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# Impact of direct-acting antiviral therapy on metabolic profiles and adiponectin serum level in different categories of patients with chronic hepatitis C infection

Ahmed Samir Allam*, Mohamed Lotfy Abd Elmeged, Sameh Mohamed Ghaly, Osama Ashraf Ahmed, Gina Gamal Naguib and Ahmed Samir Abohalima

## Abstract

**Background:** Infection with the hepatitis C virus (HCV) is a worldwide health problem. HCV infection is linked to a variety of metabolic abnormalities as it interferes with lipid metabolism, causing steatosis and a wide range of adipocytokine alterations, as well as impairing glucose metabolism, resulting in a rising prevalence of insulin resistance (IR) and type 2 diabetes. Over the last few years, numerous oral anti-HCV medicines (direct-acting antivirals; DAAs) have been introduced. With DAA therapy, HCV can now be eradicated from the infected host within 12 weeks. There is a need for more research because there is minimal information on the effects of DAA therapy on metabolic profiles, lipid profiles, and adiponectin levels. Thus, the purpose of this study was to see how direct-acting antivirals (DAAs) affected metabolic profiles and serum adiponectin levels in 2 different categories of Egyptian patients with chronic hepatitis C infection. This study included 100 patients with chronic HCV who were separated into two groups. Group I consisted of 50 patients who were treated for 12 weeks with sofosbuvir, daclatasvir, and ribavirin). Group II consisted of 50 patients who were treated for 12 weeks with ombitasvir, paritaprevir, and ritonavir/ribavirin. This regimen was chosen because these patients had an eGFR of 30 ml/min. Fasting lipid profiles (total cholesterol, triglyceride, HDL, and LDL), metabolic profiles (fasting blood sugar, fasting insulin, HOMA-IR, and HbA1C), and serum adiponectin levels were measured before and after the end of treatment.

**Results:** Statistical analysis of the data showed a significant difference in the lipid profile in group I before and after treatment, as we found a significant reduction in serum triglycerides after treatment (113.2 ± 22.9 mg/dL vs 105.6 ± 23.2 mg/dL, $P < 0.001$) and a significant elevation of serum total cholesterol, LDL, and HDL after treatment (TC: 153.2 ± 20.1 mg/dL vs 174.1 ± 19 mg/dL, $P < 0.001$; LDL: 74.7 ± 9.9 mg/dL vs 93.3 ± 12 mg/dL, $P < 0.001$; HDL: 54.6 ± 10.1 mg/dL vs 57.2 ± 10.3 mg/dL, $P$ 0.010). But in group II, there was no significant difference in the lipid profile before and after treatment. We also found a significant reduction in fasting insulin, HOMA-IR, and HBA1C after treatment in group I (fasting insulin: 11.4 ± 3.3 (μU/L)/ml vs 9.7 ± 2.2 (μU/L)/ml, $P < 0.001$; HOMA-IR: 2.7 ± 0.9 vs 2.2 ± 0.6, $P < 0.001$; HBA1C: 5.6 ± 0.4 vs 5.4 ± 0.3, $P$ 0.003). But in group II, there was no significant difference in fasting insulin, HOMA-IR, and HBA1C before and after treatment. Also, we found that there were no significant changes in the serum adiponectin level in either group before or after treatment.

*Correspondence: ahm82allam@gmail.com

Internal Medicine Department, Faculty of Medicine, Gastroenterology and Hepatology Unit, Ain Shams University, Cairo, Egypt

**Conclusion:** HCV clearance with DAAs had an impact on the lipid and metabolic profiles of the patients at the end of treatment. This could depend on the type of DAAs used in the treatment, the stage of the liver disease, and the associated conditions of patients. However, serum adiponectin levels are unaffected.

**Keywords:** Hepatitis C virus, Insulin resistance, Direct-acting antivirals, Low-density lipoprotein, High-density lipoprotein, Total cholesterol

## Introduction

Hepatitis C virus (HCV) infection is a serious global health issue. It is estimated that over 80 million people are infected with the virus on a long-term basis [1]. Due to previous schistosomiasis eradication campaigns, Egypt has the greatest prevalence of HCV in the world with very high incidence rates among the elderly, rural areas, and lower social groups (predominantly genotype 4) [2].

Chronic hepatitis, cirrhosis, and HCC can all be caused by HCV infection, which causes persistent liver inflammation. Previously, anti-HCV treatment was limited to interferon (IFN)-based regimens, which can have substantial side effects and have a low cure rate. However, several oral anti-HCV drugs (direct-acting antivirals; DAAs) have been released in recent years [3].

DAAs were first used in combination with PEG-IFN and ribavirin, which improved response rates but increased toxicity [4]. Combining DAAs that target distinct stages of the viral life cycle has proven to be very effective, enabling the development of interferon-free and ribavirin-free regimens with much better therapeutic tolerance. Because of well-tolerated oral regimens, cure rates for most patient populations have now reached 90% [5].

Chronic HCV infection is linked to hepatic steatosis and hypocholesterolemia. HCV employs peripheral lipid metabolism pathways for viral assembly, and infective particle production necessitates a large number of apolipoproteins [6]. The association between chronic HCV infection and an increased prevalence of IR and type 2 diabetes mellitus (DM) has been extensively studied. IR has been demonstrated to expedite fibrosis in chronic HCV-infected patients, potentially raising the risk of cirrhosis and hepatocellular carcinoma [7] and lower rates of antiviral treatment response that is both immediate and sustained [8].

