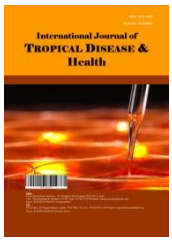

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Glucose and Lipid Profile Changes in Hepatitis C Patients After Direct Acting Antivirals Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. Chronic HCV infection is associated with development of insulin resistance and therefore type 2 Diabetes mellitus (T2DM), it is also associated with hepatic steatosis and hypocholesterolemia. The treatment by Direct Acting Antivirals (DAAs) leads to sustained virological response (SVR) in almost all infected patients and decreases liver-related as well as all-cause mortality in these patients. The evidence for the effect of DAAs therapy on T2DM is quite conflicting. Some studies agreed with the glucometabolic amelioration induced by the Sustained Virological Response (SVR) but other studies disagreed with this hypothesis. The aim of the work was to evaluate glucose and Lipid Profile changes in hepatitis C patients at 12 weeks post treatment (SVR12) by Direct Acting Antivirals Therapy.

Methods: This prospective study was carried out on 80 chronic HCV infected patients who are treatment naïve and subjected to HCV DAAs treatment (Daclatasvir + Sofosbuvir for 12 weeks +/- Ribavirin or any DAA available) with 100% SVR rate at 12 weeks with no relapse. All patients are subjected to assessment of Fasting blood glucose, HbA1C and assessment of Lipid profile; Total cholesterol, Triglycerides, HDL, LDL at baseline (pretreatment) and at end of treatment then they are followed up at SVR12.

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Results: Average HbA1C, fasting blood glucose has significantly decreased in group A diabetic patients from baseline to end of treatment and to SVR12, Average Total Cholesterol, LDL has significantly increased in group A and B from baseline to end of treatment and to SVR12 respectively. Average Triglycerides has significantly decreased from baseline to end of treatment in group A and B and to SVR12 in group A only. Average HDL has significantly increased only in group B non-diabetics from baseline to end of treatment and to SVR12.
Conclusions: Successful clearance of HCV viremia (SVR12) with DAAs treatment has been associated with significant Improvement or decrease of HbA1c and Fasting plasma glucose levels in diabetic chronic HCV infected patients, and has been associated with Rise in the Lipid profile; Total Cholesterol, LDL, HDL (non-diabetics only) while it decreases Triglycerides in both diabetic and non-diabetic chronic HCV infected patients.

Keywords: Glucose and lipid profile changes; hepatitis C; direct acting antivirals therapy.

1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting approximately 115 million people worldwide according to positivity of HCV antibodies, not all of them are currently HCV-infected, some are cleared spontaneously, others are cleared by treatment, The global prevalence of HCV according to positivity of HCV RNA is lower or 71 million people are chronic HCV infected patients worldwide with important variations between countries. Egypt has the highest prevalence of HCV in the world. In Egypt, HCV seroprevalence rates reach 13% of the population equating to an estimated 12 million Egyptians of whom around 8 million people are living with chronic HCV with or without cirrhosis or liver cancer. HCV is not only a complicated disease process but a serious public health, economic and social problem that transcends the boundaries of biomedicine.

The hepatic injury ranges from minimal histological changes to extensive fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC). People suffering from HCV infection are also at increased risk of extrahepatic manifestations and may develop Type 2 Diabetes Mellitus (T2DM) and cardiovascular complications such as acute coronary events, ischemic strokes and nephropathy. Chronic HCV infection is associated with development of insulin resistance (IR) and therefore T2DM, it is also associated with hepatic steatosis and hypocholesterolemia where HCV utilizes peripheral lipid metabolism pathways for viral assembly and requires several Apo-lipo-proteins for production of infective lipo-viro particles so patients with HCV infection show a reduction of serum total cholesterol, low-density lipoprotein (LDL), While Successful clearance of HCV viremia or sustained virological response (SVR) with Direct Acting Antivirals (DAAs) treatment has been associated with a decrease in Fasting glycaemia and rise in Total cholesterol and LDL. We aimed to evaluate glucose and Lipid Profile changes in hepatitis C patients at 12 weeks post treatment (SVR12) by Direct Acting Antivirals Therapy.

2. PATIENTS AND METHODS

This study was a prospective study which was carried out on 80 Patients with chronic HCV who were going to be treated with DAAs Therapy at Tanta University Hospital and Tanta Fever Hospital in the period from April 2019 till April 2020. All 80 patients were treatment naïve and were subjected to HCV DAAs treatment (Daclatasvir + Sofosbuvir for 12 weeks +/- Ribavirin or any DAA available).

Patients were divided into two groups:

Patients with diabetes mellitus and chronic HCV (Group A) and the other 40 patients with chronic HCV infection without diabetes (Group B) as a control group. The Inclusion criteria were patients with chronic HCV detected with quantitative polymerase chain reaction (PCR) assessment, aged 18 years or older indicated for HCV DAAs Treatment while the Exclusion criteria were General contra-indications for DAAs treatment: Patients who have been exposed to prior DAA treatment, current or prior episode of decompensated cirrhosis defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7), renal impairment whom eGFR <30 mL/min/m2, platelets count < 50000 / mm3, Hemoglobin< 10 gm/dl, Hepatocellular carcinoma (HCC), Extra-hepatic malignancy, patients with prior liver

transplantation, pregnant women, Patients who have not achieved SVR at 12 weeks of DAAs Treatment and patients taking drugs affecting lipid profile and patients with positive HBsAg were excluded.

