

A STUDY OF LIPID PROFILE AND HEPATIC STEATOSIS IN CHRONIC HEPATITIS C VIRUS INFECTED EGYPTIAN PATIENTS.

Afaf Masoud, Heba Abdella, Mostafa Hamed, Shereen A. Saleh, Amir Helmy

MD, professor of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

MD, Assistant Professor of Tropical Medicine, Tropical Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

MD, Assistant Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

MD, Lecturer of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

MD, Assistant professor of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt..

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Abstract

Background: The prevalence of steatosis in hepatitis C varies between 40% and 80%. Genotype 4 is the predominant genotype in Egypt.

Aim: is to study serum lipids and its relation to hepatic steatosis in chronic HCV infected Egyptian patients.

Patients and methods: One hundred and twenty subjects were divided into 2 groups. Group 1: 60 patients with chronic hepatitis C intended to receive antiviral therapy. Group 2: 60 normal controls. Lipid profile together with hepatic profile, abdominal ultrasound, BMI measurements were done to patients of both groups. Quantitative HCVRNA by PCR and liver biopsy with determination of grade of inflammation, stage of fibrosis and degree of hepatic steatosis were done to group 1 patients.

Results: No significant difference was found between both groups regarding serum lipid profile. 62 % of patients of group 1 had steatosis of mild degree which significantly correlated with the BMI. Patients with steatosis showed significant higher levels of total cholesterol. There was significant correlation between serum triglycerides and hepatic fibrosis, between LDL and HCVRNA by PCR and between Cholesterol/HDL ratio and AFP.

Conclusion: steatosis was found in 62 % of patients of the current study which correlated with BMI. There was correlation between LDL and viral load.

Introduction

Abbreviations:

AFP: alpha fetoprotein, ALP: alkaline phosphatase , ALT alanine aminotransferase, AMA: antimitochondrial antibody, ANA: antinuclear antibody, AST aspartate aminotransferase, BMI: body mass index, CHC: chronic hepatitis C, DM: diabetes mellites, ELISA: enzyme-linked immunosorbent assay, F: fibrosis, HAI: hepatic activity index, HBV hepatitis B virus.; HCV: hepatitis C virus; HDL: high density lipoprotein; HIV human immunodeficiency virus, IBM : International Business Machines, LDL: low density lipoprotein, NAFLD: non-alcoholic fatty liver disease, p: probability, PCR: polymerase chain reaction, RNA: Ribonucleic acid, RT: reverse transcriptase, SD: standard deviation, SPSS: Statistical Program for Social Science, TG: triglycerides

Introduction:

HCV represents a major health problem with approximately 3% of the world population that is, more than 170 million people infected (1). The highest HCV prevalence in the world occur in Egypt 20% (2). Genotype 4 is the most common genotype in the Middle East and Egypt (3), and is responsible for >90% of cases (4).

Hepatitis C virus is closely associated with lipid metabolism throughout its lifecycle (5). Steatosis is 2.5 times more prevalent in patients with HCV when compared to the general population (6) while the prevalence of steatosis in hepatitis C virus is about 40% (7).

There are two discrete forms of steatosis that may be found in patients infected with hepatitis C virus. Metabolic steatosis can coexist with HCV, regardless of genotype, in patients with risk factors such as obesity, hyperlipidemia, and insulin resistance and is considered largely to be due to alterations in host metabolism (5). The second form of hepatic steatosis in HCV patients is a result of the direct cytopathic effect of genotype 3 viral infection. Both categories of steatosis tend to fasten the progression of liver fibrosis and therefore prompt recognition and management should be initiated in patients with HCV and steatosis (8).

As the liver is the main determinant of serum lipoprotein synthesis and lipid metabolism, chronic liver diseases are often accompanied with an impaired lipid metabolism (9).

The aim of this work is to study serum lipid profile and its relation to hepatic steatosis in chronic compensated HCV infected patients.

Patients and Methods

The study was conducted on 60 patients with chronic HCV infection (Group1) diagnosed by positive ELISA for HCV Ab and HCV RNA PCR tests intended to receive antiviral treatment (Pegylated interferon and Ribavirin). Another 60 normal volunteers negative for HCV Ab, free from any systemic diseases, with no clinical or ultrasonographic features of any liver disease and matching group 1 regarding age, sex and BMI were enrolled in this study as control (Group2). The patients of group 1 were collected from the Hepatology outpatient clinic of Ain Shams University Hospitals, while the control subjects were collected from the outpatient clinics from those who present for pre employment check up and from blood donors at the Blood Bank, over the period of one year.

Exclusion criteria: patients with: co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), autoimmune hepatitis, Wilson's disease, Hemochromatosis, history of alcohol consumption more than 10 gm/day, chronic illness, malignancy, evidence of decompensated liver disease, diabetes mellitus, hypertension, those on medications influencing lipid metabolism such as lipid lowering agents, corticosteroids, non-steroid anti-inflammatory drugs or those already on antiviral treatment were all excluded from both groups.

