Effect of Direct-Acting Antiviral Therapy on Lipid Profile in Egyptian Patients with Chronic Hepatitis C Infection

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ABSTRACT

Background: Widespread metabolic disturbances are linked to chronic hepatitis virus infection. Steatosis is caused by HCV's interference with lipid metabolism. Low lipid profiles and the development of chronic liver disease are both associated with hepatitis C virus infection.

Objective: We aimed to evaluate the effect of direct-acting antiviral therapy on serum lipid profile among Egyptians with chronic hepatitis C infection.

Patients and Methods: Sixty individuals with chronic hepatitis C infection who were given direct-acting antiviral treatment were analyzed in this study. 30 naïve patients received (sofosbuvir + daclatasvir) during 12 weeks and 30 naïve Patients received (sofosbuvir + daclatasvir + ribavirin) during 12 weeks, lipid profile was done before and after treatment.

Results: In our results, the lipid profile regarding triglyceride and cholesterol, before treatment and throughout the entire follow-up, neither group differed significantly from the other, after three months, The levels of triglycerides and cholesterol were significantly high in both group with much more higher in group I. Regarding LDL and HDL no significant difference pretreatment was detected, but the increase in LDL and decrease in HDL were found in both groups and in group I was significantly higher than group II after one and three months.

Conclusion: we conclude that Direct acting antiviral drug treatment for chronic HCV infection resulted in a dramatic increase in lipid profile in these patients.

Keywords: Lipid Profile; Chronic Hepatitis C Infection; Direct-acting antiviral therapy.

INTRODUCTION

Two and a half percent of the world's population has HCV infection, making it a major threat to public health around the world. This amounts to roughly 177.5 million people (1). The Egyptian population has a greater incidence of serum anti-HCV (2). Several studies have linked HCV to poor lipid profiles, making people more susceptible to conditions like dyslipidemia, liver steatosis, and progressive fibrosis (3). It is believed that lipids may play a structural or regulatory role in the HCV life cycle. However, hypobetalipoproteinemia due to HCV binding to lipoprotein has been observed and may be a major avenue for decreasing lipid profiles during HCV infection (4).

Dysregulated blood lipid levels, specifically low levels of low-density lipoprotein cholesterol, have been found by multiple investigations with HCV infection (5), and the levels of blood triglycerides (TG) in HCV infection are poorly understood. Deposition of TG and liver steatosis have been linked to liver fibrosis in another investigation (6). The affection of chronic HCV infection's fibrosis stage by lipid profiles has only been studied in a small number of cases.

Despite the widespread use of direct-acting anti-viral medications like protease inhibitors in the West, Despite this, many nations' primary treatment for HCV infection is still the combination of ribavirin (RBV) as well as Pegylated interferon-alpha (PegIFN) for chronic hepatitis C (CHC)(7). The degree to which lipid levels rise after PegIFN/RBV therapy is largely determined by how quickly the HCV RNA is eliminated. On the other hand, a post-treatment rise in lipid levels is influenced by the presence of advanced fibrosis (8).

The serum lipid profile during DAA therapy may represent not only the pharmacological effect of DAAAs but also recovery from the disturbance of lipid metabolism caused by HCV (9). As the changes in these parameters after HCV infection cure is of interest but are not well-documented, the current study intends to analyze the influence of antiviral medicine on lipid profiles and explore the factors connected to changes in lipid profiles in CHC patients.

The goal of this research was to determine how the administration of direct-acting antiviral medication affected lipid profiles in the blood of Egyptians who were suffering from chronic hepatitis C.

PATIENTS AND METHODS

The Antiviral Therapy Center at Aswan Fever Hospital was the site of this prospective cohort study. Sixty Egyptians with chronic hepatitis C infection were studied; all were adults older than 18 and all were receiving direct-acting antiviral medication. According to the April 2019 modification to the National Committee for the Control of Viral Hepatitis protocol, patients were randomly assigned to one of two groups. Group I: Included 30 naïve patients who received (sofosbuvir + daclatasvir) for 12 weeks. Both sofosbuvir (400 mg) and daclatasvir (60 mg) are taken orally once a day. Group II: Included 30 naïve Patients received (sofosbuvir + daclatasvir + ribavirin) for 12 weeks. Both sofosbuvir (400 mg) and daclatasvir (60
mg) are taken orally once a day. Ribavirin started by 600 mg daily in two divided doses (200, 400) mg increasing according to patient tolerability.