2.1 Pretreatment Assessment

All our patients were subjected to:

- Full history taking.
- Clinical examination.
- Laboratory investigations (Complete blood count (Hb, WBCs, Platelets), Hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST], alkaline phosphatase, prothrombin time or International normalized ratio (INR)), Fasting plasma glucose, HbA1c, HbsAg, HCV Ab, PCR for HCV RNA, Alpha feto protein, Urea, Creatinine, Total Cholesterol, LDL, HDL, Triglycerides and Pregnancy test for females in child bearing period).
- We calculated Child-Turcotte Pugh score for all patients and calculated also their APRI and FIB-4 scores.
- Radiological assessment of Liver using Abdominal Ultrasound (USS) and or fibroscan and Triphasic CT to exclude patients with HCC and subclinical ascites.
- Cardiologic assessment by ECG and Echocardiogram only for patients who are 65 years older or if needed.
- Diagnosis of cirrhosis was made if evidence of cirrhosis on imaging is present or FIB-4 >3.25 or If APRI >2.0 or If Fibroscan™ stiffness >12.5 kPa were present.

2.2 Recommended Regimen

According to The Egyptian Ministry of Health and The National Committee for Control of Viral Hepatitis (NCCVH) protocol for treatment of Hepatitis C:

2.3 Daclatasvir (60mg) / Sofosbuvir (400mg) +/- Ribavirin (or any DAA available) for a duration of 12 Weeks

(The starting dose of Ribavirin is 600mg/dl and will be increased to reach dose of 1000mg/dl based on patient tolerability). Liver biochemical tests and CBC were done every 4 Weeks during treatment.

2.4 End of Treatment Assessment

At the end of DAAs treatment, we assessed quantitative HCV RNA and a hepatic function panel 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable. We also assessed HbA1c levels, Fasting Plasma glucose levels and The Lipid profile; Total Cholesterol, LDL, HDL, Triglycerides levels for all patients.

2.5 Post-Treatment Follow Up of Patients Who Achieved SVR

We estimated HCV load at 12 weeks post-treatment (SVR12).

All patients were assessed for Fasting plasma glucose changes, HbA1C changes and further assessment of Lipid profile changes of Total cholesterol, Triglycerides, HDL, LDL.

We recommended Ultrasound surveillance for HCC (with or without alpha-fetoprotein testing) every 6 months for patients with cirrhosis in addition to Upper endoscopic surveillance for esophageal varices.

2.6 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data was described using range mean and standard deviation. Significance of the obtained results was judged at the 5% level; The used tests were: Chi-square test: For categorical variables, to compare between different groups. Student t-test: For normally distributed quantitative variables, to compare between two studied groups. ANOVA with repeated measures: For normally distributed quantitative variables, to compare between more than two periods or stages, and Post Hoc test (Bonferroni adjusted) for pairwise comparisons. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups. Friedman test: For abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn's) for pairwise comparisons. Odd ratio

(OR): Used to calculate the ratio of the odds and 95% Confidence Interval of an event occurring in one risk group to the odds of it occurring in the non-risk group.

3. RESULTS

Regarding BMI and HCV load before treatment with DAAs therapy, there were significant differences between both groups (Table 1).

HbA1C levels has significantly decreased over time with treatment in group A diabetic patients from baseline to end of treatment and to after 12 weeks post treatment while no statistically significant difference between mean HbA1C at end of treatment and after 12 weeks post treatment. Regarding Fasting blood glucose, it has significantly decreased over time with treatment in group A diabetic patients from baseline to end of treatment with statistically significant difference as well as falling from baseline to after 12 weeks post treatment, while no statistically significant difference between mean fasting blood glucose at end of treatment and after 12 weeks post treatment (Table 3).

Regarding association between T2DM (group A) with various risk factors, there was a statistically significant association between T2DM (group A) and each of Age, BMI, HCV load before treatment with DAA therapy and Fib-4 score, while there was no association between T2DM (group A) and each of Sex and APRI score. In addition to that the multivariate logistic regression analysis indicates that the most potent statistically significant risk factors associated with T2DM (group A) are Age, and HCV load before treatment. Other less potent statistically significant risk factors are BMI, and FIB-4 Score (Table 4).

Regarding the factors associated with improvement of fasting blood glucose (significant >5% decrease) over time with treatment from the start of DAAs therapy to end of treatment in group A diabetic patients. The model was statistically significant and it indicated significant association between improvement of fasting glycemia with treatment and HCV load before treatment, Baseline HBA1C and Baseline Fasting blood Glucose, while it excluded association with Age, Sex, BMI, Thrombocytes, APRI Score and FIB-4 Score (Table 5).

Regarding lipid profile levels over time with treatment, Patients in the diabetic group A had significantly higher baseline LDL levels when compared to the non-diabetic group B and Patients in group A also had significantly higher baseline Triglycerides levels when compared to group B, while the mean pretreatment (baseline) Total cholesterol, HDL levels did not differ significantly between group A and group B. Group A had significantly higher mean end of treatment LDL levels than group B as well as significantly higher mean LDL levels after 12 weeks post treatment in group A versus in group B, also group A had significantly lower mean end of treatment HDL levels than group B, while the mean end of treatment and after 12 weeks post treatment of Total cholesterol , Triglycerides did not differ significantly between group A and group B (Table 6).