Lipid metabolism is intertwined with several key stages of the HCV life cycle [9]. In the peripheral circulation, lipids cover HCV particles. Every 24 h, about $10^8$ HCV particles are expected to be released from the liver into the peripheral circulation [10]. This discovery demonstrated that lipid metabolism had shifted in favor of the production of HCV particles. As a result, in an attempt to speed up reproduction, HCV may interfere with the host's lipid metabolism [3].

In many studies of plasma lipid profiles in chronic HCV infection, many observed substantial reductions in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), as well as a reduction in high-density lipoprotein cholesterol (HDL-C) in some cases [11]. Nevertheless, whether or not chronic HCV infection causes a decrease in blood triglycerides (TG) is a subject of controversy [12].

The role of adipocytokines in HCV infection is still up for discussion. Chronic HCV-4-infected patients had higher levels of circulating leptin, adiponectin, and high molecular weight (HMW) adiponectin than HCV negative controls, and these changes are connected to IR separately [13]. The hormone adiponectin has been associated with several stages of liver injury (steatosis, inflammation, and fibrosis) [14].

Sustained virological response (SVR) rates have risen by over 90% thanks to the advent of direct-acting antiviral (DAA) medicines, which have significantly improved side effect profiles. Treatment outcomes do not appear to be affected by IR or lipid changes, and data on the impact of DAA therapy on metabolic and lipid profiles is limited [15].

According to the National Committee for Control of Viral Hepatitis in Egypt, patients are categorized into one of the following two groups:

- Easy to treat group with the following criteria: treatment naïve, total serum bilirubin of 1.2 mg/dl or lower, serum albumin of 3.5 g/dl or higher, INR of 1.2 or lower, and platelet count of 150,000/$mm^3$ or higher. This group is eligible to be treated by any of the following regimens for 12 weeks: sofosbuvir and daclatasvir or Qurevo® (Ombitasvir, Paritaprevir, and Ritonavir), and Ribavirin.
- Difficult to treat group with the following criteria: Peg-INF treatment-experienced, total serum bilirubin higher than 1.2 mg/dl, serum albumin lower than 3.5 g/dl, INR higher than 1.2, and platelet count lower than 150,000/$mm^3$. This group is eligible to be treated with sofosbuvir, daclatasvir, and ribavirin for 12 weeks. The starting dose of ribavirin is 600 mg/day [16].

### Aim of the work

The purpose of this study is to evaluate how direct-acting antivirals (DAAs) affect metabolic profiles and serum levels of adiponectin in Egyptian patients with chronic hepatitis C who belong to the difficult-to-treat group and belong to patients with an eGFR of 30 ml/min or less according to the National Committee for Control of Viral Hepatitis in Egypt, 2016.

## Methods

This cohort study was performed on 100 Egyptian patients who were 18 years of age and had chronic infection with hepatitis C treated with a combination of IFN-free DAAs at the Hepatology and Virology outpatient clinic at Ain Shams University Hospital during the period from August 2018 to August 2020 after approval of the ethical committee and informed consent was taken from the patients.

Patients were divided into two groups. Group I included 50 patients with chronic hepatitis C virus infection who were treated with DAAs (sofosbuvir/daclatasvir/ribavirin) for 12 weeks (this group belongs to the difficult to treat group according to the National Committee for Control of Viral Hepatitis in Egypt, 2016). Patients in this group had one or more of the following conditions: total serum bilirubin is higher than 1.2 mg/dl, serum albumin is lower than 3.5 g/dl, INR is higher than 1.2, and platelet count is less than 150,000/mm$^3$. Group II included 50 patients with chronic hepatitis C virus infection who were treated with DAAs (ombitasvir, paritaprevir, ritonavir/ribavirin) for 12 weeks. This regimen was chosen because these patients had an eGFR of 30 ml/min.

Patients with pregnancy, obese patients (BMI $\geq$ 30), patients with diabetes mellitus, patients with decompensated liver cirrhosis (child-pugh score C), patients with hepatocellular carcinoma, patients receiving lipid-lowering agents (i.e., statins or fibrates), patients who had any form of bariatric surgery, patients on long term steatosis inducing drugs (i.e., corticosteroids, tamoxifen, and amiodarone), I.V. drug abusers, and patients with other chronic liver diseases as alcoholic liver disease, non-alcoholic fatty liver disease, drug-induced hepatitis, other viral hepatitis, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and alpha-1 antitrypsin deficiency were excluded from the study.

All patients were subjected to the following: full history taking, full clinical examination, body mass index (BMI) calculation, and laboratory investigations including complete blood count (CBC), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, HBsAg, and serum HCV RNA concentrations were determined by a commercially available quantitative assay through PCR before and after the end of treatment, Alpha-fetoprotein in the blood, creatinine in the blood, HbA1c before and after treatment, fasting blood glucose level, before and after treatment, and a fasting lipid profile (total cholesterol, triglycerides, HDL, and LDL) was obtained. Prothrombin time and INR. Fasting serum insulin levels were measured using a DRG insulin ELISA kit before and after the end of treatment. Insulin resistance was calculated using the Homeostasis Model of Assessment-Insulin Resistance Index (HOMA-IR). HOMA-IR = fasting insulin (μIU/ml) × fasting glucose (mmol/l)/22.5 [17]. Patients are considered to have insulin resistance when HOMA-IR is equal to or more than 2.5 [18]. Serum adiponectin levels were measured using the Assay Pro human adiponectin ELISA kit before and after the end of treatment. Abdominal ultrasonography. Then all the data was analyzed statistically. Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation, Student's *t* test, paired *t* test, and chi-square by SPSS V20.