Patients of this study were categorized according to BMI into three subgroups:

- Normal (BMI 19%-25%).
- Overweight (BMI 25%-30%).
- Obese (BMI more than 30%).

Methods

Written consent was taken from all patients and controls before enrollment in the study and the study was approved by the ethical committee of Ain Shams University.

Patients of both groups were subjected to the following:

- Full history taking and clinical examination.
- Laboratory investigations including: lipid profile (serum cholesterol, triglycerides, low-density lipoprotein, High-density lipoprotein), liver biochemical profile (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, alkaline phosphates, coagulation profile), viral markers including HCV antibody by ELISA test, quantitative HCV-RNA by reverse transcriptase PCR for HCV positive antibody patients, hepatitis B surface antigen, hepatitis B core antibody by ELISA, antinuclear antibody (ANA), antimitochondrial antibody (AMA), serum ceruloplasmine, serum copper test, urinary copper test, serum iron, total iron binding capacity and serum ferritin.
- Abdominal U/S to assess: liver size, echopattern, spleen size, presence of focal lesions or ascites.

Patients of Group 1 were further subjected to:

- Liver biopsy and histopathological examination: Ultrasonography-guided liver biopsies were performed under conscious sedation using a 16-gauge Klatskin needle. The length of the histological specimens was no

less than 2.5 cm. All biopsy specimens were transferred to the pathology department and placed in 10% neutral buffered formalin solution for fixation and embedded in paraffin blocks. Serial sections (sectioned at 4- μ m intervals) were concurrently stained with Hematoxylin-Eosin and Masson's trichrome. An experienced pathologist blinded to the clinical data assessed the liver biopsies regarding:

- The grading of inflammation and stage of fibrosis was according to the **Ishak Modified HAI (10)**.
 - Any other pathologies such as steatosis, cholestasis, granuloma, dysplasia or malignancy.
 - Degree of steatosis was defined as: S1 (mild steatosis): < 33% of hepatocytes affected, S2 (moderate steatosis): 33% to 66% of hepatocytes and S3 (sever steatosis): > 66% of hepatocytes affected. (11)
- Statistical analysis of the results:

Analysis of data was done by IBM computer using SPSS (Statistical Program for Social Science version 12) using Mean, SD and Range for description of quantitative variables, number and percentage for description of qualitative variables, Chi-square to compare qualitative variables between groups, Fisher exact test when one expected cell or more are less than or equal to 5, Unpaired t-test to compare quantitative variables between two groups in parametric data (SD <50% mean) and Mann Whitney in non-parametric data (SD >50% mean). Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group.

Results:

This study was conducted on 120 subjects who were divided into 2 groups. **Group 1:** included 60 patients with chronic hepatitis C viral infection, 46 (76.7%) of them were males and 14 (23.3%) were females with mean of age and BMI: (51.6+7) and (30+3.7) respectively. **Group 2** included another 60 healthy controls, 37 (61.7%) of them were males and 23 (38.3%) were females. The mean of their age and BMI was (48.9+7.5) and (29+3.8) respectively with no statistical significant difference between both groups regarding age, sex and BMI (p value >0.05).

There was none significant difference between the studied groups regarding total cholesterol, triglycerides, LDL and HDL with p value >0.05 (table 1).

Table (1): comparison regarding the lipid profile between the studied groups:

Variables	Group 1 N=60	Group 2 N=60	P
Cholesterol mg/dl	172+37	183+49	>0.05
TG mg/dl	133+69	153+101	>0.05
HDL mg/dl	46.5+15	48.6+25	>0.05
LDL mg/dl	101+37	110+40	>0.05

N: number

p: probability

As regard the histological grade of inflammation-according to *Knodell Scoring System*- in patients of Group 1, one patient (1.6%) showed grade 2/18, eight patients (13.3%) were 4/18, nine patients (15%) were 5/18, fourteen patients (23.3%) were 6/18, three patients (5%) were 7/18, four patients (6.6%) were 8/18, twelve patients (20%) were 9/18, seven patients (11.6%) were 10/18 and two patients (3.3%) were 11/18. The mean + SD of inflammation grade in Group 1 was (7+2.2).

While the stages of liver fibrosis -according to *Knodell Scoring System*-in patients of Group 1 were: F0 in one patient (1.6%), F1 in 22 patients (36.6%), F2 in 14 patients (23.3%), F3 in 10 patients (16.6%), F4 in 7 patients (11.6%), F5 in 6 patients (10%) with no patients with F6 and mean + SD of liver fibrosis=2.38+ 1.38.

Regarding the degree of hepatic steatosis 23 patients (38%) of Group 1 had no steatosis while 37 patients (62%) had steatosis ranging from 5-20% (S1) with mean + SD (6.05+ 5.8) (table2).

Table (2): Liver histopathology of group I as regards percentage of steatosis:

Steatosis %	Number	Percentage
0%	23	38%
5%	18	30%
10%	13	21.6%
15%	3	5%
20%	3	5%

As regard correlation between serum lipids and histological parameters, there was a statistically significant correlation between TG and stage of liver fibrosis (table 3, figure 1).