As Regard Total cholesterol and LDL, serum levels have significantly increased over time with treatment from baseline to end of treatment in groups A and B, as well as Total cholesterol have also significantly increased from baseline levels to after 12 weeks post treatment levels in group A from and group B, while no statistically significant difference between total cholesterol levels at end of treatment and after 12 weeks post treatment in both groups (Table 7).

Table 1. Baseline characteristics of all study groups

	Group A (n = 40)	Group B (n = 40)	P value
Age (years)	58.85 ± 9.31	57.98 ± 13.54	$^{t}p<0.523$
Sex (Male)	14 (35.0%)	16 (40.0%)	$^{x2}p=0.644$
BMI (kg/m^2)	30.70 ± 3.47	28.21 ± 4.46	$^{t}p=0.007^{*}$
HCV RNA (Before Tx)	20 (6-35) x (10)^5	13.5 (6-29) x (10)^5	$^{U}p=0.003^{*}$
SVR	40 (100.0%)	40 (100.0%)	
Child–Pugh score (A5/A6)	27/13 (67.5% / 32.5%)	30/10 (75% / 25%)	$^{x2}p=0.459$
Dual / Triple Therapy	29/11(72.5%/27.5%)	38/2 (95% / 5%)	$\chi 2p=0.073$
HTN	12 (30%)	9 (22.5%)	$^{x2}p=0.446$
Insulin Tx	15 (37.5%)		
OAD Tx	16 (51.6%)		

Table 2. Baseline laboratory data of all study groups

	Group A (n = 40)	Group B (n = 40)	P value
Hb (g/dl)	12.34 ± 0.63	12.46 ± 0.83	^{t}p= 0.469
WBCS (×10³/µl)	6908.8 ± 2285.1	6435.0 ± 1727.5	^{t}p= 0.299
Platelets (×10³/µl)	153.1 ± 17.60	182.33 ± 16.87	^{t}p= 0.841
Total Bilirubin (mg/dl)	1.1 ± 0.41	0.97 ± 0.37	^{t}p= 0.533
Direct Bilirubin (mg/dl)	0.81 ± 0.26	0.76 ± 0.25	^{t}p= 0.358
Albumin (mg/dl)	3.97 ± 0.45	3.94 ± 0.39	^{t}p= 0.750
INR	1.10 ± 0.21	1.13 ± 0.21	^{t}p= 0.595
AST (u/l)	62.55 ± 10.86	67.40 ± 14.23	^{t}p= 0.091
ALT (u/l)	52.55 ± 13.06	47.90 ± 8.12	^{t}p= 0.060
Alpha Feto Protein (ng/l)	29.0 (11.0 – 44.0)	19.50 (10.0 – 41.0)	^{U}p= 0.007*
Urea (mg/dl)	65.40 ± 15.25	51.50 ± 13.02	^{t}p<0.001*
Creatinine (mg/dl)	1.32 ± 0.18	1.19 ± 0.21	^{t}p=0.003*
HbA1C (%)	8.29 ± 1.66	4.73 ± 0.37	^{t}p<0.001*
Fasting Glucose (mg/dl)	237 (86.0 – 397.0)	96.5 (77.0 – 182.0)	^{U}p<0.001*
Total Cholesterol (mg/dl)	167.2 ± 34.44	156.0 ± 28.97	^{t}p= 0.120
Triglycerides (mg/dl)	131.5 (48.0 – 211.0)	101.5 (45.0 – 258.0)	^{U}p=0.040*
HDL (mg/dl)	51.0 ± 12.57	55.35 ± 9.72	^{t}p= 0.087
LDL (mg/dl)	91.02 ± 31.54	78.28 ± 23.93	^{t}p= 0.046*
APRI Score	1.54 (1.20 – 2.20)	1.62 (1.30 – 3.0)	^{U}p= 0.060
FIB-4 Score	5.23 ± 1.27	4.59 ± 0.99	^{t}p= 0.014*

Table 3. Mean changes of Fasting blood glucose and HbA1C levels at baseline, end of Tx, After 12w of end in group A

	Baseline	End of Tx	After 12wk of end	P value
Fasting blood glucose (mg/dl)	237 (86 – 397)	191 (71 – 453)	194 (92 – 390)	^{Fr}p<0.001*
Sig. bet. Periods	p_1<0.001*p_2<0.001*p_3=0.371			
HbA1C (%)	8.29 ± 1.66	8.06 ± 1.78	8.07 ± 1.78	^{F}p<0.001*
Sig. bet. Periods	p_1<0.001*p_2<0.001*p_3=1.000			

Table 4. Association of T2DM (group A) with various risk factors

	Univariate		Multivariate	
	P value	OR (95%CI)	P value	OR (95%CI)
Age (years)	<0.001*	1.085 (1.037–1.136)	0.019*	1.086*(1.013-1.165)
Sex (male)	0.644	0.808 (0.326–2.000)		
BMI (kg/m^2)	0.010*	1.173 (1.039–1.325)	0.242	1.083 (0.948 – 1.238)
HCV RNA (Before Tx)	0.003*	1.103 (1.033 –1.178)	0.022*	1.086*(1.012 – 1.165)
APRI Score	0.067	0.201 (0.036 –1.120)		
FIB-4 Score	0.018*	1.650 (1.089 –2.501)	0.548	0.827 (0.445 – 1.537)

As Regard Triglycerides, serum levels have significantly decreased over time with treatment from baseline to end of treatment in group A and group B, as well as serum Triglycerides have also significantly decreased from baseline levels to after 12 weeks post treatment levels in group A only, while no statistically significant difference between serum Triglycerides levels at end of treatment and after 12 weeks post treatment in both groups (Table 7).