## Results

This study is a cohort study that was performed on two groups of patients recruited from the hepatology and virology outpatient clinic at Ain Shams University Hospital (MASRI: faculty of Medicine, Ain Shams Research Institute) and Ain Shams University treatment and research unit.

Group I included 50 patients with chronic hepatitis C virus infection who were treated with DAAs (sofosbuvir/daclatasvir/ribavirin) for 12 weeks (this group belongs to the difficult to treat group according to the National Committee for Control of Viral Hepatitis in Egypt, 2016).

Group II included 50 patients with chronic hepatitis C virus infection who were treated with DAAs (ombitasvir, paritaprevir, ritonavir/ribavirin) for 12 weeks (this group belongs to the treatment of patients with an eGFR of 30 ml/min or less according to the National Committee for Control of Viral Hepatitis in Egypt, 2016).

Figure 1 shows and compares each group before and after treatment with DAAs and the two groups as regards the BMI of the study population. Patients in group I had a BMI before treatment ranging between 24.5 and 29 with a mean of 27.114 ± 1.161, BMI after treatment ranging between 25.2 and 29 with a mean of 27.252 ± 1.009. There was a statistically significant difference before and after treatment where the *p* value was 0.021. While patients in group II had BMI before treatment ranging between 24.2 and 28.4 with a mean of 26.486 ± 1.165 and BMI after treatment ranging between 24 and 28.1 with a

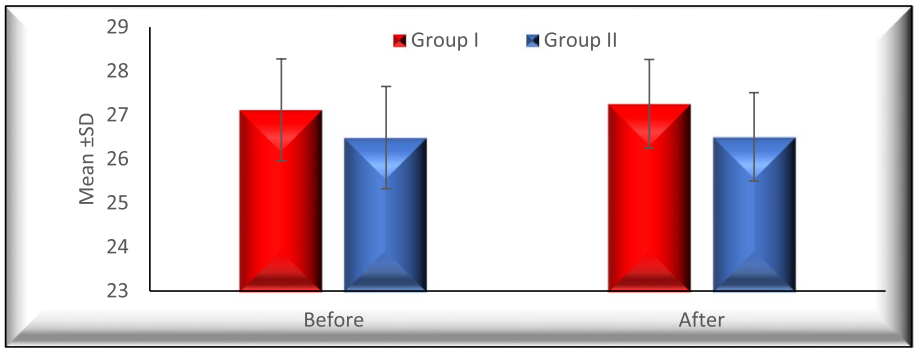


**Fig. 1** Comparison between each group before and after treatment and the two studied groups according to BMI

**Table 1** Comparison between each group before and after treatment and the two studied groups according to platelet count

| PLT | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *T* | *P* value |
| **Before** | | | | |
| **Range** | 83–287/mm$^3$ | 170–350/mm$^3$ | − 10.094 | <0.001* |
| **Mean ± SD** | 155.4 ± 47.1/mm$^3$ | 240.4 ± 36.4/mm$^3$ | | |
| **After** | | | | |
| **Range** | 98–279/mm$^3$ | 183–367/mm$^3$ | − 9.905 | <0.001* |
| **Mean ± SD** | 161.3 ± 47.6/mm$^3$ | 245.7 ± 36.9/mm$^3$ | | |
| **Differences** | | | | |
| **Mean ± SD** | − 5.9 ± 10.6/mm$^3$ | − 5.3 ± 9.4/mm$^3$ | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | <0.001* | | |

*t* Student's *t* test, *p p* value for comparing between the two groups, *PLT* platelet count

*highly significant

mean of 26.500 ± 1.008, there was no statistically significant difference between before and after treatment where the *p* value was 0.855. There was a statistically significant difference as regards BMI between the two groups where the *p* value was 0.008 before treatment and 0.001 after treatment.

Table 1 shows that patients in group I had a statistically significant difference as regards PLT before and after treatment where the *p* value was < 0.001. Also, patients in group II had a statistically significant difference as regards PLT before and after treatment, where the *p* value was <0.001. There was a statistically significant difference as regards PLT between the two groups where the *p* value was <0.001 before and after treatment.

Table 2 showed that patients in group I had a statistically significant difference as regards AST, ALT, total bilirubin, serum albumin, and INR before and after treatment, where the *p* value was 0.005. Also, patients in group II had a statistically significant difference as regards AST and INR before and after treatment, where the *p* value was 0.014. But, patients in group II had no statistically significant difference as regards ALT, total bilirubin, and serum albumin before and after treatment, where the *p* value was 0.475. There was a statistically significant difference as regards AST, ALT, total bilirubin, serum albumin, and INR between the two groups where the *p* value was <0.001 before and after treatment.

Table 3 describes and compares each group before and after treatment with DAAs and the two groups as regards the total cholesterol level of the study population. Patients in group I had total cholesterol levels before treatment ranging between 117 mg/dl and 190 mg/dl with a mean of 153.260 ± 20.101 mg/dl and total cholesterol after treatment ranging between 129 and 207 mg/dl with a mean of 174.120 ± 19.050 mg/dl. There was a significant statistical difference before and after treatment where the *p* value was <0.001. While patients in group II had total cholesterol before treatment ranging between 130 and 256 mg/dl with a mean of 174.000 ± 35.001 mg/dl, and total cholesterol after treatment ranging between 135 and 223 mg/dl with a mean of 178.200 ± 24.396 mg/dl, there was no significant statistical difference between before and after treatment where the *p* value was 0.182. There was a significant statistical difference as regards total cholesterol between the two groups before treatment, where the *p* value was <0.001, but there was no significant statistical difference after treatment, where the *p* value was 0.354.

