The impact of direct-acting antiviral treatment on lipid metabolism and insulin resistance in chronic hepatitis C patients: temporary? permanent?

Osman Özdoğan, Serkan Yaraş, Fehmi Ateş, Enver Üçbilek, Orhan Sezgin, Engin Altıntaş

Department of Gastroenterology, Mersin University School of Medicine, Mersin, Turkey

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ABSTRACT

Background/Aims: *In previous studies that investigated the impact of direct-acting antiviral (DAA) treatment on lipid metabolism and insulin resistance (IR) in chronic hepatitis C patients, the end-of-treatment or posttreatment values have been compared with baseline values. The results are inconsistent. We evaluated patients during and after the treatment.*

Materials and Methods: *A total of 121 patients were included in the study. Of these, 93 patients were treated with sofosbuvir/ledipasvir±ribavirin (RBV), and 28 patients were treated with ombitasvir/paritaprevir/ritonavir+dasabuvir±RBV. Total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), and homeostatic model assessment-insulin resistance (HOMA-IR) levels were measured at the onset of treatment, after the first month of treatment, at the end of treatment, and at 6 and 12 months after the end of treatment.*

Results: *A total of 117 patients were genotype 1. Sustained virological response was 98.4%. HOMA-IR values during treatment were significantly higher than at the beginning of treatment (p=0.0001). At 12 months, there was a decrease in HOMA-IR, but this was not statistically significant (p=0.2048). TC and LDL levels were significantly increased in the first month of treatment (TC: 159±30, 180±34 mg dL-1 and LDL: 84±28, 100±30 mg dL-1) (p<0.0001), and this increase was present during and after treatment. There was no statistically significant increase in TG (p=0.120). Both treatment regimens showed similar effects on HOMA-IR, TC, and LDL.*

Conclusion: *Patients with hepatitis C virus treated with DAA drugs showed increased IR, TC, and LDL cholesterol levels during treatment. After the end of treatment, IR went back to normal, whereas the elevated TC and LDL levels persisted indefinitely.*

Keywords: *Cholesterol, antiviral agents, hepatitis C, insulin resistance*

INTRODUCTION

Hepatitis C virus (HCV) infection causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and affects approximately 170 million people worldwide (1). HCV utilizes lipids during its life cycle, which are included in the structure of HCV. This leads to hypobetalipoproteinemia and hypocholesterolemia in the host (2, 3). It has also been shown in several studies that HCV causes metabolic changes such as insulin resistance (IR), metabolic syndrome, and diabetes through complex pathways (4, 5).

Previous studies that investigated the effects of pegylated interferon (Peg-IFN) on lipid parameters have reported conflicting findings. In one study (6), a decrease in total cholesterol (TC) and low-density lipoprotein (LDL) and an increase in triglycerides (TG) were observed during treatment, whereas in another study, an increase in LDL and TC levels, with no significant change in TG levels, was observed after treatment (7). In yet another study based on Peg-IFN, the lipid levels were found to be permanently decreased (8). In addition, other studies with Peg-IFN reported that the IR decreased in patients who achieved sustained virological response (SVR) (9-11).

Recently developed oral direct-acting antiviral (DAA) agents have provided an almost complete treatment of HCV (12). These drugs specifically target the virus-specific nonstructural proteins of HCV. However, studies on the effects of these drugs on IR and lipid metabolism have yielded conflicting results (13,14). In these studies, all values (end-of-treatment or posttreatment values) have been compared with baseline values. We searched for answers to the following questions:

1. Do these treatments have an impact on the lipid profile and IR of patients?
2. Are these effects temporary or permanent?

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Corresponding Author: ***Osman Özdoğan; smnzdgn@yahoo.com***
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3. Are these effects the result of HCV eradication or a direct effect of the drugs themselves?
4. Is there any difference between treatment regimens?

MATERIALS AND METHODS

Patients and treatment regimen

A total of 229 patients aged 18 years and older who presented at our gastroenterology clinic between May 2016 and January 2018 were included in the study. Of these, 108 patients were excluded from the study because of various factors, including dialysis, diabetes, human immunodeficiency virus- hepatitis B virus (HIV-HBV) coinfection, HCC, intravenous (IV) drug dependence, and a history of liver transplant or chronic diseases such as sickle-cell anemia or multiple myeloma and medications such as lipid-lowering agents, antihypertensive, antidiabetic, and steroids. A total of 121 patients were included in the study. Cirrhosis was diagnosed through laboratory studies, imaging, and physical examination.

Within the selected group, 47 patients were naïve, whereas 54 patients had previously undergone treatment with Peg-IFN+ribavirin (RBV), and 20 patients had been treated with a first-generation protease inhibitor (telaprevir or boceprevir)+Peg-IFN+RBV. We provided treatment with sofosbuvir/ledipasvir (SOF/LDV) to 68 patients, SOF/LDV+RBV to 25 patients, ombitasvir/paritaprevir/ritonavir (OBV/PTV/r)+dasabuvir (DSV) to 24 patients, and OBV/PTV/r DSV+RBV to 4 patients (totally, SOF/LDV±RBV=93 patients, OBV/PTV/r DSV±RBV=28 patients). Over the course of the study, 55 and 66 patients underwent treatment for 12 and 24 weeks, respectively.

