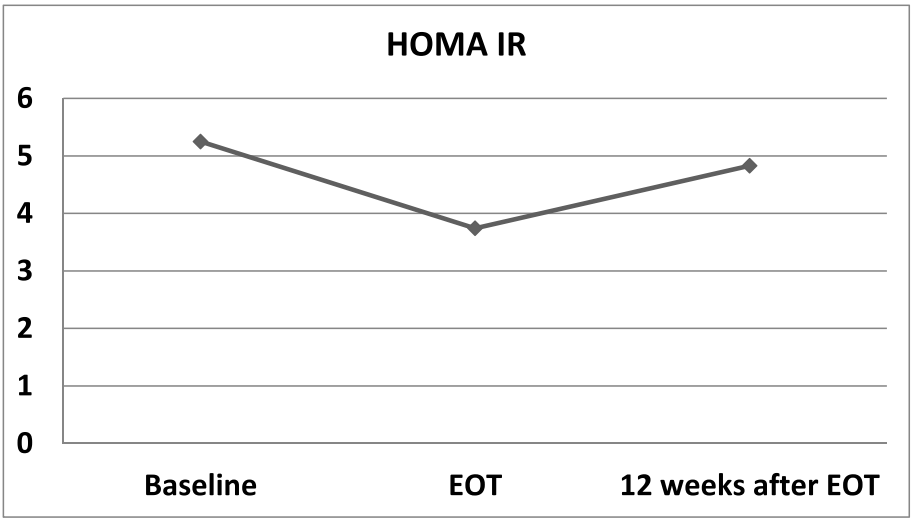

Fig. 1 Changes in HbA1c over the course of the study

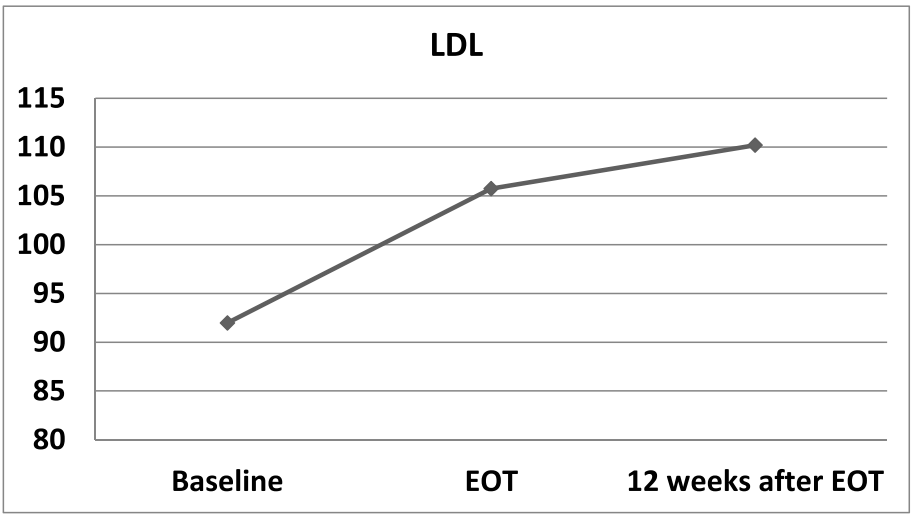

Fig. 2 Changes in serum LDL over the course of the study

comparing HbA1c levels at baseline with those at the EOT, a significant decrease was noticed (7.56 ± 1.01 vs. 7.00 ± 1.52 2; $P = 0.013$), reflecting the effect of IR on the control of plasma glucose level (Fig. 1). However, when comparing the level at the EOT to that at 12 weeks after the EOT, a significant increase was reported (7.00 ± 1.52 vs. 7.57 ± 1.17; $P = 0.000$). Lipid metabolism was significantly influenced by HCV treatment (Fig. 2). Serum cholesterol and low-density lipoproteins (LDL) levels increased significantly after the EOT (156.98 ± 43.41 vs. 172.37 ± 36.64; $P = 0.002$, and 91.97 ± 36.09 vs. 105.73 ± 30.64; $P = 0.007$, respectively), and this effect persisted at 12 weeks after EOT (156.98 ± 43.41 vs. 173.89 ± 42.62; i= 0.003, and 91.97 ± 36.09 vs. 110.19 ± 33.50; $P = 0.000$, respectively). The detailed changes in the studied parameters throughout the study checkpoints are listed in Table 1.