Table 4 describes and compares each group before and after treatment with DAAs and the two groups as regards the triglyceride level of the study population. Patients in group I had triglycerides before treatment ranging

**Table 2** Comparison between each group before and after treatment and the two studied groups according to liver profile

| | Groups | | *T* test | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **AST** | | | | |
| **Before** | | | | |
| **Range** | 30–83 U/L | 13–40 U/L | 11.966 | <0.001* |
| **Mean ± SD** | 58.6 ± 15.1 U/L | 29.680 ± 8.077 U/L | | |
| **After** | | | | |
| **Range** | 34–80 U/L | 17–40 U/L | 12.733 | <0.001* |
| **Mean ± SD** | 56.500 ± 12.402 U/L | 31.140 ± 6.673 U/L | | |
| **Differences** | | | | |
| **Mean ± SD** | 2.160 ± 5.227 U/L | − 1.460 ± 4.057 U/L | | |
| **Paired test** | | | | |
| ***P*value** | 0.005* | 0.014* | | |
| **ALT** | | | | |
| **Before** | | | | |
| **Range** | 29–92 U/L | 14–40 U/L | 12.902 | <0.001* |
| **Mean ± SD** | 59.300 ± 15.289 U/L | 26.880 ± 9.052 U/L | | |
| **After** | | | | |
| **Range** | 26–81 U/L | 15–39 U/L | 13.615 | <0.001* |
| **Mean ± SD** | 55.340 ± 12.639 U/L | 27.240 ± 7.297 U/L | | |
| **Differences** | | | | |
| **Mean ± SD** | 3.960 ± 5.533 U/L | − 0.360 ± 3.533 U/L | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.475 | | |
| **Total bilirubin** | | | | |
| **Before** | | | | |
| **Range** | 0.7–1.67 mg/dL | 0.3–1.3 mg/dL | 9.399 | <0.001* |
| **Mean ± SD** | 1.276 ± 0.215 mg/dL | 0.747 ± 0.335 mg/dL | | |
| **After** | | | | |
| **Range** | 0.8–1.7 mg/dL | 0.29–1.19 mg/dL | 10.529 | <0.001* |
| **Mean ± SD** | 1.236 ± 0.204 mg/dL | 0.743 ± 0.260 mg/dL | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.041 ± 0.078 mg/dL | 0.003 ± 0.135 mg/dL | | |
| **Paired test** | | | | |
| ***P*value** | 0.001* | 0.860 | | |
| **Serum albumin** | | | | |
| **Before** | | | | |
| **Range** | 2.6–4 g/L | 3.5–4.7 g/L | − 11.989 | <0.001* |
| **Mean ± SD** | 3.256 ± 0.315 g/L | 3.986 ± 0.293 g/L | | |
| **After** | | | | |
| **Range** | 2.8–3.9 g/L | 3.6–4.4 g/L | − 12.021 | <0.001* |
| **Mean ± SD** | 3.312 ± 0.303 g/L | 3.948 ± 0.219 g/L | | |
| **Differences** | | | | |
| **Mean ± SD** | − 0.056 ± 0.142 g/L | 0.038 ± 0.261 g/L | | |
| **Paired test** | | | | |
| ***P*value** | 0.007* | 0.308 | | |
| **INR** | | | | |
| **Before** | | | | |
| **Range** | 0.62–1.7 | 0.79–1.4 | 3.046 | 0.003* |
| **Mean ± SD** | 1.212 ± 0.212 | 1.098 ± 0.159 | | |

**Table 2** (continued)

| | Groups | | *T* test | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **After** | | | | |
| **Range** | 0.73–1.59 | 0.67–1.37 | 4.424 | <0.001* |
| **Mean ± SD** | 1.171 ± 0.191 | 1.013 ± 0.166 | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.041 ± 0.074 | 0.085 ± 0.047 | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | <0.001* | | |

*t* Student's *t* test, *p p* value for comparing between the two groups, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio

*highly significant

**Table 3** Comparison between each group before and after treatment and the two studied groups according to total cholesterol level

| **Total cholesterol** | **Groups** | | ***T* test** | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **Before** | | | | |
| **Range** | 117–190 mg/dl | 130–256 mg/dl | − 3.633 | <0.001* |
| **Mean ± SD** | 153.260 ± 20.101 mg/dl | 174.000 ± 35.001 mg/dl | | |
| **After** | | | | |
| **Range** | 129–207 mg/dl | 135–223 mg/dl | − 0.932 | 0.354 |
| **Mean ± SD** | 174.120 ± 19.050 mg/dl | 178.200 ± 24.396 mg/dl | | |
| **Differences** | | | | |
| **Mean ± SD** | − 20.860 ± 11.889 mg/dl | − 4.200 ± 21.928 mg/dl | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.182 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