Fasting blood glucose (FBG) levels, insulin level, homeostatic model assessment-insulin resistance (HOMA-IR), TC, high-density lipoprotein (HDL), LDL, and TG levels were measured at the onset of treatment, after the first month of treatment, at the end of treatment, and at 6 and 12 months after the end of treatment. The values of treatment onset were compared with values of other times. In addition, the effects of SOF/LDV±RBV (Group 1) and OBV/PTV/r+DSV±RBV (Group 2) on IR and lipid parameters were investigated separately.

Laboratory assays

Laboratory analyses were performed in our hospital using venous blood collected from the patients after at least 10 hours of fasting. Hemogram assessment was performed using Beckman Coulter LH 780, and lipid panel, liver, and renal function tests were done using Roche Cobas C501. Insulin levels were measured by electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Rotkreuz, Switzerland). The HOMA-IR value was calculated as (glucose × insulin)/405. Serological tests such as anti-HCV and HBsAg were done by ELISA (Abbott Laboratories, Chicago, IL, USA). HCV RNA levels were evaluated by a real-time polymerase chain reaction technique (Cobas Taqman 48 kit from Roche Diagnostics, Indianapolis, IN, USA). The AMPLIQUALITY HCV-TS kit (AB Analitica, Padova, Italy) was used for defining the HCV genotype.

Statistical Analysis

Mean and standard deviation were used as descriptive statistics related to continuous parameters. Analysis of variance (ANOVA) was performed to check whether there was a difference between the averages of the independent groups. Repeated measures ANOVA was used to check if there were any differences between repeated measurements. Error bars on graphs were used for visual presentation of the changes between the groups. A probability value of less than 0.05 was considered statistically significant.

Written or verbal permission was obtained for all patients, and the working protocol was designed in accordance with the ethical principles of the Declaration of Helsinki.

RESULTS

Of the 121 patients, 79 (65.3%) were female, and the mean age was 64.14±13.1 years (within the range of 24--88 years). Most of the patients (117) had genotype 1 (including 95 patients with genotype 1B, 4 patients with genotype 1A, and 18 patients with genotype 1; subtype not determined), 3 patients had genotype 2, and 1 patient had genotype 4. The HCV RNA levels were $3.394'10^3 \pm 9.419'10^3$ IU mL^{-1} (min: 1255 and max: $82.000'10^3$). Twelve patients (9.9%) had decompensated, and 19 patients (15.7%) had compensatory cirrhosis. In the whole group, the end-of-treatment response was 100%, and the SVR was 98.4%. HCV RNA disappeared in 112 patients (93%) in one month of treatment. Two non-cirrhotic patients who had previously received PEG+RBV relapsed after treatment. One patient with decompensated liver cirrhosis developed hepatic encephalopathy and died about five months after the end of treatment. Table 1 shows the pretreatment characteristics of the total group, Group 1 (SOF/LDV±RBV), and Group 2 (OBV/PTV/r±RBV).

The FBG levels of all patients were measured at the onset of treatment (FBG_0), after the first month of treat-

Table 1. Initial laboratory data and demographic characteristics.

Variables	Total group (n=121)	Group 1 (SOF/LDV±RBV) (n=93)	Group 2 (OBV/PTV/r+DSV±RBV) (n=28)	p
Age (year), mean±SD	64.14±13.1	64.14±12.8	64.14±14.3	0.473
Sex (Female), n (%)	79 (65.3)	63 (67.7)	16 (57.1)	0.307
Cirrhotic, n (%)	31 (25.6)	27 (29)	4 (14.3)	0.101
HCV RNA ×103 IU mL^{-1}, mean±SD	3.394±9.419	3.512±9.955	3.001±7.510	0.835
12-week treatment	45% (n=55)	31% (n=29)	93% (n=26)	0.0001
ALT (U l^{-1}), mean±SD	40±27.9	42.0±30.1	33.4±17.6	0.178
AST (U l^{-1}), mean±SD	47.4±25.7	50.3±26.1	37.8±22.1	0.307
FBG (mg dL^{-1}), mean±SD	96.8±12.5	97.6±12.3	94.1±13.0	0.909
Insulin (μU mL^{-1}), mean±SD	12.8±6.7	13.4±6.4	11.0±7.6	0.269
HOMA-IR, mean±SD	3.13±1.83	3.3±1.81	2.56±1.80	0.757
TG (mg dL^{-1}), mean±SD	106.6±42.5	106.3±43.3	107.7±40.3	0.859
TC (mg dL^{-1}), mean±SD	159.2±30.4	157.7±31.2	164.3±27.5	0.131
LDL (mg dL^{-1}), mean±SD	83.5±28	81.7±28.4	89.7±26.2	0.645
HDL (mg dL^{-1}), mean±SD	54.5±15.9	55.0±15.7	52.9±17.0	0.468
INR, mean±SD	1.13±0.17	1.14±0.18	1.08±0.11	0.082
Bilirubin (mg dL^{-1}), mean±SD	0.78±0.57	0.79±0.58	0.75±0.55	0.918
PLT×103 μL^{-1}, mean±SD	198.5±86.0	192.5±88.3	218.6±75.9	0.132