As Regard HDL-Cholesterol, results are quite conflicting where there is statistically significant difference between mean baseline HDL levels and end of treatment HDL levels in group B as well as there is statistically significant difference between mean baseline HDL levels and after 12 weeks post treatment HDL levels in group B only, In contrast no statistically significant difference between neither mean HDL baseline levels and end of treatment levels in group A nor between mean HDL baseline levels and after 12 weeks post treatment levels in group A, but a significant difference is present between mean end of treatment HDL levels and mean after 12 weeks post treatment HDL levels in group A (Table 7).

Table 5. Predictors of (Significant >5%) decrease of Fasting glycemia after DAAs therapy in group A

	5% Decrease of Glycemia Achieved	5% Decrease of Glycemia not Achieved	P value	OR	95% CI
Age (years)	59.50 ± 8.96	56.25 ± 10.82	0.376	.039	0.954-1.132
Sex (male)	11 (34.4%)	3 (37.5%)	0.868	0.873	0.175 – 4.352
BMI (kg/m^2)	30.97 ± 3.60	29.60 ± 2.84	0.317	1.140	0.882 –1.473
HCV RNA (Before Tx)	28 (13– 35) x (10)^5	18 (6.0 – 31) x (10)^5	0.010*	0.805	0.682 –0.949
Baseline HbA1C (%)	8.01 ± 1.41	9.41 ± 2.20	0.042*	0.601	0.368 –0.983
Baseline FBG (mg/dl)	240.6 ± 58.68	313.3 ± 130.5	0.033*	0.988	0.977 –0.999
Baseline platelets(×10^3/µl)	101.7 ± 18.78	93.75 ± 10.29	0.257	1.029	0.979–1.082
APRI Score	1.59 ± 0.27	1.56 ± 0.24	0.802	1.487	0.067–33.125
FIB-4 Score	5.32 ± 1.32	4.87 ± 1.03	0.368	1.361	0.695–2.662

Table 6. Comparison between group A and group B as regard Lipid profile levels at baseline, end of Tx, after 12w of end

		Group A (n=40)	Group B (n=40)	P value
Total Cholesterol (mg/dl)	Baseline	167.2 ± 34.44	156.0 ± 28.97	^{t}p=0.120
	End of Tx	188.1 ± 40.57	176.8 ± 35.11	^{t}p=0.188
	After 12w of end	190.3 ± 39.27	178.4 ± 30.08	^{t}p=0.132
Triglycerides (mg/dl)	Baseline	131.5 (48 – 211)	111.7 (45 – 258)	^{U}p=0.040*
	End of Tx	106.5 (38 – 193)	93.5 (45 – 248)	^{U}p=0.218
	After 12w of end	98.5 (27– 230)	96 (29 – 219)	^{U}p=0.840
HDL (mg/dl)	Baseline	51.0 ± 12.57	55.35 ± 9.72	^{t}p=0.087
	End of Tx	51.68 ± 17.32	58.45 ± 12.66	^{t}p=0.049*
	After 12w of end	54.65 ± 15.09	59.60 ± 12.70	^{t}p=0.117
LDL (mg/dl)	Baseline	91.02 ± 31.54	78.28 ± 23.93	^{t}p=0.046*
	End of Tx	113.7 ± 41.52	96.38 ± 31.71	^{t}p=0.039*
	After 12w of end	114.6 ± 37.66	97.86 ± 25.56	^{t}p=0.023*

Table 7. Mean or Median changes of Total cholesterol, serum Triglycerides, LDL, HDL, levels at baseline, end of Tx, After 12w of end in each study group

	Baseline	End of Tx	After 12wk of end	P value
Total Cholesterol (mg/dl)				
Group A (n=40)	167.2 ± 34.44	188.1 ± 40.57	190.3 ± 39.27	<0.001*
Sig. bet. periods	p_1<0.001*p_2<0.001*p_3=0.582			
Group B (n=40)	156.02 ± 28.97	176.8 ± 35.11	178.4 ± 30.08	<0.001*
Sig. bet. periods	p_1<0.001*p_2<0.001*p_3=1.000			
Triglycerides (mg/dl)				
Group A (n=40)	131.5 (48 – 211)	106.5 (38 – 193)	98.5 (27 – 230)	<0.007*
Sig. bet. Periods	p_1=0.012*p_2=0.004*p_3=0.737			
Group B (n=40)	111.7 (45 – 258)	93.5 (45 – 248)	96 (29 – 219)	<0.017*
Sig. bet. Periods	p_1=0.005*p_2=0.057, p_3=0.371			
LDL (mg/dl)				
Group A (n=40)	91.02 ± 31.54	113.7 ± 41.52	114.6 ± 37.66	<0.001*
Sig. bet. Periods	p_1<0.001*, p_2<0.001*, p_3=1.000			
Group B (n=40)	78.28 ± 23.93	96.38 ± 31.71	97.86 ± 25.56	<0.001*
Sig. bet. Periods	p_1<0.001*, p_2<0.001*, p_3=1.000			
HDL (mg/dl)				
Group A (n=40)	51.0 ± 12.57	51.68 ± 17.32	54.65 ± 15.09	0.023*
Sig. bet. Periods	p_1=1.000, p_2=0.076, p_3=0.041*			
Group B (n=40)	55.35 ± 9.72	58.45 ± 12.66	59.60 ± 12.70	<0.001*
Sig. bet. Periods	p_1=0.002*, p_2=0.003*, p_3=0.492			