Discussion

HCV infection can be associated with extrahepatic manifestations, such as IR [17, 18]. The pathophysiology of IR associated with HCV infection is controversial. Advanced fibrosis and liver cirrhosis can lead to metabolic derangements, which, in turn, result in IR [19]. IR is associated with specific HCV genotypes, G1 and G4, in which there

Table 1 Change of parameters throughout the study checkpoints

Laboratory results		Baseline	EOT	12 weeks after EOT	Comparing 3 timelines			Comparing Baseline to EOT			Comparing Baseline to 12 weeks after EOT			Comparing EOT to 12 weeks after EOT		
		No. = 46	No. = 46	No. = 46	Test value	*P* value	Sig	Test value	*P* value	Sig	Test value	*P* value	Sig	Test value	*P* value	Sig
F Ins	Median (IQR)	14.75 (9.50–22.60)	10.35 (8.60–16.00)	13.75 (9.00–18.20)	13.978[b]	0.001	**HS**	− 3.534[d]	0.000	**HS**	− 2.009[d]	0.044	**S**	− 2.005[d]	0.045	**S**
	Range	2.8–35	3.1–31.4	1.9–33												
FBS	Mean ± SD	154.08 ± 42.95	150.23 ± 74.40	157.95 ± 55.62	0.584[a]	0.528	**NS**	0.487[c]	0.629	**NS**	− 0.739[c]	0.463	**NS**	− 0.972[c]	0.336	**NS**
	Range	90–286	78–392	95–360												
HOMA	Median (IQR)	5.25 (3.35–7.65)	3.74 (2.59–5.45)	4.83 (3.72–6.66)	17.522[b]	0.000	**HS**	− 3.436[d]	0.001	**HS**	− 1.579[d]	0.114	**NS**	− 2.212[d]	0.027	**S**
	Range	0.92–24.72	0.64–30.39	0.47–25.42												
2hpp	Mean ± SD	244.28 ± 55.16	235.04 ± 85.30	246.33 ± 69.81	0.802[a]	0.448	**NS**	0.894[c]	0.376	**NS**	− 0.230[c]	0.819	**NS**	− 1.229[c]	0.225	**NS**
	Range	156–398	124–535	145–397.8												
HbA1c	Mean ± SD	7.56 ± 1.01	7.00 ± 1.52	7.57 ± 1.17	5.980[a]	0.006	**HS**	2.592[c]	0.013	**S**	− 0.052[c]	0.958	**NS**	− 3.911[c]	0.000	**HS**
	Range	5.1–9.63	4.5–11	5.6–11.3												
T Chol	Mean ± SD	156.98 ± 43.41	172.37 ± 36.64	173.89 ± 42.62	7.169[a]	0.002	**HS**	− 3.235[c]	0.002	**HS**	− 3.128[c]	0.003	**HS**	− 0.329[c]	0.744	**NS**
	Range	77–276	95–253	89–266												
TGs	Mean ± SD	105.63 ± 33.80	110.15 ± 33.31	112.65 ± 38.49	1.554[a]	0.217	**NS**	− 1.092[c]	0.281	**NS**	− 1.706[c]	0.095	**NS**	− 0.650[c]	0.519	**NS**
	Range	50–218	66–215	31–230												
HDL	Mean ± SD	44.15 ± 11.13	44.97 ± 7.30	43.22 ± 9.94	0.647[a]	0.520	**NS**	− 0.488[c]	0.628	**NS**	0.613[c]	0.543	**NS**	1.241[c]	0.221	**NS**
	Range	23–73	27–61	20–70.4												
LDL	Mean ± SD	91.97 ± 36.09	105.73 ± 30.64	110.19 ± 33.50	8.908[a]	0.000	**HS**	− 2.831[c]	0.007	**HS**	− 4.064[c]	0.000	**HS**	− 1.079[c]	0.286	**NS**
	Range	36–201.2	47–178.8	44–194.6												

P value > *0.05* non-significant, *P value* < *0.05*: significant, *P value* < *0.01* highly significant

[a] Repeated measure ANOVA test,

[b] Friedman test

[c] Paired *t* test

[d] Wilcoxon rank test

is a direct correlation between viremia and IR levels, and the development of type II DM [20]. This finding was one of the main drivers behind conducting this study, as G4 HCV is widespread in Egypt [13].

In the current study, HOMA-IR levels were significantly decreased at the EOT compared to baseline levels; however, this was not the case when baseline levels were compared with those reported at 24 weeks post-treatment. In the latter situation, there was a tendency toward a decrease, but the decrease was not statistically significant. This phenomenon has previously been reported in a previous research where obesity did not affect the results [21] and could be partly explained by the tight control of diet, and hence better glycemic control, taken by patients with diabetes during the HCV treatment period. The finding of improved IR after HCV treatment was common in most reports discussing the subject, with only a few studies reporting different results. When DAAs are first used, some reports suggested that the SOF/LED combination could worsen IR. raising the risk of hyperglycemia [22, 23]. However, later studies confirmed the acceptable safety margins of DAAS [24]. In a study that involved non-diabetic Egyptian patients who received DAAs, the mean FBS improved at the EOT, indicating better glycemic control; however, HOMA-IR was significantly increased at the EOT, indicating an increase in insulin resistance [25]. In contrast to previous findings, several studies produced results very similar to those of the present study with respect to the effect of treatment with DAAs on IR. Adinolfi et al. reported a reduction in HOMA-IR, increased insulin sensitivity, decreased insulin secretion, and reduction of serum glucose and insulin levels after treatment with DAAs in non-diabetic patients with HCV G1 and advanced liver fibrosis (F3-4) [26].