p<0.05 are considered statistically significant.
*Percent of patients receiving 12-week treatment.
HCV: hepatitis C virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FBG: fasting blood glucose; HOMA-IR: homeostatic model assessment-insulin resistance; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PLT: platelet; SOF/LDV: sofosbuvir/ledipasvir; RBV: ribavirin; OBV/PTV/r: ombitasvir/paritaprevir/ritonavir; DSV: dasabuvir.

Table 2. The FBG, insulin, HOMA-IR, TG, TC, LDL, and HDL course of the whole group.

Variables	Onset of treatment	First month of treatment	End of treatment	6 months after the end of treatment	12 months after the end of treatment	p
FBG (mg dL^{-1}), mean±SD	96.7±12.5	101.6±17.1	100.2±15.1	100.4±14.1	100.1±14.5	0.013
Insulin (μU mL^{-1}), mean±SD	12.84±6.7	16.33±9.9	15.03±9.1	13.19±7.2	11.46±5.2	<0.001
HOMA-IR, mean±SD	3.13±1.82	4.22±2.96	3.86±2.83	3.36±2.2	2.85±1.42	0.003
TG (mg dL^{-1}), mean±SD	106.6±42.5	116.7±59.9	113.5±61.2	110.7±53.6	112.7±53.1	0.120
TC (mg dL^{-1}), mean±SD	158.0±30.4	179.9±34.1	187.5±36.8	182.5±35.3	178.8±32.6	<0.001
LDL (mg dL^{-1}), mean±SD	83.5±28.0	100.3±30.1	106.9±35.7	102.4±31.3	100.2±29.6	<0.001
HDL (mg dL^{-1}), mean±SD	54.5±15.9	56.6±16.0	58.4±16.8	58.5±15.7	56.3±14.9	0.0198

p<0.05 are considered statistically significant.
FBG: fasting blood glucose; HOMA-IR: homeostatic model assessment-insulin resistance; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

ment (FBG_1), at the end of treatment (FBG_ET), and at 6 (FBG_6) and 12 (FBG_12) months after the end of treatment (Table 2). Only at the first month of treatment, the FBG levels were significantly higher than before treatment (p=0.021) (Figure 1).

When the treatment values were compared with the pre-treatment values, insulin levels were significantly higher in the first month of treatment (p=0.001) and at the end of treatment (p=0.004) but were found to be significantly lower 12 months after treatment (p=0.013) (Table 2 and Figure 1).

