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Metabolic Changes in Egyptian Patients with HCV Related Chronic Liver Disease after Oral Antiviral Therapy

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Abstract

Background: Hepatitis C Virus (HCV) has complex interactions with human lipid metabolism leading to down regulation of cholesterol level. Interferon (IFN) therapy has been shown to decrease cholesterol even further during treatment but increase after successful HCV eradication. With the availability of second-generation direct acting antiviral agents (DAA) the effect of suppressing and eliminating HCV on lipid metabolism warrants re-evaluation.

Aim of the work: Goal of our study is evaluation of the changes in lipid profile after treatment of chronic HCV infection with oral antiviral medications in diabetic patient who attended to Al-Azhar University specialized hospital, in the period from December 2017 to March 2018.

Methods: In this prospective study conducted on 90 HCV patients related chronic liver disease, all patients received Sofosbuvir (SOF) & Daclatasvir (DCV) as a dual therapy for 3 months. They were divided according to the presence or absence of diabetes mellitus (DM) and hyperlipidaemia into three main groups; Group I: included30 diabetic hyperlipidaemic patients with chronic HCV infection, Group II: included 30 non-diabetic hyperlipidaemic patients with chronic HCV infection and Group III: which included 30 non-diabetic non-dyslipidaemia patients with chronic HCV infection. Changes of lipid profile in HCV patients on treatment with DAA were assessed by checking fasting lipid profile at base line, then at the end of treatment (i.e. 12th week of treatment), and finally 3 months after treatment (i.e. 24th week of treatment). Treatment was considered successful when patients became non-viremia as identified by negative HCV RNA serum polymerase chain reaction (PCR) at 12 weeks from the end of the treatment regimens; this is called sustained virological response (SVR).

Results: On treatment there was a statistically significant increase in total cholesterol level (TCHOL) which was maintained after the end of therapy. changes in TCHOL were driven by changes in low-density lipo-protein (LDL) cholesterol, whereas high-density lipo-protein (HDL) cholesterol and very low-density lipo-protein (VLDL) cholesterol showed no significant changes. There were also no significant changes in triglyceride (TG) level on treatment.

Conclusion: Supressing and eliminating HCV with DAAs increased TCHOL but had no effect on TG level.

Keywords: Psoriasis; IRIS; HIV; AIDS; Cart; ART; Autoimmune disease

Introduction

HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and hepatocellular carcinoma (HCC). Approximately, 130–150 million people are infected with HCV each year, besides an estimated 399 000 people die from complications of HCV including cirrhosis, malignant neoplastic disease (HCC) and liver failure [1]. Unluckily, many people with HCV only know about their infection when they experience symptoms of cirrhosis or liver cancer [2]. Chronic HCV infection is associated with hepatic steatosis and hypocholesterolaemia [3]. HCV utilizes peripheral lipid metabolism pathways for viral assembly and requires several apo-lipoproteins for production of infective particle [4,5], so patients with HCV infection show a reduction of serum TCHOL and LDL and Apo-lipoprotein B (Apo-B) levels [6]. The field of HCV therapeutics has evolved rapidly; in 2013, the treatment of HCV was transformed by the introduction of a new class of medicines called direct-acting antivirals (DAAs). An 8-12-week course of these medicines can cure more than 90% of persons with chronic HCV infection. These new oral treatments offer tremendous opportunities and hope to all those who are infected [7]. Successful clearance of HCV viremia with immunomodulatory therapy (Peg INF and ribavirin) has been associated with a decrease in TCHOL and LDL [8]. But the impact of DAAs on lipid metabolism is thus far uncharacterized, so it's evaluated in our study.

Methods and Materials

Prospective study was conducted at Al-Azhar university specialized hospital where 90 HCV patients related chronic liver disease were selected. All patients received SOF & DCV as a dual therapy for 3 months at HCV treatment clinic in the period from December 2017 to March 2018. All patients signed an informed written consent after explanation of the aim of the study and the study details. They were divided according to the presence or absence of DM and hyperlipidaemia into three main groups; Group I: included 30 diabetic hyperlipidaemic patients with chronic HCV infection, Group II:

included 30 non-diabetic hyperlipidaemic patients with chronic HCV infection and Group III: which included 30 non-diabetic non-dyslipidaemia patients with chronic HCV infection. Changes of lipid profile on treatment with DAA were assessed by checking fasting lipid profile at base line, then at the end of treatment (i.e. 12th week of treatment), and finally 3 months after treatment (i.e. 24th week of treatment). Treatment was considered successful when patients became non-viremic as identified by negative HCV RNA serum PCR at 12 weeks from the end of the treatment regimens; this is called SVR. All patients were subjected to detailed history taking including age, sex, history of other comorbid conditions such as DM, hypertension, Cardiac disease and renal failure, history of drugs including antidiabetic, antihypertensive or antihyperlipidemic drugs , history of previous treatment with anti-HCV medicines (e.g. peg INF plus ribavirin, SOF plus Ribavirin or other combination regimens) were also evaluated and measurement of body mass index (BMI). Before starting DAA therapy, laboratory tests were carried out that included, twelve hours fasting plasma lipid profile {included serum CHOL, LDL, HDL, VLDL and T.G level}, eight hours fasting plasma glucose (FPG), Two hours post prandial blood sugar (2HPPBS), glycosylated haemoglobin (HbA1c), qualitative HCV RNA polymerase chain reaction test, liver enzymes, serum bilirubin, serum albumin, and the international normalized ratio(INR), serum creatinine, and complete blood picture (CBC). During the study period, all patients were advised to maintain their usual diet regimen and physical activity. Application of inclusion and exclusion criteria was taking in consideration The Egyptian National HCV Control Program guide lines; inclusion criteria included the following: the age range was between 18 and 75 years and all patients tested positive for serum real time HCV RNA PCR, while exclusion criteria included the following :patients who are co-infected with HIV or HBV, patients who <18 or >75 years old, Pregnant female, patients who has HCC or other extrahepatic malignancy, Whose Total serum total bilirubin more than 3mg/dl, Serum albumin less than 2.8 g/dl , INR more than 1.7, Platelet count less than 50,000/mm, Renal impairment with estimated glomerular filtration rate (e GFR) less than 30 ml/minute, Non-compliant patients, whose haemoglobin (Hb) level less than 10 g/dl and HbA1C>9% .

Results

Groups		At base (N=30)	12 Wk (N=30)	24 wk (N=30)	ANOVA P-Value
	Variables				
(mg/dl) CHOL	Mean	228.1	243.4	247	<0.001*
	± SD	12.1	8.5	9.8	
(mg/dl) LDL	Mean	158.2	175.3	177.3	<0.001*
	± SD	8.3	8.4	8.1	
(mg/dl) HDL	Mean	36.1	37.1	36.7	<0.001*
	± SD	3.1	2.3	2.6	
(mg/dl) TG	Mean	178	178.5	180.5	<0.001*
	± SD	9.02	8.9	7.04	
(mg/dl) VLDL	Mean	35	35.5	36.1	<0.001*
	± SD	2.1	2.8	2.04	

Table 1: Comparison between studied lipid profiles (at base, 12 week and 24 week) in group I (Diabetic Dyslipidemic).

Table 1 shows highly statistically significant difference (p-value<0.001) in TCHOL and LDL level (at base, 12 week and 24 week) in group I, No statistically significant difference (p-value>0.05) in HDL, TG and VLDL levels (at base, 12 week and 24 week) in group I.

Groups		At base (N=30)	12 Week (N=30)	24 Week (N=30)	ANOVA P-Value
	Variables				
(mg/dl) CHOL	Mean	221.1	226.7	231	<0.001*
	± SD	6.6	5.7	6.1	
(mg/dl) LDL	Mean	138.2	155.2	157.4	<0.001*
	± SD	4.03	8.02	8.4	
(mg/dl) HDL	Mean	37.5	39	38.5	0.05

	± SD	2.1	2.5	2.4	
	Mean	170	171	172.5	
(mg/dl) TG	± SD	7.3	7.5	6.4	0.4
	Mean	34	34.2	34.5	
(mg/dl) VLDL	± SD	2.3	2.5	2.8	0.7

Table 2: Comparison between studied lipid profiles (at base, 12 week and 24 week) as in group II (Non-Diabetic Dyslipidemic)

Table 2 shows highly statistically significant difference (p-value<0.001) in TCHOL and LDL levels (at base, 12 week and 24 week) in group II and no statistically significant difference (p-value>0.05) in HDL, TG and VLDL levels (at base, 12 week and 24 week) in group II.

