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Research Article

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Metabolic Alterations in Patients with Chronic Hepatitis C Infection in Tripoli, Libya

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ABSTRACT

Hepatitis C Virus (HCV) infection is associated with extra-hepatic manifestations, which are sometimes more serious than the viral hepatic disease itself. It is well recognized in many studies that chronic hepatitis C infection is related to hypolipidemia and type II diabetes. In Libya, literature has failed to show any previous studies on this subject and herein, our study aimed to investigate these metabolic alterations in chronically infected hepatitis C -patients. Between January 2011 and March 2012, we compared a group of 100 patients with chronic hepatitis C with another group of 100 patients with dermatological diseases and who were negative for HCV. Both groups were matched for age and sex, but confounding factors were excluded. The means of fasting serum cholesterol (CHOL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), triglyceride (TG), fasting blood sugar (FBS) and body mass index (BMI) were compared among both groups. In our study we found that the means were less among infected subjects in the level of CHOL, TG, LDL and VLDL, but were higher for HDL and FBS. These differences were statistically significant for TG ($P = 0.001$), LDL ($P = 0.007$), VLDL ($P = 0.001$), HDL ($P = 0.001$) and FBS ($P = 0.005$); however, they were not significant for CHOL level ($P = 0.309$). When the data were reanalyzed after excluding diabetic patients, we got the same results for total lipid profile (TLP), but for FBS the difference was not statistically significant ($P = 0.2$). Our study concluded that chronic HCV infection was associated with alterations in lipid metabolism and diabetes militias (DM) among Libyan patients.

Keywords- *HCV; Extra-hepatic manifestation; Type II diabetes; Hypolipidemia.*

INTRODUCTION

Hepatitis C virus (HCV) is an RNA virus belonging to the *Hepacivirus* genus of the family Flavivirida and it is the second most common chronic viral infection, affecting nearly 200 million people worldwide.[1,2] Exposure to HCV often leads to a chronic hepatic inflammation and extrahepatic manifestations (EHM).[2,3] Most patients do not show hepatic symptoms and present with EHM as the first sign of HCV infection.[4]The most frequent reported EHM is mixed cryoglobulinemia. However, there are other manifestations have been reported, such as cryoglobulinaemic nephropathy, thyroid diseases, autoimmune gastritis, idiopathic pulmonary fibrosis, Sjögren or Sjögren-like syndromes, membrano-proliferative glomerulonephritis, porphyria cutaneatarda, lichen planus, leukoclasticvasculitis, necrolyticacral erythema, β-cell non-Hodgkin lymphomas,and less frequently type II diabetes mellitus.[5,6] At least one of these EHM is present in 40%-74% of chronic HCV infected cases.[7]The infected extra-hepatic tissues might act as a reservoir for the virus and play a role in persistence and reactivation of the infection as well as an etiological agent of these EHM.[4] The pathogenic mechanisms of the EHM appears to be immunologically mediated in majority of cases, with features of autoimmunity in many.[3]

However, there are not any organ-specific antibodies detected in 20%-40% of these cases, which might be the results of β lymphocyte stimulation by HCV or the HCV-induced anti-LKM1 recognition of specific antigens.[7,8]

Hepatitis C virus infection has also been reported with alterations in lipid metabolism.[9] Abnormal serum lipid profile and apo-lipoproteins are a common finding in patients with chronic liver disease being caused by many factors, but the alterations in lipid metabolism in HCV infected patients seem to be more specific and have recently been suggested.[5] The interaction between lipoprotein metabolism and the HCV has been reported by several studies. The virus binds to and enters cells appears to be a complicated mechanism.