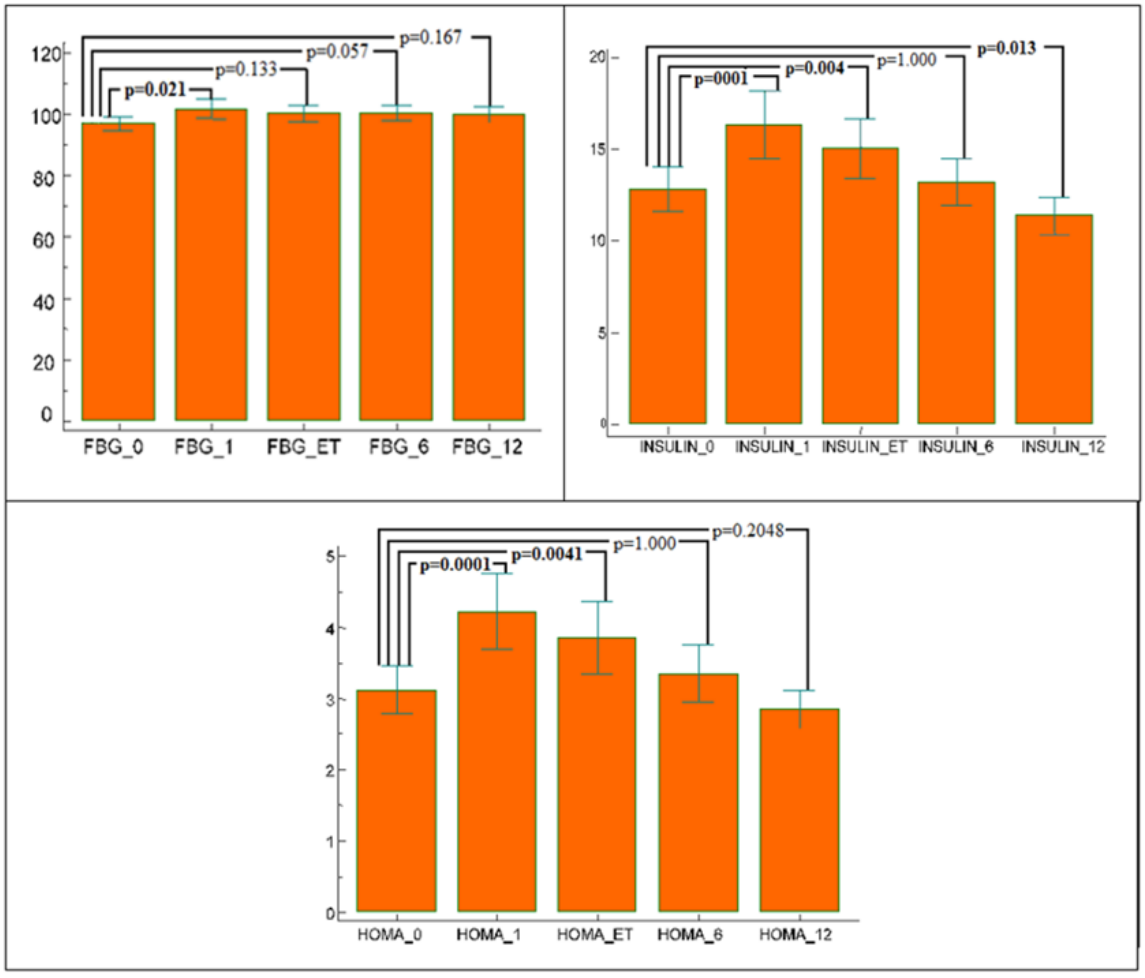

Figure 1. The FBG, insulin, and HOMA-IR course of the whole group (FBG [mg dL^{-1}] and insulin [μU mL^{-1}]) All values have been compared with baseline values. p<0.05 are considered statistically significant. FBG: fasting blood glucose, 0: at the onset of treatment, 1: first month of treatment, ET: at the end of treatment, and 6 and 12: months after the end of treatment.

The HOMA-IR value was significantly higher in the first month of treatment (p=0.0001) and at the end of treatment (p=0.0041), compared with the pretreatment values. HOMA-IR only decreased (not normalized) 12 months after treatment, but this was not statistically significant (p=0.2048) (Table 2 and Figure 1).

The average pretreatment TG level of the entire study group was slightly elevated compared with other months of treatment, but this was not statistically significant (p=0.120) (Table 2 and Figure 2).

The TC and LDL levels of the study group at all time points after the start of treatment were statistically higher than the pretreatment levels (p<0.0001) (Table 2 and Figure 2).

The average HDL level of the entire study group was found to be significantly higher at the end of treatment (p=0.0006) and six months after treatment (p=0.0001) (Table 2 and Figure 2).

We also investigated whether these drugs have different effects (n=31, 26%) on IR and lipid parameters in patients with cirrhosis. According to levels of at the onset of treatment, HOMA-IR, TC, LDL, and HDL levels were not statistically different in cirrhotic and noncirrhotic groups, but TG levels were significantly lower in the cirrhotic group (Table 3). Similar changes were observed in both groups during and after treatment on IR and lipid parameters (Table 3).

A total of 32 patients (26.5%) received DAA with RBV. HOMA-IR levels in patients receiving RBV increased at the on-