**Exclusion Criteria:** Conditions such as pregnancy, Child-Pugh score C who had decompensated liver cirrhosis, Hepatocellular Carcinoma, and chronic or heavy alcohol use are all risk factors, Patients on lipid-lowering agents (such as statins or fibrates), patients on long-term steatosis-inducing drugs (like amiodarone, tamoxifen, corticosteroids), patients who abused intravenous drugs, patients who were morbidly obese or diabetic, and patients who declined participation were excluded from the study.

**All patients were subjected to the following:** A complete medical history, physical examination, and BMI determination=$\frac{\text{mass(kg)}}{(\text{height (m)})^2}$.

**Laboratory investigations:** Pre- and post-treatment serum HCV RNA concentrations were measured using a commercially available quantitative assay via polymerase chain reaction (PCR), as well as complete blood count, liver function tests (serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, and Prothrombin time), serum creatinine, lipid profile (serum triglyceride (TG), serum HDL (good) cholesterol, and serum LDL (bad) cholesterol), and Prothrombin time.

**Ethical consent:** The study was sanctioned by the Academic and Ethical Committee of Ain Shams University. Acceptance of participation in the trial was contingent on the patient providing written informed permission. All procedures involving human subjects in this study have been performed in compliance with the principles outlined in the World Medical Association’s Declaration of Helsinki on human research ethics.

**Statistical analysis:**

The IBM SPSS software suite, version 21.0, was used to input the data into the computer. Quantitative and percentage descriptions were used for qualitative information. The Chi-square test was used to compare groups based on category factors. For regularly distributed data, we use mean and standard deviation, but for non-normally distributed data, we use median, minimum, and maximum. When comparing three or more populations, the F-test is used unless the data are normally distributed, in which case the independent t-test is used (ANOVA). That will be put to good use. The results of the significance tests were reported as two-tailed probabilities. The obtained results were deemed significant at the 5% level. The Chi-Square Test: Since it focuses mostly on frequency distributions, it is a test of the relationship between qualitative nominal variables. Is there a statistically significant difference between the observed and predicted frequencies? The cutoff for significance was set at $P = 0.05$.

**RESULTS**

**Table (1):** The T.G. differences between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I SOF+Dacla “n=30”</th>
<th>Group II sof+dacla+ribavirin “n=30”</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (mg/dL) Mean±S.D.</td>
<td>135.3± 31.3</td>
<td>150.4± 31.9</td>
<td>1.76</td>
<td>0.0662</td>
</tr>
<tr>
<td>After one month of treatment (mg/dL) Mean±S.D.</td>
<td>146.4± 34.4</td>
<td>158.1± 34.4</td>
<td>1.08</td>
<td>0.1176</td>
</tr>
<tr>
<td>After three months of treatment (mg/dL) Mean±S.D.</td>
<td>150.9± 35.6</td>
<td>158.1± 35.2</td>
<td>0.904</td>
<td>0.2386</td>
</tr>
<tr>
<td>ANOVA test P-value</td>
<td>8.25</td>
<td>6.05</td>
<td>0.013*</td>
<td>0.043*</td>
</tr>
</tbody>
</table>

**Table (2):** Comparison of cholesterol levels between both groups

Table (2) displays a contrast in cholesterol levels between the two groups studied. A comparison of cholesterol levels over time showed no statistically significant difference between the two groups ($P > 0.05$), however, there was a statistically significant correlation between the two groups ($P < 0.05$).
Table (3) displays a contrast in LDL levels between the two groups studied. One and three months into treatment, there was a statistically significant difference in LDL levels between the two groups (P < 0.05), Although there was no discernible variation before antiviral therapy, (P > 0.05). Each group's interval times were statistically significantly related to one another. (P < 0.05).