**Table 4** Comparison between each group before and after treatment and the two studied groups according to triglyceride level

| **Triglyceride** | **Groups** | | ***T* test** | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **Before** | | | | |
| **Range** | 60–142 mg/dl | 67–194 mg/dl | − 1.175 | 0.243 |
| **Mean ± SD** | 113.220 ± 22.933 mg/dl | 120.320 ± 36.072 mg/dl | | |
| **After** | | | | |
| **Range** | 53–152 mg/dl | 65–168 mg/dl | − 3.599 | 0.001* |
| **Mean ± SD** | 105.660 ± 23.272 mg/dl | 124.100 ± 27.763 mg/dl | | |
| **Differences** | | | | |
| **Mean ± SD** | 7.560 ± 11.608 mg/dl | − 3.780 ± 23.342 mg/dl | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.258 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

between 60 and 142 mg/dl with a mean of 113.220 ± 22.933 mg/dl, and triglycerides after treatment ranging between 53 and 152 mg/dl with a mean of 105.660 ± 23.272 mg/dl. There was a significant statistical difference before and after treatment where the *p* value was <0.001. While patients in group II had triglycerides before treatment ranging between 67 and 194 mg/dl with a mean of 120.320 ± 36.072 mg/dl and triglycerides after treatment ranging between 65 and 168 mg/dl with a mean of 124.100 ± 27.763 mg/dl, there was no significant statistical difference between before and after treatment where the *p* value was 0.258. There was no significant statistical difference as regards triglyceride between the two groups before treatment, where the *p* value was 0.243, but there was a significant statistical difference after treatment, where the *p* value was 0.001.

Table 5 describes and compares each group before and after treatment with DAAs and the two groups as regards the HDL level of the study population. Patients in group I had HDL before treatment ranging between 32 and 73 mg/dl with a mean of 54.660 ± 10.149 mg/dl, HDL after treatment ranging between 34 and 75 mg/dl with a mean of 57.280 ± 10.321 mg/dl. There was a significant statistical difference before and after treatment where the *p* value was 0.010. While patients in group II had HDL before treatment ranging between 40 and 74 mg/dl with a mean of 56.500 ± 10.009 mg/dl, HDL after treatment ranging between 40 and 72 mg/dl with a mean of 54.580 ± 8.026 mg/dl, there was a significant statistical difference between before and after treatment where the *p* value was 0.042. There was no significant statistical difference as regards HDL between the two groups, where

**Table 5** Comparison between each group before and after treatment and the two studied groups according to HDL Level

| HDL | Groups | | *T* test | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **Before** | | | | |
| **Range** | 32–73 mg/dl | 40–74 mg/dl | − 0.913 | 0.364 |
| **Mean ± SD** | 54.660 ± 10.149 mg/dl | 56.500 ± 10.009 mg/dl | | |
| **After** | | | | |
| **Range** | 34–75 mg/dl | 40–72 mg/dl | 1.460 | 0.147 |
| **Mean ± SD** | 57.280 ± 10.321 mg/dl | 54.580 ± 8.026 mg/dl | | |
| **Differences** | | | | |
| **Mean ± SD** | − 2.620 ± 6.925 mg/dl | 1.920 ± 6.512 mg/dl | | |
| **Paired test** | | | | |
| ***P*value** | 0.010* | 0.042* | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

**Table 6** Comparison between each group before and after treatment and the two studied groups according to LDL Level

| LDL | Groups | | *T* test | |
|---|---|---|---|---|
| | **Group I** | **Group II** | ***t*** | ***P* value** |
| **Before** | | | | |
| **Range** | 56–94 mg/dl | 60–140 mg/dl | − 4.501 | <0.001* |
| **Mean ± SD** | 74.700 ± 9.921 mg/dl | 91.140 ± 23.844 mg/dl | | |
| **After** | | | | |
| **Range** | 59–114 mg/dl | 60–128 mg/dl | − 0.166 | 0.869 |
| **Mean ± SD** | 93.300 ± 12.090 mg/dl | 93.760 ± 15.491 mg/dl | | |
| **Differences** | | | | |
| **Mean ± SD** | − 18.600 ± 7.762 mg/dl | − 2.620 ± 18.147 mg/dl | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.312 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

the *p* value was 0.364, 0.147 before and after treatment, respectively.

Table 6 describes and compares each group before and after treatment with DAAs and the two groups as regards the LDL level of the study population. Patients in group I had LDL before treatment ranging between 56 and 94 mg/dl with a mean of 74.700 ± 9.921 mg/dl, LDL after treatment ranging between 59 and 114 mg/dl with a mean of 93.300 ± 12.090 mg/dl. There was a significant statistical difference before and after treatment where the *p* value was <0.001. While patients in group II had LDL before treatment ranging between 60 and 140 mg/dl with a mean of 91.140 ± 23.844 mg/dl, LDL after treatment ranging between 60 and 128 mg/dl with a mean of 93.760 ± 15.491 mg/dl, there was no significant statistical difference between before and after treatment where the *p* value was 0.312. There was a significant statistical difference as regards LDL between the two groups before treatment, where the *p* value was <0.001, but there was no significant statistical difference after treatment, where the *p* value was 0.869.