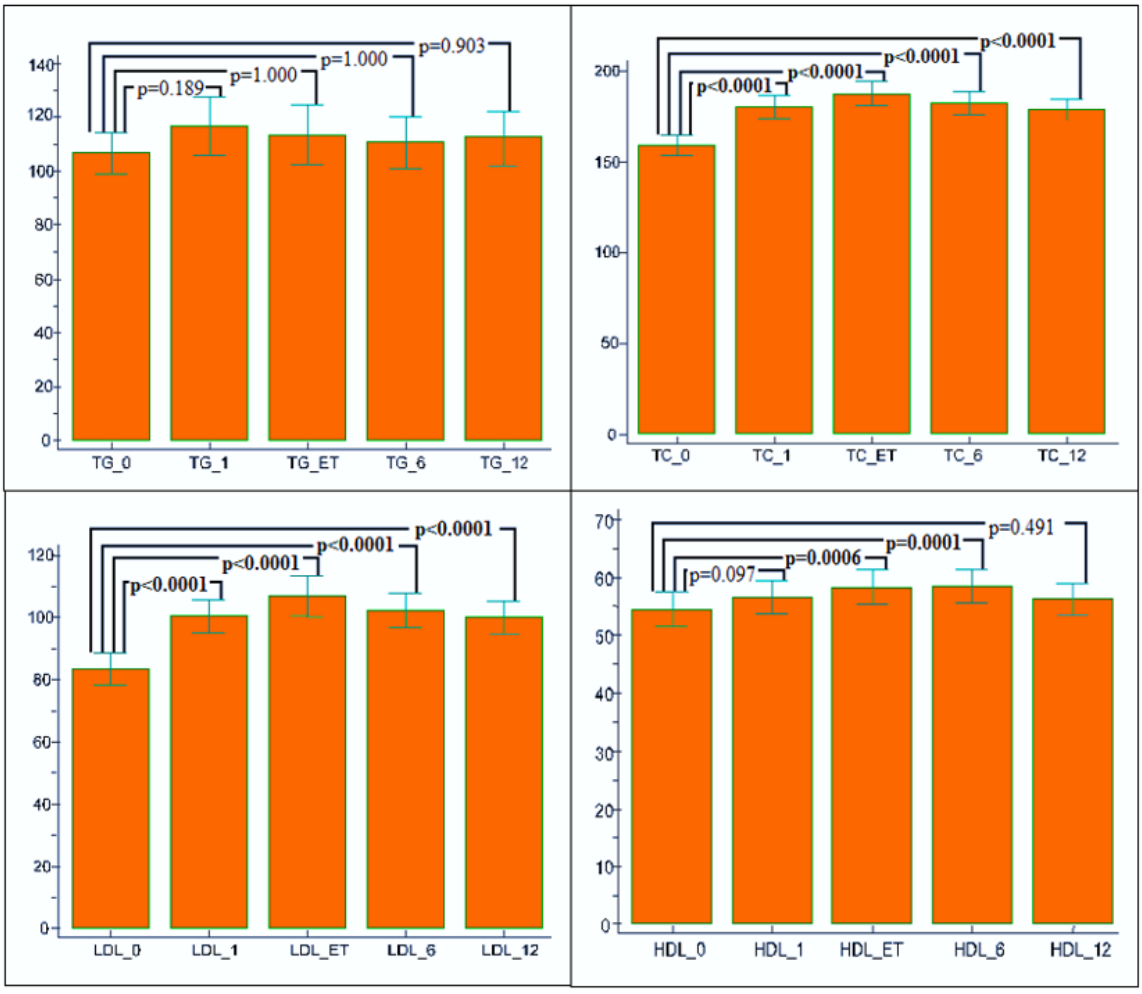

Figure 2. TG, TC, LDL, and HDL course of the whole group (mg dL^{-1}). All values have been compared with baseline values. p<0.05 are considered statistically significant. HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol, TG: triglycerides, 0: at the onset of treatment, 1: first month of treatment, ET: at the end of treatment, and 6 and 12: 6 and 12 months after the end of treatment, respectively.

set of treatment, at the first month of treatment, and at the end of treatment (3.2±1.3, 5.0±3.6, and 4.2±3.2, respectively, p<0.001), and returned to baseline at 6 and 12 months after treatment (3.3±1.4 and 3.2±1.1, respectively, p>0.05). There was no significant change in TG levels at, after, and during treatment (113±37, 109±39, 107±42, 112±35, and 107±41 mg dL^{-1}, respectively, p>0.05). Similar to that of the whole group, the TC and LDL levels of the patients who received RBV at all time points after the start of treatment were statistically higher than the pretreatment levels (for TC, 155±29, 172±28, 176±31, 174±37, and 170 ± 31; for LDL, 82±26, 94±25, 99±25, 97±31, and 94±28 mg dL^{-1}; *P*<0.001).

The effects of SOF/LDV (Group 1) and OBV/PTV/r + DSV (Group 2) on IR and lipid parameters were investigated separately. There were no differences between the groups in terms of age, sex, HCV RNA levels, cirrhosis, AST, ALT, bilirubin, International Normalised Ratio (INR), TC, LDL, HDL, TG, or other parameters (Table 1). When the effects of the DAA drugs on HOMA were examined, it was observed that both drug combinations caused transient IR during the treatment period (p<0.0001, Table 4). It was also observed that both DAA groups showed parallel increases in TC and LDL levels during and after treatment (p<0.0001) (Table 4). In terms of the effects on the TG level, Group 1 showed no significant increase (p=0.121), whereas Group 2 showed a significant increase during treatment (p=0.031) (Table 4). After treatment, the TG values in Group 2 returned to the pretreatment levels. Only during treatment, HDL increased in Group 1

Table 3. HOMA-IR, TG, TC, LDL, and HDL course of the cirrhosis (n=31) and noncirrhotic (n=90).

