Impact of sustained virological response on metabolic disorders in diabetic chronic hepatitis C virus patients after treatment with generic sofosbuvir and daclatasvir

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Objectives To evaluate the effect of generic sofosbuvir and daclatasvir (SOF/DCV) treatment on the glycemic state and insulin resistance as well as lipid profiles of those who achieved sustained virological response (SVR) in diabetic chronic hepatitis C virus (CHC) patients.

Methods We retrospectively reviewed 114 CHC patients with evidence of type 2 diabetes that were treated with generic SOF/DCV between May 2016 and August 2017. Baseline demographic and laboratory data were recorded. At 12-week post end of therapy (SVR12), glycemic state and insulin resistance as well as lipid profiles were re-evaluated and compared with baseline.

Results A total of 98 diabetic CHC patients were finally included and were responders. A significant decline in the glycemic state as well as Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values ($P \leq 0.0001$) was observed, but HOMA-S showed a statistically significant increase ($P \leq 0.0001$) at SVR12 in comparison to baseline values. Also, a significant increase in serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol levels was observed at SVR12 compared to baseline, but serum triglycerides levels showed a significant decrease. Logistic regression showed that the higher baseline HOMA-IR was a significant predictive variable of a decrease ≥20% of HOMA-IR, while higher baseline HOMA-IR and baseline triglycerides emerged as the only significant predictors of the Δ increase LDL-C level at SVR12.

Conclusion SOF/DCV-based therapy led to an improvement of glycemic state associated with a global worsening of lipid profile. Further studies are strongly warranted to evaluate the cardiovascular balance between amelioration of insulin resistance and negative changes of the lipid profile. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Hepatitis C virus (HCV) infection is a complex disease that is associated with clinically significant metabolic alterations, including glucose and lipid metabolism [1,2]. The mechanisms of these metabolic alterations are triggered by several components such as the host innate metabolic profile, genetic profile of the HCV, and stage of liver disease. Moreover, there are increasing reports indicating an association between HCV infection and type 2 diabetes mellitus (T2DM) that affects one-third of individuals with chronic HCV infections [3,4]. T2DM is characterized by insulin resistance, increased hepatic glucose metabolism, and a defect in insulin secretion. Additionally, patients with HCV and T2DM have more rapid progression of chronic liver disease, worse clinical outcomes including higher rates of liver cirrhosis, decompensation, and hepatocellular carcinoma (HCC) and increase the risk for liver failure and mortality [5–7].

Also, HCV is a unique virus that utilizes host lipid metabolism for its life cycle and replication. It depends on very low-density lipoproteins (LDLs) to infect hepatocytes and interfere with the production of free fatty acids, and increasing steatosis in the host. Therefore, HCV infection is associated with downregulation of lipid metabolism which is characterized by decreased serum lipoprotein [low-density lipoprotein cholesterol (LDL-C)] and total cholesterol (TC), predisposing to dyslipidemia, and progression of the liver disease in the form of hepatic steatosis and advanced fibrosis [8] that can lead to HCC development [9].

In the historical era of interferon (IFN)-based therapy, T2DM and insulin resistance were associated with a decreased rate of sustained virological response (SVR), regardless of viral genotype [10], but alterations of glucose metabolism associated with HCV infection were reported to be reversible after the achievement of SVR [11]. Concerning the effect of IFN on lipids, IFN itself affects the regulation of serum lipid concentrations, directly and indirectly modulating lipid metabolism in hepatocytes, adipocytes, and enterocytes [12]. Therefore, the clearance of HCV achieved by IFN-based therapy is known to ameliorate disturbed lipid metabolism [13]. The recent

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introduction of direct-acting antiviral agents (DAAs) offers an opportunity for global HCV eradication due to the increase in SVR rates with short treatment durations and low rates of adverse events. SVR is associated with a reduction in hepatic decompensation, variceal bleeding, HCC incidence, overall liver- and nonliver-related mortality [14]. Glucose and lipid abnormalities do not appear to be predictive of treatment outcomes after DAAs therapy [15]. Therefore, it may be of particular interest to know whether HCV eradication may revert metabolic derangements in diabetic chronic HCV patients (CHC) and its impact on clinical outcome in these patients.

This study aimed to evaluate the effect of generic sofosbuvir and daclatasvir (SOF/DCV) treatment on the glycemic state and insulin resistance as well as lipid profiles of those who achieved SVR in diabetic CHC patients.