However, several cellular receptors have been proposed

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as mediating the binding and entry of virus into the cells, namely scavenger receptor class β type I receptor, and the low-density lipoprotein receptor (LDL-R).[10] In addition; there is growing evidence to suggest an association between chronic HCV infection and diabetes, and these two common diseases are capable of causing significant long-term complications.[11]The prevalence of type II diabetes in HCV- infected patients is much higher than that in the general population and patients with other chronic hepatic diseases.[12] The pathogenic mechanisms by which HCV leads to type II diabetes are not fully understood however, HCV infection has been linked to immunologic disorders that may trigger an immune reaction against the β-cell of the pancreas, which leads to diabetes.[12,13] Other reported studies suggest that the greater prevalence of diabetes among patients with HCV could be caused by hepatic insulin resistance, which would result from hepatic steatosis or a direct effect of HCV proteins on insulin signaling pathways.[9]

Our research aimed to investigate the metabolic alterations in chronically HCV-infected patients in Libya in order to fulfill the gap in the literature

MATERIALS AND METHODS

***Study population*:**

A total of 100 cases (study group) diagnosed with chronic HCV infection attending the OPD of IDD of Tripoli Medical Centre (TMC were selected. Other 100 patients (control group) with dermatological diseases were selected from the OPD of BOMH for dermatological diseases and who were not infected with hepatitis B virus (HBV), HCV or human immune deficiency virus (HIV). This group was matched by age and sex with the study group. The selection of participants for the current research was carried out by a systematic random sampling method. Our investigation lasted for 15 months, from January 2011 to March 2012. The immunological tests for HCV, HBV and HIV were done in BOMH, while biochemistry analysis for TLP, FBS and liver function test (LFT) were done in TMC.

None of the enrolled subjects in both study groups had a family history of hyperlipidemia, were alcoholic, had liver cirrhosis, hepatocellular carcinoma, HIV or HBV. None of the enrolled subjects in the control group were having elevated liver enzymes or HCV. Patients on interferon (IFN) or other antiviral drugs or had a history of exposure to drugs influencing lipid metabolism, such as lipid-lowering agents, corticosteroids or retinoids were excluded from the study. A standard cases sheet was used to collect the following data: name, age, sex, place of residence, date of diagnosis of HCV and duration of the disease, history of hyperlipidemia or DM and date of diagnosis, duration of the disease and treatment used (insulin or oral hypoglycemic drugs), history of alcohol intake, family history of hyperlipidemia, any treatment that could interfere with lipid profile, any other chronic illnesses or chronic medication. Weight, height and BMI were calculated according to the formula of weight (kg) divided by height square meter (weight/ height square).

***Blood sampling and assay methods*:**

Fasting blood samples of 10cc were taken from the study group and collected in plane tubes for biochemistry investigations including CHOL, TG, LDL and HDL, whereas the blood samples for FBS were collected in fluoride anti-coagulant containers. Other one hundred blood samples were taken from the patients attending the OPD of BOMH (control group) and they were investigated for biochemistry tests (FBS, CHOL, TG, LDL, HDL and LFT). VLDL was calculated in accordance with the formula triglyceride level divided by five.

The collected samples were allowed to clot completely in plane tubes then centrifuged at (3000 rpm) for 10 minutes to separate the serum, while the collected samples in fluoride anti-coagulant containers were centrifuged at (3000 rpm) for 10 minutes to separate the plasma. The collected sera for immunological tests were stored in the freezer at -20°C and were tested once every week in BOMH, while the serum and the plasma for biochemistry tests were kept in an ice box after centrifuged to be transferred to the laboratory in TMC for processing and analysis.

***Immunology testing*:**

The control group samples were submitted for detection of HCV-Ab, HBsAg and anti-HIV-Ab by Enzyme Linked Immunosorbent Assay kit (ELISA) using fully automated machine called (Hepanostika®/ UK).

***Biochemical testing*:**

The biochemistry testing method is an in vitro diagnostic test intended for the quantitative determination of CHOL, TG, LDL, HDL, FBS and LFT (ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBI) in the serum using an automated analyzer called (Dimension system/ USA).

***Statistical analysis*:**

The data set was organized and analyzed using Microsoft SPSS Statistics 11.0. Frequency, percentage, mean and SD used for description of statistic. *T. test* and *Chi-square* used for inferential statistics and the level of statistical significance for all the tests was a value <0.05.