4. DISCUSSION

Patients in our study had an average age of 58.42 years, with average 58.85 ± 9.31 years in group A and average 57.98 ± 13.54 years in group B with no significant difference between groups. Regarding Sex, there was no significant difference in sex between both groups. Average body mass index (BMI) in all our patients was 29.46 kg/m2 with an average 30.7 kg/m2 in group A and 28.21 kg/m2 in group B with significant difference between groups which is explained by the fact that obesity is a high-risk factor for development of T2DM. (Ganz et al., 2014) (Schnurr et al., 2020) [1,2]. Median baseline HCV load was 20 (6-35) x105 u/ml in group A and 13.5 (6-29) x105 u/ml in group B with significant difference between groups. Increased risk of HCV infection in T2DM patients is due to the repeated, invasive medical procedures that T2DM patients usually undergo, exposing them to blood borne infections (Guo et al., 2013) [3] , this result was in accordance with (Moucari et al., 2008) [4] who showed that Insulin Resistance (IR) in HCV patients was associated with a high serum HCV RNA level and (Huang et al., 2007) [5] who concluded that a significant link between T2DM and HCV viremia existed in the HBV/HCV endemic areas. As Regard Past Medical History, 21 patients (26.25%) were hypertensive, of whom 12 patients (15%) were in group A and 9 patients (11.25%) were in group B with significant difference between groups which could be explained by close association between hypertension, T2DM and metabolic syndrome [6]. (Halpern et al., 2010). In our study, there was a mild elevation in median Alpha feto protein (AFP) of all patients in agreement with (Di Bisceglie et al., 2005) [7] who concluded that serum AFP values were frequently elevated among patients with advanced chronic hepatitis C even in the absence of HCC. That elevation was higher in group A (diabetics) than group B (nondiabetics) in disagreement with (Yang et al., 2018) [8] who concluded that T2DM was associated with lower AFP. As Regard Urea, Creatinine there was significant difference between groups (higher in group A) which could be attributed to microalbumiuria that complicates long standing T2DM (diabetic nephropathy) in group A patients. (Lou et al., 2019) [9]. Fibrosis Fib-4 score was higher in group A (diabetics) than group B (non-diabetics) and this was in accordance with (El Sagheer et al., 2018) [10] who reported that HOMA-IR and the fasting insulin showed a progressive increase with advancing stage of hepatic fibrosis. T2DM is associated with multiple risk factors that predispose insulin resistance (IR) in genetically susceptible individuals and hence T2DM in general population, So that we performed a univariate logistic regression model to predict the risk factors that were associated with T2DM (group A) in chronic HCV infected patients. We reported that each of the following is a significant risk factor for development of T2DM in HCV infected patients; Age ($p<0.001$; OR (95% C.I) 1.085 (1.037 – 1.136)) and this was in agreement with (Drazilova et al., 2018) [11] who reported that the predictive factors for baseline T2DM were higher age, higher BMI, and F4 fibrosis and no association was found between HCV RNA levels, the duration of HCV infection, gender or previous treatment. The Third National Health and Nutrition Examination Survey (NHANES-III), concluded that out of 9841 subjects evaluated, in which 8.4% had T2DM and 2.1% were anti-HCV-positive, the adjusted OR for T2DM in subjects older than 40 years was 3.8 compared to those without HCV infection, (Elhawary et al., 2011) [12] concluded that the diabetic patients in the HCV group were older than the non-diabetic HCV cases. Our results were also in agreement with (Chehadeh et al., 2009) [13] who showed that older age (≥ 50 years) was a risk factor for T2DM in HCV patients and (Mangia et al., 1998) [14] who found age and cirrhosis were associated with T2DM. BMI ($p = 0.010$; OR (95% C.I) 1.173 (1.039 – 1.325)) and this was in agreement with (Drazilova et al., 2018) (11] and in agreement with (Mehta et al., 2001) [15] who suggested that HCV increased the risk of diabetes especially in HCV patients who were already at high risk of developing diabetes, i.e. because affected by severe obesity or older than 65: these persons, during Follow Up (FU), were 11 times more likely to develop diabetes than HCV-negative individuals. Also (Saleh et al., 2015) [16] concluded that Chronic hepatitis C patients who had family history for diabetes mellitus, older age, and higher BMI were at high risk to develop diabetes mellitus type II. While this was in disagreement with (Lin et al., 2016) [17] who showed an increased risk of developing diabetes for HCV seropositive vs. HCV sero-negative individuals (hazard ratio 1.53, 95% confidence interval [CI] 1.29–1.81), and this was independent of age and BMI and in disagreement also with (El Sagheer et al., 2018) [10] who concluded that despite being non-obese, non-diabetic, or prediabetic, 45% of patients had IR >3, and the mean fasting insulin and HOMA-IR were significantly higher in the

patients group in comparison with control subjects.

Fibrosis Fib-4 score (p = 0.018; OR (95% C.I) 1.650 (1.089 – 2.501)) is a significant risk factor for development of T2DM in HCV infected patients in agreement with (Drazilova et al., 2018) and (El Sagheer et al., 2018) [10,11].