Materials and methods

Patient population

This retrospective observational cohort study comprised 114 chronic HCV patients with evidence of type 2 diabetes that were treated with generic SOF/DCV for either 12 or 24 weeks between May 2016 and August 2017. Eligible patients were aged 18 years or older with seropositivity of HCV antibodies and detectable HCV RNA, treatment-naïve or treatment-experienced, any BMI and stage of hepatic fibrosis as assessed by Fibrosis-4 (FIB-4) calculation. The exclusion criteria were non-HCV-related causes for liver disease, for example, HBV co-infection, HIV infection, the presence of decompensated liver disease, a diagnosis of active HCC, or extrahepatic malignancy at baseline, and patients on lipid-lowering agents. Additionally, failure to achieve SVR, loss of follow-up, or missing clinical information represented exclusion criteria for this study.

Diabetes mellitus was diagnosed by a previously established diagnosis of diabetes mellitus, currently taking any form of oral hypoglycemic/insulin or two consecutive visits with either fasting glucose level ≥126 mg/dl (7.0 mmol/L) or hemoglobin A1c (HbA1c) ≥6.5%, or random plasma glucose ≥200 mg/dL (11.1 mmol/L) in persons with symptoms of hyperglycemia or hyperglycemic crisis [16].

The FIB-4 index was used to estimate the liver stiffness before treatment with a cutoff value of <1.45 indicative of non-significant fibrosis (<F2), whereas a cutoff value of >3.25 indicative of cirrhosis (F4) [17].

Patients were treated with generic SOF in a dose of 400 and 60 mg of generic DCV, both once daily, either for 12 or 24 weeks in agreement with the national protocol issued by the HCV treatment program in Egypt. The treatment duration either for 12 or 24 weeks depends on whether the patients were either 'easy-to-treat group' or 'difficult-to-treat group'. The 'easy-to-treat group included those who were treatment-naive, had no advanced fibrosis or cirrhosis (clinically and ultrasonographic examination) with FIB-4 <3.25, albumin ≥3.5 mg/dl, total serum bilirubin <1.2 mg/dl, INR <1.2, and platelet count ≥150 000 mm^3, while the 'difficult-to-treat group included those who were treatment-experienced, had advanced fibrosis and cirrhosis (clinically and ultrasonographic examination) with FIB-4 ≥3.25, albumin <3.5 mg/dl, or total serum bilirubin ≥1.2 mg/dl, or INR ≥1.2, or platelet count <150 000mm^3. None of these patients received ribavirin (RBV). The virological efficacy in these patients was determined by the negativity of serum HCV RNA 12 weeks after the end of treatment (SVR12).

Demographic data and laboratory tests

The demographic data including gender, age, BMI (kg/m^2), and type of received antidiabetic agents at the initiation of therapy were collected. At baseline and 12 weeks after the end of therapy (EOT) (SVR12), the diabetic CHC patients were evaluated for hematological, and biochemical parameters as follows: complete blood count, total serum bilirubin, serum transaminases (ALT and AST), serum albumin, prothrombin concentration), serum creatinine, and alpha-fetoprotein (AFP) that were measured using standard techniques. In addition, metabolic parameters including serum lipids [triglycerides, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C)], fasting plasma glucose (FPG), 2 h postprandial blood glucose (2h-PPBG), hemoglobin A1c (HbA1c), and fasting serum insulin were also measured at baseline and SVR12.

HOMA was used to evaluate insulin resistance and β-cell function by the following formulas at baseline and SVR12: HOMA-IR = ([fasting glucose (mg/dl) × fasting insulin (mIU/L)]/405); HOMA-β% = [360 × fasting insulin (mIU/L)]/[fasting glucose (mg/dl)] – 63); and HOMA-S% = 1/log [fasting insulin (mIU/L)] + log [fasting glucose (mg/dL)]. The HOMA-IR cutoff above 1.9 indicates insulin resistance [18].

Moreover, improvement of insulin resistance was defined as a reduction of HOMA-IR within reference ranges, or a decrease ≥20% was observed after treatment compared to baseline.

Written informed consent was obtained from each patient before receiving treatment. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the faculty of Medicine, Cairo University.