Table 7 describes and compares each group before and after treatment with DAAs and the two groups as regards the FBS of the study population. Patients in group I had FBS before treatment ranging between 3.8 and 6.7 mmol/L with a mean of 5.448 ± 0.771 mmol/L, FBS after treatment ranged between 4.3 and 6.7 mmol/L with a mean of 5.290 ± 0.602 mmol/L, there was no significant statistical difference before and after treatment where the *p* value was 0.066. While patients in group II had FBS before treatment ranging between 4.2 and 6.5 mmol/L with a mean of 5.176 ± 0.613 mmol/L and FBS after treatment ranging between 4.3 and 6.2 mmol/L with a mean of 5.204 ± 0.422 mmol/L, there was no significant statistical difference between before and after treatment where the *p* value was 0.699. There was a significant

**Table 7** Comparison between each group before and after treatment and the two studied groups according to fasting blood sugar

| FBS (mmol/L) | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *t* | *P* value |
| **Before** | | | | |
| **Range** | 3.8–6.7 mmol/L | 4.2–6.5 mmol/L | 1.953 | 0.054* |
| **Man ± SD** | 5.448 ± 0.771 mmol/L | 5.176 ± 0.613 mmol/L | | |
| **After** | | | | |
| **Range** | 4.3–6.7 mmol/L | 4.3–6.2 mmol/L | 0.827 | 0.410 |
| **Mean ± SD** | 5.290 ± 0.602 mmol/L | 5.204 ± 0.422 mmol/L | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.158 ± 0.594 mmol/L | − 0.028 ± 0.508 mmol/L | | |
| **Paired test** | | | | |
| ***P*value** | 0.066 | 0.699 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups, *FBS* fasting blood sugar

*highly significant

**Table 8** Comparison between each group before and after treatment and the two studied groups according to fasting insulin level

| Fasting insulin | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *t* | *P* value |
| **Before** | | | | |
| **Range** | 4–19 mIU/L | 3–14 mIU/L | 6.005 | <0.001* |
| **Mean ± SD** | 11.480 ± 3.315 mIU/L | 7.620 ± 3.109 mIU/L | | |
| **After** | | | | |
| **Range** | 5–16 mIU/L | 3–13 mIU/L | 3.119 | 0.002* |
| **Mean ± SD** | 9.720 ± 2.214 mIU/L | 8.220 ± 2.582 mIU/L | | |
| **Differences** | | | | |
| **Mean ± SD** | 1.760 ± 3.255 mIU/L | − 0.600 ± 2.695 mIU/L | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.122 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

statistical difference as regards FBS between the two groups before treatment, where the *p* value was 0.054 but there was no significant statistical difference after treatment, where the *p* value was 0.410.

Table 8 describes and compares each group before and after treatment with DAAs and the two groups as regards the fasting insulin level of the study population. Patients in group I had fasting Insulin before treatment ranged between 4 and 19 mIU/L with a mean of 11.480 ± 3.315 mIU/L, fasting insulin after treatment ranged between 5 and 16 mIU/L with a mean of 9.720 ± 2.214 mIU/L. There was a significant statistical difference before and after treatment where the *p* value was <0.001. While patients in group II had fasting Insulin before treatment ranging between 3 and 14 mIU/L with a mean of 7.620 ± 3.109 mIU/L, fasting Insulin after treatment ranging between 3 and 13 mIU/L with a mean of 8.220 ± 2.582 mIU/L, there was no significant statistical difference between before and after treatment where the *p* value was 0.122. There was a significant statistical difference as regards fasting insulin between the two groups where the *p* value was <0.001 before treatment and 0.002 after treatment.

Table 9 describes and compares each group before and after treatment with DAAs and the two groups as regards the HOMA-IR of the study population. Patients in group I had HOMA-IR before treatment ranging between 0.67 and 4.9 with a mean of 2.795 ± 0.999 and HOMA-IR after treatment ranging between 1 and 4.5 with a mean of 2.263 ± 0.691. There was a significant statistical difference before and after treatment where the *p* value was <0.001. While patients in group II had HOMA-IR before treatment ranging between 0.6 and 4 with a mean of 1.794 ± 0.895 and HOMA-IR after treatment ranging between 0.6 and 3 with a mean of 1.918 ± 0.670, there was no significant statistical difference between before and after treatment where the *p* value was 0.277. There was a significant statistical difference concerning HOMA-IR between the two groups where the *p* value was <0.001, 0.013 before and after treatment, respectively.

**Table 9** Comparison between each group before and after treatment and the two studied groups according to HOMA-IR

| HOMA-IR | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *t* | *P* value |
| **Before** | | | | |
| **Range** | 0.67–4.9 | 0.6–4 | 5.280 | <0.001* |
| **Mean ± SD** | 2.795 ± 0.999 | 1.794 ± 0.895 | | |
| **After** | | | | |
| **Range** | 1–4.5 | 0.6–3 | 2.532 | 0.013* |
| **Mean ± SD** | 2.263 ± 0.691 | 1.918 ± 0.670 | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.533 ± 0.994 | − 0.124 ± 0.798 | | |
| **Paired test** | | | | |
| ***P*value** | <0.001* | 0.277 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

**Table 10** Comparison between each group before and after treatment and the two studied groups according to HbA1c

| HbA1c | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *t* | *P* value |
| **Before** | | | | |
| **Range** | 4.9–6.2 % | 4.9–6.1% | 2.680 | 0.009* |
| **Mean ± SD** | 5.602 ± 0.404 % | 5.394 ± 0.372% | | |
| **After** | | | | |
| **Range** | 4.7–6.2% | 4.9–5.8% | 0.249 | 0.804 |
| **Mean ± SD** | 5.466 ± 0.384% | 5.450 ± 0.241% | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.136 ± 0.308% | − 0.056 ± 0.355% | | |
| **Paired test** | | | | |
| ***P*value** | 0.003* | 0.270 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