Variables	Onset of treatment	First month of treatment	End of treatment	6 months after the end of treatment	12 months after the end of treatment	p
HOMA-IR						
Cirrhotic, mean±SD	3.07±1.44	4.39±2.85	4.21±3.47	3.69±2.35	3.03±1.44	<0.001
Noncirrhotic, mean±SD	3.15±1.95	4.17±3.00	3.73±2.58	3.29±2.16	2.79±1.35	<0.001
p	0.819	0.718	0.417	0.333	0.421	–
TG (mg dL^{-1})						
Cirrhotic, mean±SD	92.6±31.5	101.5±60.6	99.2±42.0	92.7±39.4	96.9±37.1	0.255
Noncirrhotic, mean±SD	111.5±44.8	121.8±59.2	118.4±66.1	116.9±56.4	118.2±56.4	0.313
p	0.032	0.103	0.133	0.029	0.055	–
TC (mg dL^{-1})						
Cirrhotic, mean±SD	150.7±29.2	170.3±35.9	175.2±34.6	174.5±35.9	169.9±29.4	<0.001
Noncirrhotic, mean±SD	162.1±30.3	183.4±32.8	191.8±36.8	186.0±34.8	182.2±33.2	<0.001
p	0.071	0.057	0.030	0.117	0.069	–
LDL (mg dL^{-1})						
Cirrhotic, mean±SD	75.2±28.0	89.2±30.6	93.5±29.7	93.0±31.1	90.6±26.1	<0.001
Noncirrhotic, mean±SD	86.4±27.6	104.1±29.1	111.5±36.5	105.6±30.5	103.5±30.1	<0.001
p	0.056	0.017	0.015	0.052	0.036	–
HDL (mg dL^{-1})						
Cirrhotic, mean±SD	56.9±17.4	60.8±16.0	61.9±16.0	63.0±16.3	59.9±15.6	0.015
Noncirrhotic, mean±SD	53.7±15.4	55.1±15.9	57.9±17.0	57.0±15.3	55.1±15.0	0.042
p	0.335	0.089	0.185	0.067	0.124	–

p<0.05 are considered statistically significant.
HOMA-IR: homeostatic model assessment-insulin resistance; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

(p<0.001), but decreased in Group 2 (p=0.008) (Table 4). After treatment, the HDL values in both groups returned to the pretreatment levels.

DISCUSSION

There is a strong interaction between the virus particles and intracellular lipids during the HCV life cycle, especially during viral replication and hepatocyte entry, leading to hypocholesterolemia in these patients (15). The relationship between HCV infection and IR is complex. Patients develop IR in the early stages of HCV infection, and this resistance seems to increase as fibrosis progresses (16). We aimed at finding answers to some questions: First, can these alterations in metabolism be ameliorated by the eradication of HCV virus using the newly developed DAA drugs? Are these alterations permanent? Second, do DAA agents have direct effects on these parameters, distinct from HCV eradication? Third, is there the difference between treatment regimens? Are these changes permanent?

In our study, we found a permanent increase in LDL and TC and a statistically insignificant increase in TG during the treatment of HCV with DAAs. Carvalho et al. (17) showed that in patients with SVR one year after treatment, the levels of TG and TC increased significantly, but HDL and LDL cholesterol levels showed no change. In a study by Endo et al. (14), patients who showed a permanent response to SOF/LDV treatment had sharply increased LDL and TC levels during the early treatment period. These levels returned to normal after treatment. There was also a significant increase in the TG level, and the HDL level showed a decline after treatment. Morales et al. (18) showed that the LDL and TC levels were higher after treatment with SOF. Gitto et al. (19) studied patients with cirrhosis and reported that in the majority of their patients (81%), LDL increased from 80±26 to 102±34 (p<0.001), and TC increased from 154±34 to 170±37 (p<0.001). These increases were seen when the initial values were compared with the values after six months of treatment. No significant change was found

Table 4. Effects of SOF/LDV (Group 1) and OBV/PTV/r + DSV (Group 2) on HOMA-IR, TG, TC, LDL, and HDL.

Variables	Onset of treatment	First month of treatment	End of treatment	6 months after the end of treatment	12 months after the end of treatment	p
HOMA-IR						
Group 1, mean±SD	3.30±1.81	4.39±2.78	4.14±2.96	3.57±2.27	2.99±1.40	<0.001
Group 2, mean±SD	2.56±1.80	3.68±3.51	2.92±2.12	2.65±1.87	2.40±1.43	<0.001
p	0.060	0.265	0.045	0.053	0.053	–
TG (mg dL^{-1})						
Group 1, mean±SD	106.3±43.3	114.6±59.9	106.2±47.8	110.0±52.9	112.7±53.8	0.121
Group 2, mean±SD	107.7±40.3	123.6±60.8	137.7±89.8	113.1±56.8	112.9±51.4	0.031
p	0.877	0.487	0.016	0.791	0.990	–
TC (mg d^{-1})						
Group 1, mean±SD	157.7±31.2	181.9±34.2	186.4±34.5	181.7±36.3	177.1±29.8	<0.001
Group 2, mean±SD	164.3±27.5	174.9±33.7	191.2±44.1	187.8±31.9	185.7±40.4	<0.001
p	0.314	0.346	0.549	0.428	0.219	–
LDL (mg dL^{-1})						
Group 1, mean±SD	81.7±28.4	100.3±30.8	105.4±36.0	100.5±31.5	97.5±27.6	<0.001
Group 2, mean±SD	89.7±26.2	100.4±28.0	111.9±34.6	108.8±30.3	109.0±34.4	<0.001
p	0.185	0.989	0.402	0.224	0.072	–
HDL (mg dL^{-1})						
Group 1, mean±SD	55.0±15.7	58.9±16.2	60.9±17.0	59.2±15.8	57.0±14.9	<0.001
Group 2, mean±SD	52.9±17.0	49.0±13.0	50.0±13.5	56.3±15.5	54.1±14.8	0.008
p	0.550	0.004	0.002	0.403	0.376	–

p<0.05 are considered statistically significant.
HOMA-IR: homeostatic model assessment-insulin resistance; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

in HDL and TG levels in that study. The reason for the absence of changes in HDL and TG levels was that HCV makes use of LDL cholesterol (not TG and HDL cholesterol) during its life cycle.