Statistical analysis

All statistical analyses were carried using STATA 15.1 Copyright 1985-2017 StataCorp LLC. Descriptive statistics were done and categorical variables were expressed as frequencies (%) while numerical data expressed as median (interquartile range) or mean (SD) according to normality. A comparison between different groups was done using the Chi-squared test for the categorical variables and the Kruskal–Wallis rank test for the numerical variables. Logistic regression analysis was done to determine baseline predictive variables associated with a decrease ≥20% of HOMA-IR and Δ increase LDL-C value at SVR12. The P value <0.05 was defined as statistically significant.

Results

Of the 114 chronic HCV patients receiving generic SOF/DCV for either 12 or 24 weeks, 16 patients were excluded because they failed to achieve SVR (n = 8), discontinued their treatment (n = 4), or lost follow-up (n = 4). Therefore, the remaining 98 diabetic CHC patients fulfilled the inclusion criteria and were included in the final statistical

analysis. The baseline clinical characteristics of these patients are listed in Table 1. The mean age was 51.54 years with female predominance (55.1%). Their mean BMI was 29.4 (3.5) kg/m^2. All diabetic patients were HCV treatment-naïve (100%) and 32.7% of them were cirrhotic. All enrolled patients completed either 12 or 24 weeks of generic SOF/DCV therapy and had a minimum follow-up of 12 weeks after the EOT. They had undetectable HCV PCR at EOT and all patients achieved SVR12. The baseline mean values of FPG, HbA1c, and serum fasting insulin were 102.7 (21) mg/dl, 7.05 (1.08)%, and 16.51 (1.94) (mIU/L), respectively. In addition, the baseline median values of HOMA-IR, HOMA-β, and HOMA-S were 4.32 (3.42–5.63), 119.63 (98.5–209.4), and 0.35 (0.32–0.36), respectively. All included patients had insulin resistance at baseline HOMA-IR ≥1.9. Antidiabetic treatment was oral hypoglycemic agents in 43 (43.9%) patients and insulin in 11 (11.2%) patients; both insulin and oral hypoglycemic agents in 44 (44.9%) patients. Also, the baseline mean values of serum triglycerides, total cholesterol (TC), LDL-C, and HDL-C were 139.44 (36.44), 131.8 (17.1), 76.03 (13.3), and 37.03 (6.5) mg/dl, respectively.

Twelve weeks after the EOT, a significant decrement of serum fasting glucose ($P = 0.0002$), insulin levels ($P \leq 0.0001$), and HbA1c levels ($P \leq 0.0001$) was observed; similarly, a significant reduction of median HOMA-IR value ($P \leq 0.0001$) was observed, besides a decrease of HOMA-β was observed with no statistical significance ($P = 0.4$), but HOMA-S showed a statistically significant increase ($P \leq 0.0001$) in comparison to baseline values. Overall, 5.1% (5/98) of patients had HOMA-IR <1.9, while 94.9% (93/98) of patients had HOMA-IR ≥1.9. Moreover, 76.5% (75/98) of patients showed a decrease ≥20% in HOMA-IR levels, while 23.5% (23/98) patients showed an increase in HOMA-IR levels after the achievement of SVR12. As expected, a significant decrease in serum transaminases (AST and ALT) ($P \leq 0.0001$), total serum bilirubin ($P \leq 0.0001$), and FIB-4 (<0.0001) also occurred, while nonsignificant changes in serum albumin, platelet count, and AFP were noted ($P = 0.2$, 0.98, and 0.9, respectively) as shown in Table 2.

After HCV clearance, a significant increase in serum TC, LDL-C, and HDL-C levels was observed at SVR12 with respect to baseline, but serum triglycerides levels showed a significant decrease after HCV clearance as shown in Table 2. Regarding the changes in LDL-C post-treatment, we have 60 (61.2%) patients with increase in LDL-C, 35 (35.7%) patients showed a decline in LDL-C, and 3 (3.1%) patients who had no change in LDL-C.

Subgroup analysis for the changes in glucose abnormalities and lipid profiles according to the hepatic fibrosis stage before and after HCV clearance was shown in Table 3.

Concerning the baseline predictive variables for improvement of HOMA-IR as a decrease ≥20% at SVR12 compared to baseline, higher baseline HOMA-IR was found to be a significant predictive variable of improvement as shown in Table 4. On the other hand, at the multivariate analysis, higher baseline HOMA-IR and baseline triglycerides emerged as the only significant predictors of the Δ increase LDL-C level at SVR12 as shown in Table 5.