Groups		At base (N=30)	12 Week (N=30)	24 Week (N=30)	ANOVA P-Value
	Variables				
(mg/dl) CHOL	Mean	165	181.2	186.1	
	± SD	10.6	6.9	6.1	<0.001*
(mg/dl) LDL	Mean	89	107.5	109.2	
	± SD	5.1	17.01	7.5	<0.001*
(mg/dl) HDL	Mean	56.4	57.5	57	
	± SD	2.04	1.9	1.7	0.09
(mg/dl) TG	Mean	90	91	92	
	± SD	3.7	4.1	4.1	0.2
(mg/dl) VLDL	Mean	17.5	18	18.4	
	± SD	2.4	2.1	2.4	0.3

Table 3: Comparison between studied lipid profiles (at base, 12 week and 24 week) as in group III (Non-Diabetic non-Dyslipidaemia).

Table 3 shows-highly statistically significant difference (p-value<0.001) in CHOL and LDL levels (at base, 12 week and 24 week) in group III, no statistically significant difference (p-value>0.05) between HDL, TG and VLDL levels (at base, 12 week and 24 week) in group III.

Groups at 0:24 weeks	Group 1 (N=30)	Group 2 (N=30)	Group 3 (N=30)	ANOVA P-Value	
CHOL (%)	Mean	8.56	9.52	10.1	
	± SD	7.21	4.37	7.7	0.009
LDL (%)	Mean	12.35	14.02	11.9	
	± SD	8.14	6.66	9.58	0.4
HDL (%)	Mean	2.44	2.8	1.2	
	± SD	10.17	6.21	5.11	0.7
TG (%)	Mean	1.51	1.58	2.25	
	± SD	3.91	4.75	4.12	0.8
VLDL (%)	Mean	3.5	1.53	6.15	
	± SD	8.45	5.69	13.66	0.2

Table 4: Comparison between studied groups as regard % of increased lipid profile items at 0:24 weeks.

Table 4 shows no statistically significant difference (p-value>0.05) between studied groups as regard % of increased CHOL, LDL, HDL, TG and VLDL at 0:24 weeks.

Group 1	(r)	p=value
% increased CHOL *vs.* age	-0.3	0.1
% increased CHOL *vs.* BMI	0.09	0.6
% increased CHOL *vs.* baseline CHOL	-0.8	<0.001**

Table 5: Correlation study between % of increased CHOL (0:24) and (age, BMI & base line CHOL) in group I

Table 5 shows-Highly statistically significant (p-value<0.001) Negative correlation (r=-0.5) between % of increased CHOL (0:24) and base line CHOL in group I, no statistically significant (p-value >0.05) correlation between % of increased CHOL (0:24) and (age & BMI) in group I.

Group 1	(r)	p=value

% increased CHOL *vs.* age	0.4	0.9
% increased CHOL *vs.* BMI	0.2	0.4
% increased CHOL *vs.* baseline CHOL	-0.7	<0.001**

Table 6: Correlation study between % of increased CHOL (0:24) and (age, BMI & base line CHOL) in group 1

Table 6 shows-highly statistically significant (p-value<0.001) Negative correlation (r=-0.7) between % of increased CHOL (0:24) and base line CHOL in group II, no statistically significant (p-value>0.05) correlation between % of increased CHOL (0:24) and (age & BMI) in group II.

Group 1	(r)	p=value
% increased CHOL *vs.* age	0.3	0.1
% increased CHOL *vs.* BMI	0.07	0.7
% increased CHOL *vs.* baseline CHOL	-0.9	<0.001*

Table 7: Correlation study between % of increased CHOL (0:24) and (age, BMI& base line CHOL) in group III

Table 7 shows highly statistically significant (p-value<0.001) negative correlation (r=-0.9) between % of increased CHOL (0:24) and base line CHOL in group III and no statistically significant (p-value>0.05) correlation between % of increased CHOL (0:24) and (age & BMI) in group III.