*highly significant

Table 10 describes and compares each group before and after treatment with DAAs and the two groups as regards the HbA1c of the study population. Patients in group I had an HbA1c before treatment ranging between 4.9 and 6.2% with a mean of 5.602 ± 0.404% and an HbA1c after treatment ranging between 4.7 and 6.2% with a mean of 5.466 ± 0.384%. There was a significant statistical difference before and after treatment where the *p* value was 0.003. While patients in group II had HbA1c before treatment ranging between 4.9 and 6.1% with a mean of 5.394 ± 0.372%, HbA1c after treatment ranging between 4.9 and 5.8% with a mean of 5.450 ± 0.241%, there was no significant statistical difference between before and after treatment where the *p* value was 0.270. There was a significant statistical difference as regards HbA1c between the two groups before treatment, where the *p* value was 0.009 but there was no significant statistical difference after treatment, where the *p* value was 0.804.

Table 11 describes and compares each group before and after treatment with DAAs and the two groups as regards the serum adiponectin level of the study population. Patients in group I had serum adiponectin before treatment ranging between 1.5 and 30 µg/ml with a mean of 11.958 ± 7.800 µg/ml and serum adiponectin after treatment ranging between 1 and 27 µg/ml with a mean of 11.734 ± 7.793 µg/ml. There was no significant statistical difference before and after treatment where

**Table 11** Comparison between each group before and after treatment and the two studied groups according to serum adiponectin level

| Serum adiponectin | Groups | | *T* test | |
|---|---|---|---|---|
| | Group I | Group II | *t* | *P* value |
| **Before** | | | | |
| **Range** | 1.5–30µg/ml | 1.8–40 µg/ml | − 1.902 | 0.060 |
| **Mean ± SD** | 11.958 ± 7.800 µg/ml | 15.454 ± 10.394 µg/ml | | |
| **After** | | | | |
| **Range** | 1–27 µg/ml | 1.5–34 µg/ml | − 1.122 | 0.265 |
| **Mean ± SD** | 11.734 ± 7.793 µg/ml | 13.514 ± 8.067 µg/ml | | |
| **Differences** | | | | |
| **Mean ± SD** | 0.224 ± 5.240 µg/ml | 1.940 ± 6.987 µg/ml | | |
| **Paired test** | | | | |
| ***P*value** | 0.764 | 0.055 | | |

*t* Student's *t* test, *p p* value for comparing between the two groups

the *p* value was 0.764. While patients in group II had serum adiponectin before treatment ranging between 1.8 and 40 µg/ml with a mean of 15.454 ± 10.394 µg/ml, serum adiponectin after treatment ranging between 1.5 and 34 µg/ml with a mean of 13.514 ± 8.067 µg/ml, there was no significant statistical difference between before and after treatment where the *p* value was 0.055. There was no significant statistical difference as regard serum adiponectin between the two groups where the *p* value was 0.060, 0.265 before and after treatment respectively.

## Discussion

Hepatitis C is a disease that affects people all over the world. In 2015, the World Health Organization estimated that 71 million people worldwide were living with chronic HCV infection, equating to a global prevalence of 1%. There are significant regional variations. In other countries, such as Egypt, the prevalence is greater than 10% [19].

HCV infection causes persistent liver inflammation, which can lead to chronic hepatitis, cirrhosis, and hepatocellular cancer. Until recently, anti-HCV treatment was limited to interferon (IFN-based regimens), which can produce serious adverse effects and have a low cure rate [3]. The introduction of direct-acting antivirals (DAAs), or oral drugs that directly stop the replication cycle of HCV, resulted in a significant improvement in HCV therapy. These drugs provide better sustained virological responses (SVRs) than interferon-based regimens, take less time to treat, are taken orally, and have fewer adverse effects. Individual DAAs differ in terms of therapeutic efficacy, genotypic efficacy, side effects, and drug-drug interactions (DDIs), and they must be administered in conjunction with at least one additional DAA [20].

Chronic hepatitis virus infection is linked to a wide range of metabolic abnormalities. HCV interferes with lipid metabolism, causing steatosis and a wide range of adipocytokine alterations, as well as impairing glucose metabolism, resulting in a rise in the prevalence of insulin resistance (IR) and type 2 diabetes. This link is significant because the presence of IR has been linked to an elevated risk of fibrosis in various studies. Also, fewer people have a rapid and durable response to antiviral medication [8].

The effects and linkages between DAAs and changes in lipid profile and IR continue to emerge as a result of ongoing research. However, many of these effects have yet to be proven and remain disputed [21]. Because both HCV infection and changes in adipocytokines like adiponectin are important in lipid and glucose metabolism, their possible link has piqued researchers' interest [22].

Since there is limited information on the effects of DAA therapy on metabolic profiles, lipid profiles, and adiponectin levels, we investigated the changes in lipid profiles, metabolic profiles, and adiponectin levels associated with the use of DAA therapy for infection with hepatitis C type 4, which is responsible for nearly all cases of HCV infection in Egypt, the country with the highest rate of hepatitis. Although there have been other studies of this type, few, if any, have focused on type 4 HCV, which is the subject of this study.