Higher HCV load before DAA treatment (p = 0.003; OR (95% C.I) 1.103*(1.033 – 1.178)) is a significant risk factor for development of T2DM in HCV infected patients in agreement with (Lin et al., 2016) [17] who showed an increased risk of developing diabetes for HCV-seropositive vs. HCV-seronegative individuals (hazard ratio 1.53, 95% confidence interval [CI] 1.29–1.81) and (Huang et al., 2007) [5] who showed that HCV viremia was the leading significant factor associated with T2DM, followed by male gender, hypertension, body mass index, and age and this is in agreement also with (Yuan et al., 2020) [18] who reported that HCV-RNA ≥ 6.55 log IU/mL was risk factor for T2DM in HCV but this was in disagreement with (Drazilova et al., 2018) [11] who reported that there was no association between HCV RNA levels, and development of type 2 DM. Using multivariate logistic regression analysis, we reported that the most potent significant risk factors for development of T2DM in chronic HCV infected patients were; Age (p = 0.019; OR (95% C.I) 1.086 (1.013 – 1.165)) and Higher HCV load before treatment (p = 0.022; OR (95% C.I) 1.086 (1.012 – 1.165)).

In our present study we observed a significant decrease of average baseline HbA1c levels in group A diabetic patients at end of treatment from (average 8.29 ± 1.66 to 8.06 ±1.78%; p1<0.001) and a significant decrease of median baseline fasting plasma glucose at end of treatment from (median 237 (86 -397) to 191 (71 - 453) mg/dl; p1<0.001) in agreement with (Drazilova et al., 2018) [11] A systematic review of multiple studies concluded that DAA therapy improved fasting glucose and HbA1C in patients with T2DM, and with prediabetes, thus reducing antidiabetic treatment in some of the patients, That was in agreement also with (Ciancio et al., 2018) [19] who concluded that a significant improvement of glycemic control was observed in diabetic patients with Chronic Hepatitis C (CHC) who obtained SVR with a clinically de- escalation of antihyperglycemic therapy. (Pavone et al., 2016) [20] showed that HCV suppression after DAA treatment was associated with a marked decrease in Fasting Blood Glucose (FBG) values to below the normal cutoff after only 4 weeks of treatment. In addition to (Hum et al., 2017) [21] who found that SVR was associated with improved glycemic control, with decreased HbA1C levels and reduced insulin requirements but this was associated with SVR in patients without severe hepatic fibrosis or cirrhosis, while (Abdel Alem et al., 2017) [22] reported that whatever the stage of hepatic fibrosis there was improvement in FBG and HbA1c values following Sofosbuvir- based treatment regimens. Our results were in concordance with a recent review with a metanalysis (Carnovale et al., 2019) [23] that demonstrated the improvement of hyperglycemia in diabetic patients with CHC achieving SVR after treatment with DAAs. Also, this was in agreement with (Fabrizio et al., 2017) [24] who reported that DAA played a role in reducing FBG levels, not only in course of therapy but also after the End of Treatment, suggesting that molecular pathways causing insulin resistance and alterations of glucose homeostasis might be inhibited by the rapid suppression of HCV replication and concurrent systemic inflammation. Our results were not similar to (Chaudhury et al., 2017) [25] who showed that the significant differences in HbA1c changes by SVR status were limited to those with baseline HbA1c >7.2% and non-cirrhotic subjects and this difference may be referred to the fact that our patients were child A but the previous study included all grades of cirrhosis. Our results were in contradiction with (Stine et al., 2017) [26] who demonstrated that HbA1c improvement was attributable to clinical management of diabetes with pharmacologic therapy rather than a primary process of viral clearance itself as nearly one-third of their cohort had increasing dosages of their anti-hyperglycemic therapy. In our study no increase of antihyperglycemic drugs was needed.

In our study, the follow up of group A diabetic patients indicated that the significant improvement (decrease) of baseline HbA1c levels was also observed at 12 weeks post treatment (SVR12) from (average 8.29 ± 1.66 to 8.07 ± 1.78%; p2<0.001), Similarly the significant improvement (decrease) of baseline fasting plasma glucose was observed at 12 weeks post treatment (SVR12) from (median 237 (86 – 397) to 194 (92 – 390) mg/dl; p2<0.001). This was in agreement with (Gilad et al., 2019) [27] who reported that treatment of HCV with direct-acting antiviral agents was associated with improved diabetes in a significant portion of patients with reduction in HbA1c and that among responders,

this effect was sustained over 1.5 years of follow-up and also in agreement with (Weidner et al., 2018) [28] who reported that Successful elimination of HCV by DAA treatment was associated with long-term decrease of glucose levels. While this was in disagreement with (Li et al., 2019) [29] who concluded that Successful hepatitis C virus treatment among patients with type 2 diabetes significantly reduced HbA1c transiently after treatment, but these decreases were not sustained, and that in less than three years after sustained virologic response (SVR), HbA1c rebounds to levels similar to untreated/treatment failure patients. These results were different from our study because we followed up our patients for only 12 weeks after end of treatment.