Table 1. Baseline characteristics of the studied population ($n = 98$)

Parameters	Mean (SD)
Age (years)	51.54 (6.91)
Gender	
Male/female	44 (44.9%)/54 (55.1%)
BMI (kg/m^2)	29.4 (3.5)
Antidiabetic agents	
OHG	43 (43.9%)
Insulin	11 (11.2%)
Both insulin and OHG	44 (44.9%)
Baseline laboratory data	
Platelet count (10^3/mm^3)	195.53 (122.41)
ALT (U/L)	50.18 (39.34)
AST (U/L)	47.54 (25.57)
Total bilirubin (mg/dl)	2.02 (1.27)
Albumin (g/dl)	3.44 (0.90)
Prothrombin concentration, median (IQR)	62.5 (47–92)
AFP (ng/ml)	12.95 (5.61)
Creatinine (mg/dl)	1.10 (0.32)
Blood glucose parameters	
Fasting blood glucose (mg/dl)	102.7 (21)
2 h postprandial blood glucose (mg/dl)	187.22 (44.47)
HbA1c (%)	7.05 (1.08)
Fasting insulin (mIU/l)	16.5 (1.94)
HOMA-IR, median (IQR)	4.32 (3.42–5.63)
HOMA-IR (<1.9 and ≥1.9) (*n*, %)	0/98 (100%)
HOMA-β, median (IQR)	119.6 (98.5–209.4)
HOMA-S, median (IQR)	0.35 (0.32–0.36)
Lipid profile	
Triglycerides (mg/dl)	139.44 (36.44)
Total cholesterol (mg/dl)	131.8 (17.1)
LDL-cholesterol (mg/dl)	76.03 (13.3)
HDL-cholesterol (mg/dl)	37.03 (6.5)
Stage of hepatic fibrosis by FIB-4 (*n*, %)	
Noncirrhotic	66 (67.3%)
Cirrhotic	32 (32.7%)
FIB-4, median (IQR)	2.11 (1.01–3.73)

Unless otherwise stated numerical data are expressed as mean (SD) or median (IQR).

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis 4 score; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Discussion

Metabolic derangements, including insulin resistance and dyslipidemia, are emerging causes of morbidity and mortality at a global level. CHC is another major public health issue. Besides the chronic liver diseases, HCV is associated with extrahepatic manifestations such as disordered glucose and lipid metabolism that contributes to disease progression and influences response to therapy. However, it was reported that metabolic complications of HCV may improve after treatment-induced eradication of HCV (SVR), implicating a causative role of ongoing viral replication [19], which ultimately leads to an improvement of patients' survival and provides a significant public health benefit.

Therefore, this study aimed to evaluate the effect of generic SOF/DCV on the changes in the glycemic state and insulin resistance as well as lipid profiles of those who achieved SVR in diabetic CHC patients. Also, we evaluated insulin resistance using various equations such as HOMA-IR, the most commonly used, which depends on the fasting serum glucose and insulin levels, and indirect markers such as HOMA-β for pancreatic β-cell function and HOMA-S (QUICKI) for insulin sensitivity. To our knowledge, HOMA-β and HOMA-S have not been widely evaluated, particularly following treatment with DAAs.

Table 2. The changes in laboratory parameters, blood glucose parameters, and lipid profiles at baseline and SVR12