We also investigated whether the DAA drugs had different effects on the lipid parameters. The SOF/LDV and OBV/PTV/r+DSV drug combinations had similar effects on the TC and LDL levels, with increased levels in both groups. Whereas OBV/PTV/r+DSV showed significant increases in TG levels during treatment, there was no significant change in TG levels in the SOF/LDV group. Additionally, in the OBV/PTV/r+DSV group, the HDL decreased during the treatment period, but this was not statistically significant, whereas the HDL significantly increased during treatment in the SOF/LDV group. Two studies comparing LDV/SOF with daclatasvir (DCV)/asunaprevir reported that the increases in TC and LDL during the first weeks and during the course of treatment were higher in the LDV/SOF group (14, 20). However, in one of these studies, 4-12 weeks after the end of the treatment, the changes were similar between both DAAs (14). Another study showed that different DAA agents such as SOF/RBV, SOF/simeprevir, SOF/DCV±RBV, SOF/LDV±RBV, and OBV/PTV/r±DSV±RBV have similar effects on the lipid parameters (21). Specifically, there were increases in TC and LDL and no changes in HDL and TG. In our study, we did not detect any differences between the DAAs in terms of their effects on LDL and TC.

The increase in LDL and TC in the first month of treatment probably reflects a change in lipid metabolism resulting from the inhibition of HCV replication (HCV RNA disappeared in 112 patients [93%] in one month of treatment). In our study, we hypothesized that the persistence of high LDL and TC levels after treatment could be attributed to persistent eradication of HCV. Our data suggest that DAA drugs do not have a direct effect on LDL and TC, and that the increase in lipid parameters is related to the complete inhibition of HCV replication.

The similarity of the effects of SOF/LDV and OBV/PTV/r+DSV on cholesterol levels further validated our hypothesis. In addition, the increase in LDL observed after HCV suppression was similar to that seen in other studies performed in patients who achieved SVR with IFN-based therapy (7, 22).

In previous studies, HCV infection has been shown to cause IR (4, 5, 16). Therefore, the eradication of HCV is expected to eliminate IR. In the Virahep-C study with Peg-IFN, HCV patients with IR who achieved viral clearance showed an improvement in the HOMA-IR index 24 weeks after the completion of treatment (23). However, previous studies of IR with DAA treatment have shown contradictory results. Carvalho et al. (17) studied DAAs and found no significant changes in glucose values one year after the treatment, whereas HOMA-IR values showed a significant increase. Conversely, a study performed by Gitto et al. (19) showed that HOMA-IR decreased (from 3 to 2.7, $p<0.001$) when comparing the initial values and those obtained six months after the end of treatment. In another study, it was determined that FBG, insulin, and HOMA-IR did not change during treatment and 12 weeks after the procedure (24). In our study, we found that HOMA-IR increased during the treatment. This increase was attributed to increased insulin level rather than to glucose levels. However, this elevation in HOMA-IR disappeared after treatment with a statistically insignificant decrease about six months after treatment. We observed that this effect was similar in both treatment groups (SOF/LDV and OBV/PTV/r+DCV). Our findings suggest that the increase in HOMA-IR during treatment may be due to temporary IR caused by DAA agents independent of HCV eradication.

In our study, no difference was found between cirrhotic and noncirrhotic patients in terms of course of lipid parameters and IR. There are few head-to-head studies investigating lipid parameters and IR in patients with cirrhosis treated with DAA. One of these studies showed similar results (24). However, in this study, pretreatment insulin levels and HOMA-IR values were higher in patients with cirrhosis. In our study, it was thought that IR was not detected because of the absence of diabetic patients.

In our study, we found that RBV had no different effect on IR and lipid parameters. A recent study with OBV/PTV/r+DSV has showed an increase in TG, TC, and LDL levels during and after treatment. HOMA-IR, FBG, and insulin levels were not changed during and after treatment. In this study, only LDL and HbA1c levels were affected in the group receiving RBV (LDL and HbA1c levels decreased during treatment) (24).

The most important deficiency of our study was that patients did not monitor weight change. However, we know that DAA drugs do not cause significant weight change.