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Group I SOF+Dacla “n=30”</th>
<th>Group II sof+dacla+ribavirin “n=30”</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (mg/dL) Mean±S.D.</td>
<td>159.6± 29.2</td>
<td>156.6± 35.1</td>
<td>0.901</td>
<td>0.3587</td>
</tr>
<tr>
<td>After one month of treatment (mg/dL) Mean±S.D.</td>
<td>171.7± 32.2</td>
<td>162.9± 36.9</td>
<td>1.14</td>
<td>0.1645</td>
</tr>
<tr>
<td>After three months of treatment (mg/dL) Mean±S.D.</td>
<td>175.8± 32.4</td>
<td>163.7± 37.5</td>
<td>1.45</td>
<td>0.0938</td>
</tr>
<tr>
<td>ANOVA test P-value</td>
<td>15.2</td>
<td>6.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.001*</td>
<td>0.023*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Comparison of LDL between both groups

<table>
<thead>
<tr>
<th>LDL</th>
<th>Group I SOF+Dacla “n=30”</th>
<th>Group II sof+dacla+ribavirin “n=30”</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (mg/dl) Mean±S.D.</td>
<td>107.9± 23.2</td>
<td>119.6± 28.5</td>
<td>1.85</td>
<td>0.067</td>
</tr>
<tr>
<td>After one month of treatment (mg/dl) Mean±S.D.</td>
<td>114.7± 26.4</td>
<td>137.8± 34.3</td>
<td>9.58</td>
<td>0.0053*</td>
</tr>
<tr>
<td>After three months of treatment (mg/dl) Mean±S.D.</td>
<td>117.0± 26.6</td>
<td>138.5± 34.4</td>
<td>8.58</td>
<td>0.0095*</td>
</tr>
<tr>
<td>ANOVA test P-value</td>
<td>6.52</td>
<td>12.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.039*</td>
<td>0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (4) displays a comparison of HDL levels between the two groups. After one and three months of treatment, there was a statistically significant difference in HDL levels between the two groups (P < 0.05), Although there was no apparent variation before antiviral therapy, (P > 0.05). Each group's interval times were statistically significantly related to one another. (P < 0.05).

<table>
<thead>
<tr>
<th>HDL</th>
<th>Group I SOF+Dacla “n=30”</th>
<th>Group II sof+dacla+ribavirin “n=30”</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (mg/dl) Mean±S.D.</td>
<td>40.9± 7.0</td>
<td>41.5± 6.6</td>
<td>0.98</td>
<td>0.125</td>
</tr>
<tr>
<td>After one month of treatment (mg/dl) Mean±S.D.</td>
<td>34.8± 6.6</td>
<td>39.6± 6.5</td>
<td>6.98</td>
<td>0.0030*</td>
</tr>
<tr>
<td>After three months of treatment (mg/dl) Mean±S.D.</td>
<td>33.7± 6.4</td>
<td>36.3± 6.6</td>
<td>3.25</td>
<td>0.007*</td>
</tr>
<tr>
<td>ANOVA test P-value</td>
<td>12.52</td>
<td>5.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0013*</td>
<td>0.016*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (5) displays a comparison of HCV PCR results between the two groups. No significant difference in HCV PCR levels was found between the two groups over time (P > 0.05), while across all groups, there was a statistically significant correlation between interval times (P < 0.05).
DISCUSSION

Infection with the hepatitis C virus is a worldwide epidemic. It raises the chances of getting liver cancer, liver cirrhosis, and chronic liver disease. The liver plays a crucial role in lipid metabolism, and the hepatitis C virus has been related to both decreased lipid profiles and the development of chronic liver disease. Several studies have linked HCV to poor lipid profiles, making people more susceptible to conditions like dyslipidemia, liver steatosis, and progressive fibrosis.

It is believed that lipids may play a structural or regulatory role in the HCV life cycle. However, hypobetalipoproteinemia due to HCV binding to lipoprotein has been observed and may be a major avenue in decreasing lipid profiles during HCV infection. Serum triglyceride (TG) levels are poorly understood, and some studies have found dysregulated serum lipid levels in HCV infection, particularly low levels of low-density lipoprotein cholesterol (LDLC). Deposition of TG and liver steatosis, according to another study, may contribute to liver fibrosis. The effect of chronic HCV infection’s fibrosis stage on lipid profiles has only been studied in a small number of cases. The lipid profile during DAA therapy may represent not only the pharmacological effect of DAAs but also recovery from the disturbance of lipid metabolism caused by HCV.

The lipid profile showed no statistically significant difference in baseline triglyceride or cholesterol levels between the two groups in our study. On the other hand, at the end of follow-up after three months, it was found that there was a significant increase in triglyceride and cholesterol in the two groups, but the increase in group I (Sof+Dacla) was more than the increase in group II (sof+dacla+ribavirin). Regarding LDL and HDL, the levels of the two variables pre-treatment were matched without significant difference, the increase in LDL and decrease in HDL in group I was significantly higher than the increase in group II after one and three months, on the other hand on comparing the level of LDL and HDL pre-treatment with the final follow up after 3 months, it was found that there was a significant increase in LDL and decrease in HDL in the two groups.