Parameters	Baseline	SVR12	*P* value
Laboratory parameters			
ALT (U/L)	35.5 (27–60)	28 (23–42)	**<0.0001**
AST (U/L)	38.5 (30–56)	25 (18–34)	**<0.0001**
Total bilirubin (mg/dl)	1.7 (1.1–2.4)	1.2 (1–1.8)	**<0.0001**
Albumin (g/dl), mean (SD)	3.44 (0.90)	3.54 (0.86)	0.2
Prothrombin concentration	62.5 (47–92)	78 (55–95)	**0.0003**
Creatinine (mg/dl)	1.2 (1–1.3)	1.1 (0.9–1.2)	0.2
AFP (ng/ml)	12 (8–17)	12 (8–17)	0.9
Platelet count (10^3/mm^3)	177 (86–280)	176 (95–260)	0.98
Blood glucose parameters			
Fasting blood glucose (mg/dL), mean (SD)	110.82 (25.1)	101.89 (15.7)	**0.0002**
2 h post-prandial blood glucose (mg/dl), mean (SD)	187.22 (44.5)	122.98 (34.9)	**<0.0001**
HbA1c (%)	7.1 (6.2–8.1)	6.65 (5.8–7.3)	**<0.0001**
Fasting insulin(mIU/l), mean (SD)	16.51 (1.94)	12.54 (1.78)	**<0.0001**
HOMA-IR	4.32 (3.42–5.63)	3.19 (2.61–3.7)	**<0.0001**
HOMA-IR (<1.9 and ≥1.9) (n, %)	0/ 98 (100%)	5 (5.1%)/93 (94.9%)	–
HOMA-β	119.63 (98.5–209.4)	113.7 (87.43–167.54)	0.4
HOMA-S, mean (SD)	0.34 (0.02)	0.38 (0.02)	**<0.0001**
Lipid profile			
Triglycerides (mg/dl)	148.5 (112–167)	145 (100–165)	**0.01**
Total cholesterol (mg/dl), mean (SD)	131.8 (17.1)	149.6 (30.4)	**<0.0001**
LDL-cholesterol (mg/dl), mean (SD)	76.03 (13.3)	93.4 (24.14)	**<0.0001**
HDL-cholesterol)mg/dl(, mean (SD)	37.03 (6.5)	39.41 (5.6)	**0.0002**
FIB-4	2.11 (1.01–3.73)	1.56 (0.92–2.8)	**<0.0001**

Data are expressed either as mean (SD) or median (IQR). Statistically significant values are in bold.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis 4 score; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; SVR12, sustained virological response at week 12 after end of therapy.

Table 3. Changes in blood glucose parameters and lipid profiles according to fibrosis stage before and after hepatitis C virus clearance

	Noncirrhotic (*n* = 66)			Cirrhotic (F4) (*n* = 32)		
Parameters	Baseline	SVR12	*P* value	Baseline	SVR12	*P* value
Blood glucose parameters						
Fasting blood glucose (mg/dl), mean (SD)	111.5 (24.93)	103.47 (16.04)	**0.007**	109.41 (25.73)	98.62 (14.53)	**0.007**
2 h postprandial blood glucose (mg/dl),mean (SD)	189.34 (43.83)	123.76 (35.17)	**<0.001**	182.84 (46.16)	121.37 (34.7)	**<0.001**
HbA1c (%), median (IQR)	6.9 (6.1–7.8)	6.4 (5.7–7)	**<0.001**	7.8 (6.6–8.2)	7 (6.05–7.45)	**<0.001**
Fasting insulin (mIU/L)	16.40 (1.98)	12.43 (1.61)	**<0.001**	16.75 (1.88)	12.77 (2.09)	**<0.001**
HOMA-IR, median (IQR)	4.32 (3.45–5.62)	3.23 (2.64–3.73)	**<0.001**	4.34 (3.39–5.77)	3.07 (2.52–3.57)	**<0.001**
HOMA-β, median (IQR)	115.14 (95.2–213.33)	106.15 (84.9–164.4)	0.3	131.47 (100.14–207.4)	139.92 (100.9–177.96)	0.8
HOMA-S, mean (SD)	0.34 (0.02)	0.38 (0.02)	**<0.001**	0.34 (0.02)	0.38 (0.03)	**<0.001**
Lipid profile						
Triglycerides (mg/dl) (median (IQR)	157.5 (110–170)	155 (110–170)	0.2	136.5 (112.5–157.5)	132 (89–145)	**0.005**
Total cholesterol (mg/dl), mean (SD)	131.71 (18.83)	154.73 (30.44)	**<0.001**	131.87 (12.92)	139.47 (28.05)	**0.07**
LDL-cholesterol (mg/dl), mean (SD)	75.47 (14.34)	97.32 (24.76)	**<0.001**	77.19 (10.92)	85.22 (20.91)	**0.02**
HDL-cholesterol (mg/dl), mean (SD)	36.83 (7.18)	39.75 (5.96)	**<0.001**	37.44 (4.76)	38.69 (4.58)	0.1

Data are expressed either as mean (SD) or median (IQR). Statistically significant values are in bold.
HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; SVR12, sustained virological response at week 12 after end of therapy.