Discussion

HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and HCC Chronic HCV infection is associated with hepatic steatosis and hypocholesterolaemia [3]. HCV utilizes peripheral lipid metabolism pathways for viral assembly and requires several apo-lipo-proteins for production of infective particles [4,5], so patients with HCV infection show a reduction of serum TCHOL, LDL and Apo-B levels [6]. Successful clearance of HCV viremia with immunomodulatory therapy (Peg INF and ribavirin) has been associated with a rise in TCHOL, and LDL [1]. But the impact of DAAs on lipid metabolism is thus far uncharacterized. In this study we found that there was an increase in TCHOL from baseline to 24 weeks of treatment in the studied groups, and this increase was highly statistically significant (p-value<0.001). In group I; TCHOL was (228.1 ± 12.1 mg/dl) at baseline, then (243.4 ± 8.5 mg/dl) at 12 weeks, and (247 ± 9.8 mg/dl) at 24 weeks, in group II; TCHOL was (211.1 ± 6.6 mg/dl) at baseline, then (226.7 ± 5.7 mg/dl) at 12 weeks, and (231 ± 6.1 mg/dl) at 24 weeks. In group III; TCHOL was (165 ± 10.6 mg/dl) at baseline, then (181.2 ± 6.9 mg/dl) at 12 weeks, and (186.1 ± 6.1 mg/dl) at 24 weeks. There were no significant statistical differences between the studied groups as regard the rise in TCHOL (p-value>0.05), In group I; the percent of increase in TCHOL from baseline to week 12 was (7.01 ± 6.73mg/dl), and from baseline to week 24 was (8.56± 7.21 mg/dl). In group II; the percent of increase in TCHOL from baseline to week 12 was (7.50 ± 4.13mg/dl), and from baseline to week 24 was (9.52 ± 4.37 mg/dl),In group III; the percent of increase in TCHOL from baseline to week 12 was (10.16 ± 6.76, mg/dl), and from baseline to week 24 was (10.1 ± 7.70 mg/dl).This increase in total cholesterol was driven by mainly increase in LDL, as we found that there was an increase in LDL in the studied groups and this increase was highly statistically significant (p-value<0.001), In group I; LDL was (158.2 ± 8.3 mg/dl) at baseline, then (175.3 ± 8.4 mg/dl) at 12 weeks, and (177.3 ± 8.1 mg/dl) at 24 weeks, In group II; LDL was (138.2 ± 4.03, mg/dl) at baseline, then (155.2 ± 8.02 mg/dl) at 12 weeks, and (157.4 ± 8.4, mg/dl) at 24 weeks, In group III; LDL was (89 ± 5.1 mg/dl) at baseline, then (107.5 ± 17.01, mg/dl) at 12 weeks, and (109.2 ± 7.5 mg/dl) at 24 weeks. There was no significant statistical difference, between the studied groups as regard the rise in LDL (p-value>0.05), In group I; the percent of increase in LDL from baseline to week 12 was (11.11 ± 8.49, mg/dl), and from baseline to week 24 was (12.35 ± 8.14 mg/dl),In group II; the percent of increase in LDL from baseline to week 12 was (12.38 ± 5.78, mg/dl), and from baseline to week 24 was (14.02 ± 6.66 mg/dl),In group III; the percent of increase in LDL from baseline to week 12 was (11.8 ± 6.86 mg/dl), and from baseline to week 24 was (11.9 ± 9.58 mg/dl).As regard HDL, VLDL and TG. There was no significant statistical difference in any group neither in at 12th week, nor 24th weeks of the study as compared with base line levels (p-value>0.05). Our findings of increase in TCHOL, and LDL, after eradication of HCV can be explained by a return to 'normal' pre-infection lipid patterns after elimination of the effect of HCV on lipid levels. Our results were in agreement with Mausset et al. [8], who found that there was a rapid significant increase of TCHOL (by a median +17 'IQR: 6-32' at end of treatment and by median +22 'IQR: 1-43' at 12 weak after end of treatment) and LDL-cholesterol (by a median +13 'IQR:3-24' at end of treatment and by median +17 'IQR:-2-39'at 12 weak after end of treatment) as compared with baseline values (P<0.001, respectively) in a larger number of patients treated with a variety of DAA combinations while HDL-cholesterol and TG levels remain unchanged during and after therapy [8]. Our results were also in agreement with [9] ,who found that HDL and TG levels did not change over time of treatment with various DAA combinations, but the mean TCHOL and LDL values were significantly increased (from 154 ± 34 to 170 ± 37 mg/dL, p<0.001 and from 80 ± 26 to 102 ± 34 mg/dL, p<0.001, respectively) [9-10]. In this study, there was a highly statistical significant (p-value<0.001) negative correlation between the percent of increased TCHOL (0:24) and base line TCHOL in the studied groups, but there was no statistical significant (p-value>0.05) correlation between percent of increased TCHOL (0:24) and other variables (e.g. age , sex , BMI & presence or absence of DM) in the studied groups and this was in agreement with Mausset al. [8], who found that there were no risk factors for increase TCHOL except lower baseline TCHOL [8].

Conclusion:

This study concluded that there is significant increase in TCHOL mainly driven by increase in LDL cholesterol after successful clearance of HCV by DAA regardless presence or absence of Diabetes.

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