In order to predict the factors that were independently associated with improvement (decrease) of fasting glycaemia over time with treatment from the start of DAAs to end of treatment in group A diabetic patients, we further sub grouped group A into 2 groups upon achievement or non-achievement of significant more than or equals 5% decrease of their fasting plasma glucose at end of treatment. We found that from 40 diabetic patients (group A), Thirty three patients 82.5% had more than or equals 5% decrease in their fasting plasma glucose level at end of treatment while 7 patients 17.5% have not achieved that, then we performed a univariate logistic regression model which reported that the most important predictors of significant more than or equals 5% decrease of fasting glycaemia with treatment are; Higher Baseline HbA1c levels (P = 0.042; OR (95% C.I) 0.601(0.368-0.983)), Higher Baseline Fasting plasma Glucose levels (P = 0.033; OR (95% C.I) 0.988 (0.977-0.999)) in agreement with (Hum et al., 2017) [21] who concluded that Patients with poorer glycemic control at baseline who had a higher pretreatment HbA1c level had a greater improvement, nearly a 1% drop in the HbA1c, associated with SVR and (Chaudhury et al., 2017) [25] reported that the only significant differences in HbA1c changes by SVR status were limited to those with baseline HbA1c >7.2% and non-cirrhotic subjects. Higher HCV load before treatment (P = 0.010; OR (95% C.I) 0.805 (0.682 – 0.949)) is an important predictor of significant more than or equals 5% decrease of fasting glycaemia with treatment and this was in agreement with (Hashim et al., 2017) [30] who concluded that improvement of glycemic control with DAAs was significantly associated with higher baseline HCV load. These results were in contradiction with (Yuan et al., 2020) [18] who found that higher baseline HCV RNA levels is a negative factor for glucose improvement because a high serum HCV RNA level was associated with IR and (Moucari et al., 2008) [4] who concluded that Patients with a higher baseline HCV RNA levels had more difficult improvement of their glucose than patients with lower baseline HCV RNA levels. These different results may be due to small number of patients included in our study. We compared our groups; group A (40 diabetic CHC infected patients) with group B (40 non-diabetic CHC infected patients) as regard lipid profile changes at baseline, end of treatment and at 12 weeks post treatment (SVR12) and observed that at baseline, LDL in group A diabetic patients (average 91.02 ± 31.54 mg/dl) was higher than the group B nondiabetics (average 78.28 ± 23.93 mg/ld.); (P < 0.046) and that Triglycerides in group A (median 131.5 (48 – 211) mg/dL) was higher than group B (median 111.7 (45 – 258) mg/dL); (P < 0.040). At end of treatment, LDL in group A (average 113.7 ± 41.52 mg/dl) was still higher than group B (average 96.38 ± 31.71 mg/dl); (P = 0.039) while HDL in group A (average 51.68 ± 17.32 mg/dl) was lower than group B (average 58.45 ± 12.66 mg/dl); (P = 0.049). we observed that the significant higher LDL levels in group A than group B at baseline and at end of treatment was maintained at 12 weeks post treatment (SVR12) in group A (average 114.6 ± 37.66 mg/dl) versus (average 97.86 ± 25.56 mg/dl) in group B; (P = 0.023)) which could be explained by the fact that T2DM is a cardiovascular risk factor that is associated with high LDL. (Drazilova et al., 2018) [11].

We observed that Total cholesterol level increased significantly over time with treatment from baseline to end of treatment in group A diabetic patients (from average 167.2 ± 34.44 to 188.1 ± 40.57 mg/dl; p1<0.001) and in group B non-diabetics (from average 156.02 ± 28.97 to 176.8 ± 35.11 mg/dl; p1<0.001) as well as LDL levels increased significantly over time with treatment from baseline to end of treatment in group A (from average 91.02 ± 31.54 to 113.7 ± 41.52 mg/dl; p1<0.001) and in group B (from average 78.28 ± 23.93 to 96.38 ± 31.71 mg/dl; p1<0.001).These results were in agreement with (Hashimoto et al., 2016) [31] who observed a rapid increase in serum LDL and Total Cholesterol in HCV-infected Japanese patients between baseline and treatment day 28 under the treatment of their HCV infection with IFN-free DAA therapy, Their results showed that the

increase was strongly dependent on the type of HCV therapy, DCV/ASV combination therapy resulted in weaker increases in serum LDL-C and Total Cholesterol compared to LDV/SOF combination therapy. Our results were also in agreement with (Townsend et al., 2015) who described marked increase in serum low-density lipoprotein cholesterol (LDL-C) in HCV mono-infected or HCV/HIV coinfected patients treated with sofosbuvir and ribavirin (SOF/RBV) or ledipasvir/sofosbuvir combination therapy and report that the increase in serum LDL-C during HCV therapy was independent of the type of HCV therapy, and was likely reflective of the host's response to HCV suppression. In Addition to (EL-Lehleh et al., 2019) [32] who concluded that Successful eradication of HCV was associated with an increase in the serum level of TC, TGs, LDL-C, and HDL-C irrespective of the therapy protocol (DCV + SOF ± RBV), While (Graf et al., 2020) [33] observed a significant increase in total cholesterol, HDL, and LDL during and after antiviral therapy. Moreover, their results show a dynamic change of serum lipid parameters with a significant increase in lipid parameters and CAP (a measure of liver steatosis) values from baseline to follow-up. In agreement with (Endo et al., 2017) [34] who reported a significant increase in LDL-C during and after treatment in patients with chronic HCV genotype 1b infections, who were treated with DAA therapy. In our follow up of lipid profile changes, at 12 weeks post treatment (SVR12) in both groups we observed significant increase in Total cholesterol levels in group A (from average 167.2 ± 34.44 to 190.3 ± 39.27 mg/dl; p2<0.001) and in group B (from average 156.02 ± 28.97 to 178.4 ± 30.08 mg/dl; p2<0.001), Similarly significant increase in LDL levels was detected at 12 weeks post treatment (SVR12) levels in group A (from average 91.02 ± 31.54 to 114.6 ± 37.66 mg/dl; p2<0.001) and in group B (from average 78.28 ± 23.93 to 97.86 ± 25.56 mg/dl; p2<0.001). These results were in agreement with (Lacerda et al., 2018) [35] who followed up patients with DAA-SVR and found a progressive and significant increase of LDL-C, VLDL-C and Triglycerides, our results were also in agreement with (Naguib et al., 2019) [36] who concluded that eradication of HCV with DAAs was associated with increased level of low-density lipoproteins, Total Cholesterol and Triglycerides levels and observed that Total Cholesterol (TC), Triglycerides (TG) and LDL-C significantly increased gradually over the course of the therapy, which continued after treatment discontinuation, in addition to (Özdoğan et al., 2020) [37] who concluded that Patients with hepatitis C virus treated with DAA drugs showed increased TC, and LDL cholesterol levels during treatment. After the end of treatment, the elevated TC and LDL levels persisted indefinitely, While this was in disagreement with (Meissner et al., 2015) [38] who reported that HCV clearance by sofosbuvir (SOF) and ribavirin (RBV) led to early increase of LDL, but these lipid changes disappeared later during treatment.