Our findings have important clinical implications. Successful elimination of HCV with generic SOF/DCV treatment leads to improved HCV-associated impaired glucose metabolism. In particular, a significant drop in fasting serum glucose and HbA1c is noted, and this was in line with the published literature limited to T2DM patients treated with DAAs [20–22]. Also, a significant reduction of serum insulin levels, insulin resistance levels either HOMA-IR or HOMA-β, and an improvement in insulin sensitivity (HOMA-S) had been observed and this was in agreement with previous data that showed that the reduction of serum insulin and insulin resistance levels might occur following SVR [23,24]. Moreover, data from our study demonstrated that there was a significant improvement in fasting serum glucose level, HbA1c, serum insulin levels, HOMA-IR with an increase in insulin sensitivity, but a nonsignificant change in HOMA-β occurred in diabetic patients who achieved SVR regardless of the stage of hepatic fibrosis. The explanation of the improvement of glycemic state and insulin resistance in diabetic CHC patients has not been completely understood, but evidence suggests that HCV may interact with glucose metabolism through several mechanisms contributing to the development of insulin resistance and T2DM. It may directly inhibit the insulin signaling pathway with downregulation of glucose transporter 2, degradation of insulin receptor substrate-1 (IRS-1) through the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) activation and suppression of phosphorylation of tyrosine on IRS-1. HCV also impairs phosphorylation of Akt leading to a reduction of insulin stimulation. Moreover, HCV core protein plays an important role in the production of proinflammatory

Table 4. Rates of patients who showed Homeostatic Model Assessment of Insulin Resistance improvement in the whole treated population and baseline predictive factors for this improvement

			Univariate analysis	
Parameters	Decreased by ≥20% ($n=75$)	No decrease by at least 20% ($n=23$)	OR (95% CI)	*P* value
Age (years)	51.28 (6.79)	52.39 (7.39)	0.98 (0.91–1.05)	0.5
Gender Male/female	34/41	10/13	0.93 (0.36–2.38)	0.9
BMI (kg/m^2), mean (SD)	29.48 (3.47)	29.15 (3.53)	1.03 (0.90–1.18)	0.7
Baseline ALT (U/L), (median (IQR)	36 (27-58)	34 (24-77)	1.004 (0.99–1.02)	0.5
Baseline AST (U/L), (median (IQR)	38 (30-58)	41 (25-52)	1.01 (0.99–1.03)	0.2
Presence of cirrhosis, *n* (%)	26/75 (34.6%)	6/23 (26%)	1.50 (0.53–4.27)	0.4
Baseline fasting blood glucose (mg/dl), mean (SD)	115.16 (24.81)	96.65 (20.69)	1.04 (1.01–1.06)	**0.003**
Baseline fasting insulin (mIU/L), mean (SD)	16.85 (1.79)	15.41 (2.07)	1.57 (1.15–2.15)	**0.004**
Baseline HOMA-IR (median (IQR)	4.75 (3.76-5.89)	3.42 (2.83–4.14)	2.34 (1.41–3.87)	**0.001**
Baseline cholesterol (mg/dL), mean (SD)	131.19 (16.88)	133.65 (17.90)	0.99 (0.96–1.02)	0.5
Baseline triglycerides (mg/dL), (median (IQR)	146 (113–166)	156 (102–172)	0.99 (0.98–1.007)	0.4
Baseline HDL-C (mg/dl), mean (SD)	36.59 (6.74)	38.48 (5.41)	0.99 (0.96–1.03)	0.8
Baseline LDL-C (mg/dl), mean (SD)	75.87 (13.06)	76.56 (13.06)	0.95 (0.88–1.03)	0.2

Statistically significant values are in bold.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FIB-4, fibrosis 4 score; HbA1c, hemoglobin A1c; HOMA-insulin resistance, Homeostatic Model Assessment of Insulin Resistance; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; OR, odds ratio.