RESULTS

Most of the participants (95.5%) in both groups were Libyans. In the study group; 92% were Libyan, 5% Egyptian, 2% Palestinian and only 1% Moroccan, whereas in the control group; 99% were Libyan and 1% were Moroccan. Among all the participants, 14.5% were having the diagnosis of DM. In the study group;18% were diabetics compared to 11% in the control group (P=0.114). When we compared the BMI between the study group and control group (Table 1), we found overweight, obesity and morbid obesity were less frequent among the study group, whereas the frequency of underweight and normal weight was higher among study group (P = 0.652).

The means of CHOL, TG, LDL and VLDL were lower among study group compared to control group with statistical significance for TG, LDL and VLDL (P value =.001, .007, 0.001 respectively) but was not significant

for CHOL level (P =0.309).Where the means of HDL and FBS were higher among study group with statistical significance (P value = .001, .005, respectively (Table 2: Figure 1).

As DM itself can affect the lipid profile especially for uncontrolled diabetes and since we have only 29 diabetic patients in both groups, we reanalyzed the data after exclusion of these diabetic patients, we reached the same results for TLP but for FBS the difference was not statistically significant (P = 0.2), (Table 3).

Table 1: Socio-demographic characteristics of the study and control group.

Character	Study group	Control group	*P* value
***Age* (mean ±SD)**	40.5±15	40.4±14.9	0.977
<20years	6%))6	5%))5	
20-40years	48%))48	52%))52	
41-65years	37%))37	34%))34	
>65years	9%))9	9%))9	
Sex			0.557
Male	58%))58	58%))58	
Female	42%))42	42%))42	
Address			0.012
Inside Tripoli	58%))58	74%))74	
Outside Tripoli	42%))42	26%))26	
Nationality			0.064
Libyan	92%))92	99%))99	
Egyptian	5%))5	0(%)	
Moroccans	1%))1	1%))1	
Palestinians	2%))2	0%))0	
History of diabetes			0.114
Diabetic	18%))18	11%))11	
Not diabetic	82%))82	89%))89	
BMI			0.652
Under weight	5%))5	2%))2	
Normal	49%))49	44%))44	
Over weight	28%))28	31%))31	
Obese	17%))17	21%))21	
Morbid obese	1%))1	2%))2	

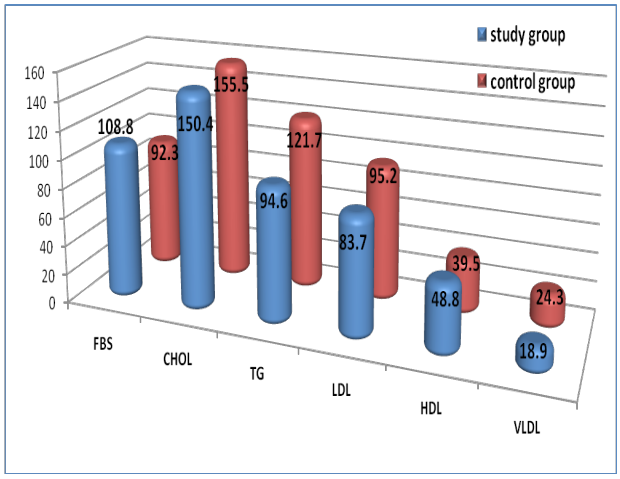

Figure 1: Percentage of lipid profile and FBS among study and control group.

Table 2: The mean of lipid profile and blood sugar between study and control group.

Parameter	Study group (mean ±SD)	Control group (mean ±SD)	*P* value
CHOL	150.4 ±34.7	155.5 ±36.5	0.309
TG	94.6 ±50.1	121.7 ±65.5	0.001
LDL	83.7 ±29.2	95.2 ±30	0.007
HDL	48.8 ±15.3	39.5 ±10	0.001
VLDL	18.9 ±10	24.3 ±13	0.001
FBS	108.8 ±49	92.3 ±32.1	0.005

CHOL; Cholesterol, TG; Triglyceride, LDL; Low density lipoprotein, HDL; High density lipoprotein, VLDL; Very low density lipoprotein, FBS; Fasting blood sugar.