As Regard HDL changes, there was statistically significant increase of baseline HDL levels at end of treatment in group B nondiabetic patients (from mean 55.35 ± 9.72 to 58.45 ± 12.66 mg/dl; p1=0.002) which was detected at 12 weeks post treatment (SVR12) (from mean 55.35 ± 9.72 to 59.60 ± 12.70 mg/dl; p2=0.003) in agreement with (El Sagheer et al., 2018) (EL-Lehleh et al., 2019) (Graf et al., 2020) (10,32,33). Our results showed that Triglycerides levels significantly decreased from baseline to end of treatment in group A diabetic patients from (median 131.5 (48 – 211) to 106.5 (38 – 193) mg/dl; p1=0.012) and in group B non-diabetics from (median 111.7 (45 – 258) to 93.5 (45 – 248) mg/dl; p1=0.005), Moreover the significant decrease in Triglycerides levels was detected at 12 weeks post treatment (SVR12) only in group A from (median 131.5 (48 – 211) to 98.5 (27 – 230) mg/dl; p2=0.004) but not in group B patients. This was in agreement with (El Sagheer et al., 2018) [10] who discussed this feature in Egyptian patients with chronic HCV genotype 4 using sof/sim – based therapy, they found a significant reduction in serum triglycerides, Fasting Blood Glucose, Fasting Insulin and HOMA-IR and a significant elevation of total serum cholesterol, LDL-C and HDL-C and LDL/HDL ratio. Our results were different from (Endo et al., 2017) [34] who reported that there was no significant change in triglyceride levels during and after treatment in patients with chronic HCV genotype 1b infections, who were treated with DAAs therapy, In addition to (Mauss et al., 2016) [39] a German multicenter cohort study on (520) HCV and HIV-HCV co-infected patients treated with direct-acting antivirals agents and concluded that Suppressing and eliminating HCV with IFN-free DAA regimens increased cholesterol levels, but had no effect on triglycerides. Our results were in contradiction with (Lacerda et al., 2018) (EL-Lehleh et al., 2019) (Naguib et al., 2019) (32,35,36) where they all report a significant increase in Triglycerides levels at the end of DAAs treatment.

5. SUMMARY

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. Chronic HCV infection is associated with development of insulin resistance and therefore type 2 Diabetes mellitus (T2DM), it is also associated with hepatic steatosis and hypocholesterolemia. The treatment by Direct Acting Antivirals (DAAs) leads to sustained virological response (SVR) in almost all infected patients and decreases liver-related as well as all-cause mortality in these patients. The evidence for the effect of DAAs therapy on T2DM is quite conflicting. Some studies agreed with the glucometabolic amelioration induced by the Sustained Virological Response (SVR) but other studies disagreed with this hypothesis.

The aim of the work was to evaluate glucose and Lipid Profile changes in hepatitis C patients at 12 weeks post treatment (SVR12) by Direct Acting Antivirals Therapy.

This prospective study was carried out on 80 chronic HCV infected patients who are treatment naïve and subjected to HCV DAAs treatment (Daclatasvir + Sofosbuvir for 12 weeks +/- Ribavirin or any DAA available) with 100% SVR rate at 12 weeks with no relapse. All patients are subjected to assessment of Fasting blood glucose, HbA1C and assessment of Lipid profile; Total cholesterol, Triglycerides, HDL, LDL at baseline (pretreatment) and at end of treatment then they are followed up at SVR12.

Our results showed that the average HbA1C, fasting blood glucose has significantly decreased in group A diabetic patients from baseline to end of treatment and to SVR12, Average Total Cholesterol, LDL has significantly increased in group A and B from baseline to end of treatment and to SVR12 respectively. while the average Triglycerides has significantly decreased from baseline to end of treatment in group A and B and to SVR12 in group A only. On the other hand, the average HDL has significantly increased only in group B non-diabetics from baseline to end of treatment and to SVR12.

6. CONCLUSION

Successful clearance of HCV viremia (SVR12) with DAA treatment has been associated with significant Improvement or decrease of HbA1c and Fasting plasma glucose levels in diabetic chronic HCV infected patients, and has been associated with rise in the Lipid profile; Total Cholesterol, LDL, HDL (non-diabetics only) while it decreases Triglycerides in both diabetic and non-diabetic chronic HCV infected patients.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

All patients signed an informed consent.

ETHICAL APPROVAL

The study protocol was approved by the research ethics committee of Faculty of Medicine, Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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