In conclusion, DAA drugs are effective agents in the treatment of HCV. The increase in LDL and TC is probably due to altered lipogenesis after removal of the effects of HCV on host lipid metabolism, rather than a direct response to DAAs. In other words, DAA drugs appear to have no additional effects on TC and LDL. However, DAA agents cause transient IR.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Mersin University School of Medicine (Decision Date: March 05, 2016; Decision No: 2016/201.)

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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REFERENCES

1. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-73. [Crossref]
2. Huang H, Sun F, Owen DM, et al. Hepatitis C virus production by human hepatocytes dependent on assembly and secretion of very low-density lipoproteins. Proc Natl Acad Sci 2007; 104: 5848-53. [Crossref]
3. Felmlee DJ, Hafirassou ML, Lefevre M, Baumert TF, Schuster C. Hepatitis C virus, cholesterol and lipoproteins-impact for the viral life cycle and pathogenesis of liver disease. Viruses 2013; 5: 1292-324. [Crossref]
4. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology 2008; 134: 416-23. [Crossref]
5. Huang JF, Yu ML, Dai CY, et al. Reappraisal of the characteristics of glucose abnormalities in patients with chronic hepatitis C infection. Am J Gastroenterol 2008; 103: 1933-40. [Crossref]
6. Ramcharran D, Wahed AS, Conjeevaram HS, et al. Virahep-C Study Group. Associations between serum lipids and hepatitis C antiviral treatment efficacy. Hepatology 2010; 52: 854-63. [Crossref]

7. Corey KE, Kane E, Munroe C, Barlow LL, Zheng H, Chung RT. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up. Hepatology 2009; 50: 1030-7. [Crossref]
8. Qing S, Ji D, Li B, et al. Improvement of glucose and lipid metabolism with pegylated interferon-α plus ribavirin therapy in Chinese patients chronically infected with genotype 1b hepatitis C virus. Ann Saudi Med 2015; 35: 293-7. [Crossref]
9. Dai CY, Huang JF, Hsieh MY, et al. Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. J Hepatol 2009; 50: 712-8. [Crossref]
10. Delgado-Borrego A, Jordan SH, Negre B, et al. Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. Clin Gastroenterol Hepatol 2010; 8: 458-62. [Crossref]
11. Arase Y, Suzuki F, Suzuki Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. Hepatology 2009; 49: 739-44. [Crossref]
12. Kowdley KV, Gordon SC, Reddy KR, et al. ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370: 1879-88. [Crossref]
13. Townsend K, Meissner EG, Sidharthan S, et al. Interferon-free treatment of hepatitis C virus in HIV/hepatitis C virus-coinfected subjects results in increased serum low-density lipoprotein concentration. AIDS Res Hum Retroviruses 2015; 32: 456-62. [Crossref]
14. Endo D, Satoh K, Shimada N, Hokari A, Aizawa Y. Impact of interferon-free antivirus therapy on lipid profiles in patients with chronic hepatitis C genotype 1b. World J Gastroenterol 2017; 23: 2355-64. [Crossref]
15. Mazumdar B, Banerjee A, Meyer K, Ray R. Hepatitis C virus E1 envelope glycoprotein interacts with apolipoproteins in facilitating entry into hepatocytes. Hepatology 2011; 54: 1149-56. [Crossref]
16. Hsu CS, Liu CJ, Liu CH, et al. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. Liver Int 2008; 28: 271-7. [Crossref]
17. Carvalho JR, Velosa J, Serejo F. Lipids, glucose and iron metabolic alterations in chronic hepatitis C after viral eradication - comparison of the new direct-acting antiviral agents with the old regimens. Scand J Gastroenterol 2018; 53: 857-63. [Crossref]
18. Morales AL, Junga Z, Singla MB, Sjogren M, Torres D. Hepatitis C eradication with sofosbuvir leads to significant metabolic changes. World J Hepatol 2016; 8: 1557-63. [Crossref]
19. Gitto S, Cicero AFG, Loggi E, et al. Worsening of Serum Lipid Profile after Direct Acting Antiviral Treatment. Ann Hepatol 2018; 17: 64-75. [Crossref]
20. Hashimoto S, Yatsuhashi H, Abiru S, et al. Rapid increase in serum low-density lipoprotein cholesterol concentration during hepatitis C interferon-free treatment. PLoS One 2016; 11: e0163644. [Crossref]
21. Mauss S, Berger F, Wehmeyer MH, et al. Effect of antiviral therapy for HCV on lipid levels. Antivir Ther 2016; 21: 81-8. [Crossref]
22. Tada S, Saito H, Ebinuma H, et al. Treatment of hepatitis C virus with peg-interferon and ribavirin combination therapy significantly affects lipid metabolism. Hepatol Res 2009; 39: 195-9. [Crossref]
23. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C.Gastroenterology 2011; 140: 469-77. [Crossref]
24. Doyle MA, Galanakis C, Mulvihill E, Crawley A, Cooper CL. Hepatitis C Direct Acting Antivirals and Ribavirin Modify Lipid but not Glucose Parameters. Cells 2019; 8(3). pii: E252. doi: 10.3390/cells8030252. [Crossref]