Table 3: Lipid profile and FBS for study and control group after excluding patients with DM.

Biochemical result	Study group (mean ±SD)	Control group (mean ±SD)	*P* value
CHOL	151 ±34.8	155.5 ±37.9	0.419
TG	90 ±46	120.8 ±66.2	0.001
LDL	84.6 ±29.1	95.1 ±30.8	0.024
HDL	49.7 ±15.2	40.1 ±9.8	0.001
VLDL	18 ±9.2	24.2 ±13.2	0.001
FBS	90.9 ±14.3	85.2 ±15.8	0.20

CHOL; Cholesterol, TG; Triglyceride, LDL; Low density lipoprotein, HDL; High density lipoprotein, VLDL; Very low density lipoprotein, FBS; Fasting blood sugar.

DISCUSSION

Hepatitis C virus (HCV) infection is a major public health problem worldwide with an estimated prevalence of 3%.[14] The prevalence of HCV in North Africa and Arabian countries, including Libya ranges between 1.4% and 2.1%, though it was reached up to 19.3% in Egypt. More than 28 million people in African countries are chronically infected by HCV and chronic hepatitis reported to occur in 55-80% of infected patients. However; extrahepatic manifestations (EHMs) of HCV infection have been reported in 40% to 75% of patients and these EHMs can affect a variety of body systems with significant morbidity and mortality.[2,6,15]The majority of these EHMs are suggested to be immunologically-mediated.

Chronic HCV infection leads to up regulation of the humoral immune system, which subsequently leads to increases in monoclonal and polyclonal autoantibodies. These autoantibodies will form circulating immune complexes which deposited in blood vessels, resulting in complement activation and extrahepatic injury.[17,18]

In this study, we compared the TLP and blood sugar levels between the HCV-infected group and non-infected controls. As a result, we found that HCV infected patients had significantly lower mean LDL level ($P< 0.007$), TG ($P< 0.001$), VLDL ($P< 0.001$) and they had lower mean of CHOL level which was not statistically significant ($P< 0.309$). However; those patients had significantly higher mean of HDL level ($P< 0.001$) compared with controls.

Recently, several previous studies have linked chronic HCV infection with certain EHMs, such as alterations in lipid metabolism and T2DM.[7,9] Although changes in serum lipid profile and apolipoproteins are commonly found in patients with chronic hepatic illness of any cause, the association between HCV and lipid metabolism seems to be more specific. The mechanisms of altered lipid metabolism, especially hypobetalipoproteinaemia in chronic hepatitis C (CHC) infected patients are not understood well, thus certain host metabolic and viral factors are likely to be involved in the pathogenesis.[19] The postulated mechanisms include the binding of viral particles to human HDL, LDL and VLDL[20-22], the impaired hepatocyte assembly of VLDL through microsomal transfer protein inhibition; and the entry of virus through the LDL receptor into hepatocytes.[5,9,20]

Our findings were in agreement with the studies[20,21] that had observed the low CHOL level in HCV-infected patients compared with control patients, but their results reached a statistical significance in contrast to ours. However, regarding HDL levels they reported no difference among the two groups, but our results reached a statistical significance in HCV infected group.[9,20,21] Siagris *et al*. (2006) study showed that TG and HDL levels were similar in both groups and HDL was significantly lower in CHC infected patients.[22]

These differences could be due to the small sample size in our study and certain virologic parameters, and risk factors which need to be determined and explored by further epidemiological studies in our country. The decrease in TG levels among CHC infected patients as reported in this study and in the research conducted by Marzouk *et al*. (2007), in Egypt, could be explained through lipid metabolic processes associated with the viral replication.[9] Nevertheless, an increase in TG level has been reported during the treatment of those patients with interferon, which could be as a result of it is high concentrations competed with HCV for binding to the receptors at the time of acute infection, resulting in lower hepatocyte entry.[23,24]