Table 5. Baseline predictive variables for Δ increase low-density lipoprotein-C value in the whole treated population at SVR12

	Univariate analysis		Multivariate analysis	
Parameters	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)	1.05 (0.98–1.11)	0.1	–	–
Gender Male/female	0.99 (0.44–2.24)	0.9	–	–
BMI (kg/m^2)	1.02 (0.91–1.15)	0.7	–	–
Baseline ALT (U/L)	0.99 (0.99–1.01)	0.7	–	–
Baseline AST (U/L)	0.99 (0.98–1.01)	0.9	–	–
Presence of cirrhosis	0.61 (0.26–1.43)	0.2	–	–
Baseline HOMA-IR	2.10 (1.41–3.11)	**<0.0001**	1.77 (1.16–2.68)	**0.01**
Baseline cholesterol (mg/dl)	1.001 (0.98–1.02)	0.9	–	–
Baseline triglycerides (mg/dl)	1.03 (1.01–1.04)	**<0.0001**	1.02 (1.01–1.04)	**0.003**
Baseline HDL-C (mg/dl)	0.97 (0.91–1.03)	0.4	–	–
Baseline LDL-C (mg/dl)	0.97 (0.94–1.001)	0.06	–	–

Statistically significant values are in bold.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FIB-4, fibrosis 4 score; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; SVR12, sustained virological response at week 12 after end of therapy.

cytokines (IL-8, IL-18, TNF alpha) that suppress the insulin action in the liver and peripheral tissue causing glucose utilization by the cell to decrease [25,26]. Furthermore, the clinical consequences of insulin resistance include the development of T2DM and an increased risk of cardiovascular events (e.g., atherosclerosis) due to reduced levels of adiponectin [27], increased vessel wall stiffness [28], and oxidative stress [29]. For this reason, the decline of hepatic inflammation that follows a successful clearance of HCV could explain the significant improvement of insulin resistance, glycemic state, and clinical outcomes (e.g., atherosclerosis) in patients with established T2DM. Hence, other mechanisms not related to the improvement of hepatic inflammation and peripheral resistance might be relevant in a significant reduction of insulin resistance. The liver plays a central role in all the metabolic processes in the body, and the improvement of hepatic function in the form of significant increase of serum albumin, together with a parallel reduction of serum transaminases and total serum bilirubin after the achievement of SVR might have led to better control of synthesis, storage, and release of glucose.

Regarding the impact of HCV clearance on the lipid profiles, our data showed a significant increase in both serum TC and LDL-C levels on the one hand and a significant increase of HDL-C together with a significant decrease of TGs, on the other hand at SVR12 compared to baseline. Furthermore, regardless of the stage of hepatic fibrosis, the changes in lipid profiles in noncirrhotic patients were quite similar to cirrhotic patients. Similar results have been reported in the changes in lipid profiles during IFN-based therapy [11–13] and IFN-free treatment regimens [30–32] which showed that serum TC, LDL-C, and HDL-C levels significantly increased after viral eradication irrespective of treatment regimens or HCV genotype. However, the effect on triglycerides seems to be conflicting. These data indicate that the increase of serum LDL-C is the major contributor to the increase of serum TC as supported by previous reports [13,30]. The explanation for this phenomenon is due to the HCV life cycle is tightly linked to host lipoproteins and evidence suggests that HCV utilizes these host lipoproteins for cellular entry, replication, assembly, and secretion [33]. Chronic HCV infection is significantly associated with hypocholesterolemia (particularly with

reduced LDL levels). Therefore, HCV-associated hypolipidemia can be completely reversed after viral elimination resulting in increased levels of LDL and TC. Additionally, cholesterol is an indicator of liver function. Therefore, the more prominent increase in serum cholesterol after viral elimination might represent a faster improvement in liver pathology or inflammation.

As LDL-C plays a key role in the development and progression of atherosclerosis, leading to cardiovascular and cerebrovascular disease, we investigated the baseline predictive factors for the Δ increase LDL-C level at SVR12 and we found that higher HOMA-IR and triglycerides at baseline in a logistic regression analysis emerged as the only significant predictors of the Δ increase LDL-C level at SVR12.

This study has some limitations. First is the retrospective design of the study and the small number of included patients. Another limitation is the short-term follow-up that did not allow us to determine whether improvement in glucose abnormalities and changes in lipid profiles, particularly TC and LDL-C levels, would continue after long-period follow-up and its impact on clinical outcomes as CVD risk.

In conclusion, successful HCV elimination following SOF/DCV-based therapy led to an improvement of glycemic state and insulin resistance associated with an overall worsening of the lipid profile. However, the negative effect on the lipid profile may be at least partially compensated by the improvement of glycemic state and insulin resistance, which itself should reduce the CV risk. Therefore, patients who have one or more risk factors of CVD and are treated with DAA might be monitored for an accurate stratification of CVD risk.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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