Group I included 28 males (56%) and 22 females (44%), while Group II included 23 males (46%) and 27 females (54%). The BMI of patients in group I before treatment ranged between 24.5 and 29 with a mean of 27.114 ± 1.161 and after treatment ranged between 25.2 and 29 with a mean of 27.252 ± 1.009. There was a statistically significant difference before and after treatment in this group, where the *p* value was 0.021. While the BMI of patients in group II before treatment ranged between

24.2 and 28.4 with a mean of 26.486 ± 1.165 and after treatment ranged between 24 and 28.1 with a mean of 26.500 ± 1.008, there was no statistically significant difference before and after treatment in this group where the *p* value was 0.855**.**

As regards the changes in the platelet count, in this study, there was a significant improvement in platelet count 12 weeks after treatment with DAA in both groups, with a *P* value of <0.001 which was similar to Dahal et al. [23], findings, which studied the effect of DAA on platelets in patients with pretreatment thrombocytopenia. As well, van der Meer and Berenguer [24] concluded that improvement in platelet count in patients who reached SVR.

As regards the changes in the liver profile, this current study showed that in group I we found there was a significant improvement in the liver profile (there was a decrease in ALT, AST, total bilirubin, INR, and an increase in the serum albumin level). In group II, we found significant improvement in AST level and INR without significant changes in ALT, total bilirubin, and serum albumin level. Veldt et al. [25] concluded that there was an improvement in liver function tests in patients with chronic hepatitis C infection who reached SVR after using interferon-based therapy. Also, Miyaki et al. [26] found that there was a reduction in AST, ALT, and INR and an increase in serum albumin levels in patients who achieved SVR after DAA treatment.

As regards the changes in the lipid profile, this study illustrates a significant difference in the lipid profile in group I before and after treatment. As, we found a significant reduction in serum triglycerides and a significant elevation of serum cholesterol, LDL, and HDL at 12 weeks after treatment. This goes with Ghada et al. [21] who found a significant reduction in serum triglycerides and a significant elevation of serum cholesterol, LDL, HDL, and LDL/HDL ratio at 12 weeks post-treatment in the study conducted on 80 patients with chronic hepatitis C infection genotype 4 treated with sofosbuvir/simeprevir for 12 weeks. Also, Vanessa et al. [27] found an increase in total cholesterol and LDL levels, a decrease in triglycerides at 12 weeks post-treatment in total cholesterol and LDL levels, and a decrease in triglycerides at 12 weeks post-treatment. But in our study, there was no significant difference in the lipid profile in group II before and after treatment, which is against Ghada et al. [21] and Vanessa et al. [27].

As regards the changes in the metabolic profile, this study illustrates a significant difference in the metabolic profile in group I before and after treatment. Although we found no changes as regards fasting blood sugar before and after treatment, we found a significant reduction in fasting insulin, HOMA-IR, and HBA1C at 12 weeks after treatment. This goes with Ghada et al. [21] who found significant improvement in fasting insulin and HOMA-IR post-treatment with DAAs. It also goes with Amilcar et al. [15] who found eradication of HCV resulted in a significant drop in HbA1C in the study conducted on 60 patients with chronic hepatitis C infection treated with a Sofosbuvir based regimen, But there was no significant difference in the metabolic profile (fasting blood sugar, fasting insulin, HOMA-IR, and HBA1C) in group II before and after treatment, which goes against Ghada et al. [21] and Amilcar et al. [15].

As regards the changes in the serum adiponectin level, this study illustrates no significant difference in the serum adiponectin level in either group before and 12 weeks after treatment, where the *p* value was 0.764 in group I and the *p* value was 0.055 in group II. Ludovico and Luigi [28] documented that there was a decrease in adiponectin level 24 weeks after HCV clearance in the study conducted on 546 patients with chronic hepatitis C infection treated with pegylated interferon-a-2b and ribavirin.

## Conclusion

Eradication of chronic hepatitis C virus infection with DAAs may have an impact on the lipid and metabolic profile of patients with SVR, depending on the kind of DAAs employed and the stage of liver disease and related comorbidities of the patients. The levels of serum adiponectin, on the other hand, are unaltered.

#### Abbreviations

HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; IR: Insulin resistance; DAAs: Direct-acting antivirals; BMI: Body mass index; TC: Serum total cholesterol; TG: Serum triglycerides; LDL: Serum low-density lipoprotein; HDL: Serum high-density lipoprotein; HOMA-IR: Homeostasis Model of Assessment - Insulin Resistance index; SVR: Sustained virological response; U/S: Ultrasound; GIT: Gastrointestinal tract; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio; Na: Sodium; K: Potassium; CBC: Complete blood count; ELISA: Enzyme-linked immunosorbent assay; ANOVA: Analysis of variance; ROC-curve: Receiver operating characteristic curve; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve.

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#### Authors' contributions

A.A.S., A.M.L, G.S.M., A.O.A., N.G.G., and A.A.S. conceived and planned the experiments. A.M.L contributed to sample preparation. All authors provided critical feedback and helped shape the research, analysis, and manuscript. All authors have read and approved the manuscript.

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**Availability of data and materials**
The authors confirm that the data supporting the findings of this study are available within the article.

## Declarations

**Ethics approval and consent to participate**
All procedures performed in this study were in accordance with the ethical standards of Ain Shams University Research Committee and with the 1964 Helsinki declaration and its later amendments.
Ethics committee's reference number: 000017585.
Address: Faculty of Medicine, Ain Shams University, Cairo 11211, Egypt.
Informed written consent was obtained from each participant before enrolment in the study.

**Consent for publication**
Informed written consent to publish patient's data was signed by all participants prior to the beginning of the research.

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

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## Publisher's Note