Regarding the blood sugar levels in our study patients, we found that the HCV infected group had significantly higher mean FBS levels compared with the controls ($P< 0.05$). We also noted that 18% of the participants in the infected group were having diabetes compared to only 11% of those in the controls ($P< 0.114$). Our results concurred with previous studies carried out by Marzouk*et al* (2007), and Elhawary *et al* (2011) in Egypt, Muhammad *et al* (2010) in Faisalabad, Hwang and Chen (2006) in Taiwan. The findings of the present study disagreed with those of Butt *et al* (2009) in Pittsburgh where they reported that HCV-infected subjects were less likely to have diabetes than in the controls.[9,20,25-27]

Diabetes mellitus is a common known complication of all liver diseases. However, recently a number of clinical epidemiological and experimental studies have suggested that diabetes, especially type II, is one of the potential extra-hepatic manifestations of HCV infection, and was postulated to be due to either direct effect of HCV on glucose homeostasis or indirectly through cytokine stimulation mechanisms or secondary to HCV-induced hepatic damage. Nevertheless, recently studies have shown higher insulin resistance among patients infected with HCV irrespective of the degree of liver injury.[14,28] Another speculation that the HCV core protein impairs insulin signaling, mainly through activating tumor necrosis factor α (TNFα) and the suppressor of cytokine signaling (SOCS) family members.[19] In addition, meta-analysis studies reported that there is an approximately 1.7-fold significant increase in DM risk in patients with HCV infection. Recent large meta-analysis, the first of this kind, has reached the same conclusion.[14]

Most previous studies used a cross-sectional design and compared the prevalence of T2D in patients with chronic HCV with those had chronic liver disease**,** drug users or HIV infected patients.[28]Those studies confirmed the high prevalence of T2D among patients with chronic HCV, but could be argued that, the two populations of patients; the HCV-infected and non- infected; may have differed by certain risk factors for T2D, such as age, gender and stage of liver disease. However, in our study none of the enrolled cases had a family history of hyperlipidemia or were alcoholic. Also, all of them did not have HIV, HBV, liver cirrhosis, hepatocellular carcinoma, or were under treatment with interferon (IFN) or any other antiviral drugs. None of them had a history of drugs influencing lipid metabolism, corticosteroids or retinoids. Therefore, our study supported the results of mentioned previous studies and confirmed that diabetes, type II in particular, is one of the potential extra-hepatic manifestations of HCV infection. In addition; the two main risk factors for the increasing prevalence of type II DM in infected HCV patients were positive family history of DM and black

ethnicity as reported by Metha *et al*. (2003).[30,31]

A multivariate analysis study showed that the risk of developing T2D among HCV infection subjects increased when BMI levels increased and age decreased, so HCV infection is an independent predictor of T2D.However, two large prospective studies showed that HCV infection relocated additional risk for DM beyond that carried by BMI or age.[14,32] In contrast, a small American case-cohort study, which included only 15 HCV-infected patients, revealed that only patients who were overweight and older than 50 years had an additional DM risk.[30] When we compared the BMI among the two studied groups, we found that there was not a significant difference among them ($P< 0.652$), and our results concurred with those reported by Marzouk *et al* (2007)[9] and Nashaat (2010).[21] That could be also due to the small size sample as in our study, therefore; further large studies are needed to evaluate the importance of the interaction between HCV infection and different risk factors for diabetes.

CONCLUSION

In a comparison between HCV-infected subjects and HCV-uninfected control subjects, we found that HCV infection is associated with DM and alterations in lipid metabolism**,** consisting of an elevation in HDL cholesterol and a reduction in cholesterol, LDL and triglycerides. Therefore,, further detailed studies are needed.

Chronic HCV infection is associated with alterations in lipid metabolism and DM. In our study we found that the means of CHOL, TG, LDL, and VLDL were lower among chronic HCV-infected patients than that in the control group. However, the means of HDL and FBS were higher among the infected group when compared with the non-infected control group.

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