HOMA-IR was significantly lower at the end of DAAs treatment with SIM/SOF in an Egyptian cohort of non-diabetic naïve patients with different grades of fibrosis and G4 HCV infection [27]. In another study from Egypt, pretreatment HOMA did not differ in responders and non-responders to DAAs ($P = 0.098$), while IR decreased significantly in responders compared to those who did not achieve a sustained virologic response (SVR) ($P < 0.0001$), and HOMA improved significantly in patients with SVR than in non-responders ($P = 0.001$) [28]. These results indicate that the improvement of IR after viral eradication could be reflected in the blood glucose levels, and a parallel improvement in glycemic control can be anticipated. It is also possible that the hypoglycemic agents used should be adjusted to avoid fluctuations in the plasma glucose levels of patients following successful antiviral therapy.

In our study, HbA1c levels showed a significant decrease at EOT compared to pretreatment levels. Reductions in FBS and HbA1c have also been noted after DAA therapy in many studies [21, 29, 30]. This observation suggests a need for close monitoring for a possible reduction in anti-diabetic drugs, especially insulin and sulfonylurea, to avoid hypoglycemic events. This approach has also been suggested by other studies [31]. The need for escalating anti-diabetic therapy during HCV treatment has been reported by other studies [32]. Similar improvements in glycemic control were demonstrated, even before the era of DAAs; however, these studies were confounded by treatment-induced weight loss, a common side effect of interferon [33, 34].

Previous studies have suggested that patients with chronic HCV infection had significantly lower total cholesterol and triglyceride levels compared with healthy controls matched for age, sex, and BMI [35–37]. In the present study, both total cholesterol and LDL levels increased significantly after the EOT compared to baseline levels, while HDL levels did not show a significant change. Some studies have suggested a need for repeated measurements of serum lipid levels in patients who responded to antiviral therapy, as viral elimination may uncover some patients with previously undervalued cardiac risk [38]. An increase in serum LDL early in the course of antiviral therapy (SOF/RBV) was noted in patients who cleared the virus [3]. Similarly, an interferon-free antiviral treatment study showed a rapid increase in total LDL and HDL cholesterol levels after 4 weeks, with a rapid decline in patients who did not achieve a SVR [39]. This observation was confirmed by an Egyptian study showing a significant elevation of serum cholesterol and LDL levels after the end of a course of SOF/SIM treatment [27].

Data from literature explained these alterations in the lipid profile after HVC treatment by the fact that HCV affects the expression of some proteins involved in the lipid metabolism. It was shown that HCV increases the expression of LDL receptors on the membrane of the hepatocytes allowing more LDL molecules to enter. On the other hand, it decreases the expression of the enzyme proprotein convertase subtilin/Kexin type 9 (PCSK9) which is responsible for LDL receptor degradation. Consequently, these effects can be reversed causing an increase in plasma LDL after successful treatment of HCV [40].

Conclusions

Improvements in IR and glycemic control were noted in HCV patients at the EOT with DAAs; however, this effect was not observed 12 weeks after the commencement of treatment. An increase in the levels of total

cholesterol and LDL can be expected after treatment with DAAs.

Abbreviations
DAAs: Direct-acting antivirals; DAC: Daclatasvir; HCV: Hepatitis C virus; HBV: Hepatitis B virus; IR: Insulin resistance; MELD: Model for end-stage liver disease; OMB/PAR/RIT: Ombitasvir/paritaprevir-ritonavir; SOF: Sofosbuvir; RBV: Ribavirin; T2DM: Type 2 diabetes mellitus.

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Authors' contributions
MH, MA, and MEK conceptualized the idea and study design. MB, MA, and RF were responsible for data acquisition. HA performed the laboratory analysis. All authors shared in drafting the manuscript and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in this study involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Research Ethics Committee (REC) for human subject research at the Faculty of Medicine, Ain Shams University, in December 2016 (serial: 343/2016). Written informed consent was obtained from all individual participants included in the study.

Consent for publication
All authors agree to the journal rules for publications.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Endemic Medicine, Faculty of Medicine, Helwan University, Cairo, Egypt. [2]Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [3]Department of Endocrinology, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [4]Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

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