Consistent with our findings, Jain et al. investigated the impact of sofosbuvir and daclatasvir on the lipid profile of individuals with chronic hepatitis C. They found that both total cholesterol and LDL cholesterol levels increased significantly. The elimination of HCV appears to play a significant role in cholesterol levels, but the treatment regimen chosen (interferon or directly acting anti-viral drugs) may have an effect on lipid metabolism, as demonstrated by a 20mg/dL increase in total cholesterol levels in patients treated with interferon-based therapy.

In comparison with our study, Felmlee et al. reported that Lipid levels were changed during DAA treatment for HCV, even after SVR eradication was achieved. Increases in HDLC and LDLC were found in patients who achieved SVR, whereas triglyceride levels remained unchanged. Serum cholesterol and HDLC were significantly increased after SVR, although triglycerides and HDLC were not. This was determined by subgroup analysis of genotype 1a, 1b, and 2 infections. Similar results were seen in another study conducted on people of genotype 6, which demonstrated a similar pattern of significantly increased blood cholesterol and LDLC following SVR but no change in triglycerides or HDLC.

Higher baseline blood LDL and cholesterol levels have been suggested as potentially meaningful prognostic indicators for treatment outcomes in chronic hepatitis C patients undergoing IFN-based therapy, however, this finding has not been substantiated by additional research. Also, Kuo et al., Patients who achieved SVR had decreased serum total cholesterol levels compared to those who did not.

El-leheh et al. who compared lipid profiles of HCV patients before and after therapy to assess the impact of virus clearance on lipid levels, find certain results that are consistent with our own. They found a significant reduction in serum in cholesterol, TGs, and
LDL-C in the patients studied than the control group before treatment mean = 190.09±16.63 mg/l, P = 0.0001, 81.85±18.21 mg/l, P = 0.0001, and 118.75±15.76 mg/l, P = 0.001, respectively, no significant change in HDL-C compared to the control group statistically (17).

In the results of a previous study, it was found a significant increase in LDL-C at the end of treatment with DCV and SOF as well as at 12 weeks of follow-up: mean = 132.59±14.22 and 133.67±17.72 mg/l, respectively (P ≤ 0.05) (17). In addition, Vespastrani-Gentiliucci(18) reported that sofosbuvir-induced metabolic changes occur via a multifactorial mechanism. As a result of these variations, the study found significant alterations in several metabolic variables. Furthermore, Doyle et al. (19) conducted before-and-after research on 24 HCV patients and found that both sofosbuvir and ribavirin resulted in changes to the lipid profile.

Similar to our findings, Inoue et al. (20)’s cohort analysis of 170 HCV patients demonstrated an increase in both total and LDL cholesterol after treatment with sofosbuvir. In addition, the lipid profile of HCV patients, particularly LDL and total cholesterol, may improve with the use of sofosbuvir-containing regimens, as observed by Kanda et al. (21). A comparable significant increase in LDL and total cholesterol was also seen in a cohort study by Endo et al. (13) involving 276 individuals.

IFN regimens were associated with an increase in triglycerides, whereas sofosbuvir regimens were associated with increases in total and LDL cholesterol, but HDL showed no significant modifications in a study of 250 HCV patients conducted by Mauss et al. (22) However, they found that the levels of good cholesterol (HDL) did alter during the trial.

Furthermore, telaprevir, an NS3/4A protease inhibitor, suppresses lipid synthesis in vitro, particularly LDL-C receptor expression (23). According to another study, an increase in serum LDL-C level served as the most reliable predictor of response to telaprevir-based triple therapy (24). According to these studies, the combination of SOF and LDV may increase LDL-C because SOF can raise blood LDL-C levels. In addition, NS5A inhibitors like LDV may have a synergistic impact with SOF, leading to an immediate rise in LDL-C levels followed by a subsequent fall in both TC and LDL-C levels. There must be more research done, particularly looking at the impact of SOF on LDL-C receptor expression (24).

CONCLUSION
In this study, we could conclude that Patients with chronic HCV infection who were given either Sofosbuvir and Daclatasvir + Ribavirin or Sofosbuvir and Daclatasvir alone experienced a significant rise in their lipid profile.

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Conflict of interest: Nil.

REFERENCES