Table (3): correlation between serum lipids and hepatic inflammation and fibrosis in group I patients:

Lipid profile	HAI		Fibrosis	
	r	P	r	P
Cholesterol mg/dl	0.11	(>0.05)	0.09	(>0.05)
TG mg/dl	0.19	(>0.05)	-0.30	(<0.05)*
HDL mg/dl	0.08	(>0.05)	0.12	(>0.05)
LDL mg/dl	0.14	(>0.05)	0.03	(>0.05)
Cholesterol/HDL	-0.05	(>0.05)	-0.24	(>0.05)

* = significant

Also there was significant correlation between LDL and HCV PCR and between cholesterol/HDL ratio and AFP (p value<0.05) (table 4, figure 2).

Table (4): Correlation between serum lipids and liver enzymes, AFP and PCR in group I patients:

Lipid profile	AST		ALT		ALP		AFP		PCR	
	r	p	r	p	r	p	r	p	r	p
Chol.	-0.19	>0.05	0.09	>0.05	0.18	>0.05	0.04	>0.05	0.09	>0.05
TG	0.14	>0.05	0.19	>0.05	0.16	>0.05	0.12	>0.05	0.02	>0.05
HDL	-0.17	>0.05	-0.02	>0.05	0.13	>0.05	0.03	>0.05	0.11	>0.05
LDL	0.19	>0.05	0.17	>0.05	-0.17	>0.05	0.17	>0.05	0.29	<0.05*
Chol/HDL	-0.16	>0.05	-0.03	>0.05	0.1	>0.05	0.30	<0.05*	-0.08	>0.05

* = significant

The results showed no statistical significant correlation between BMI and grade of inflammation or stage of fibrosis with *p* value >0.05. On the other hand there was positive correlation between the BMI and steatosis in overweight and obese patients (table 5).

Table (5): Correlation between BMI and steatosis in group 1:

BMI	Number	Steatosis		P
		No (37)	Yes (23)	
Average weight	3	1 (33.3%)	2(66.6%)	P>0.05
Over weight	32	11 (34.3%)	21(65.6%)	P<0.001*
Obese	25	11 (44%)	14(56%)	P<0.05 *

There was statistically significant difference between patients with steatosis and those without regarding total cholesterol (table 6) with positive correlation between steatosis and total cholesterol as shown in (figure 3). There was no significant correlation between the degree of hepatic steatosis and stage of hepatic fibrosis in patients of Group 1 (figure 4).

Table (6): comparison between patients with and without steatosis regarding serum lipids:

Lipid profile	Steatosis No (23)	Yes (37)	t	P
Cholesterolmg/dl	163+34	179+37	2	<0.05*
TG mg/dl	124+49	139+79	0.8	>0.05
HDL mg/dl	44+10.8	48+17	0.9	>0.05
LDL mg/dl	93+34	105+39	1.2	>0.05
Cholesterol/HDL	3.96+1.056	4.35+1.69	0.9	>0.05

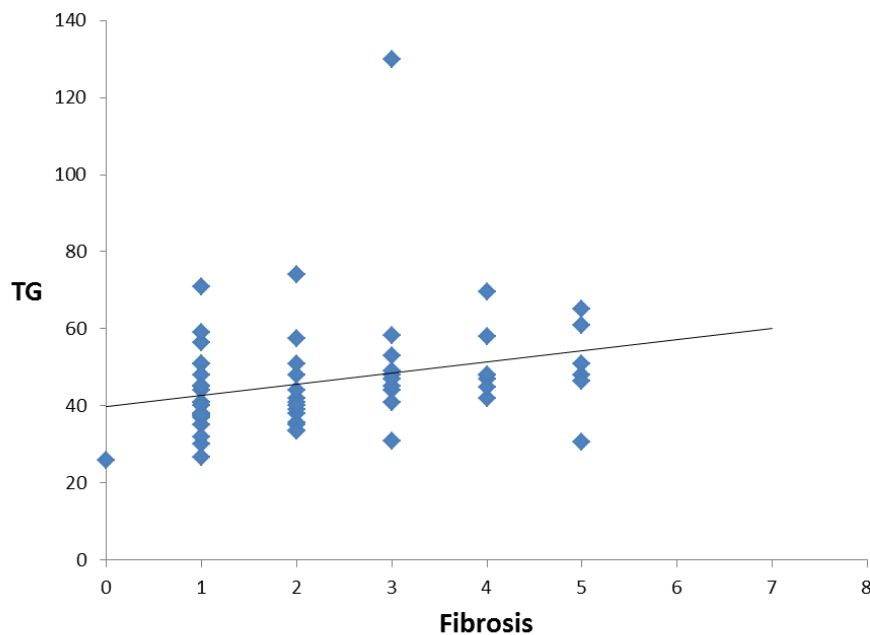


Figure (1): correlation between triglycerides and stage of liver fibrosis

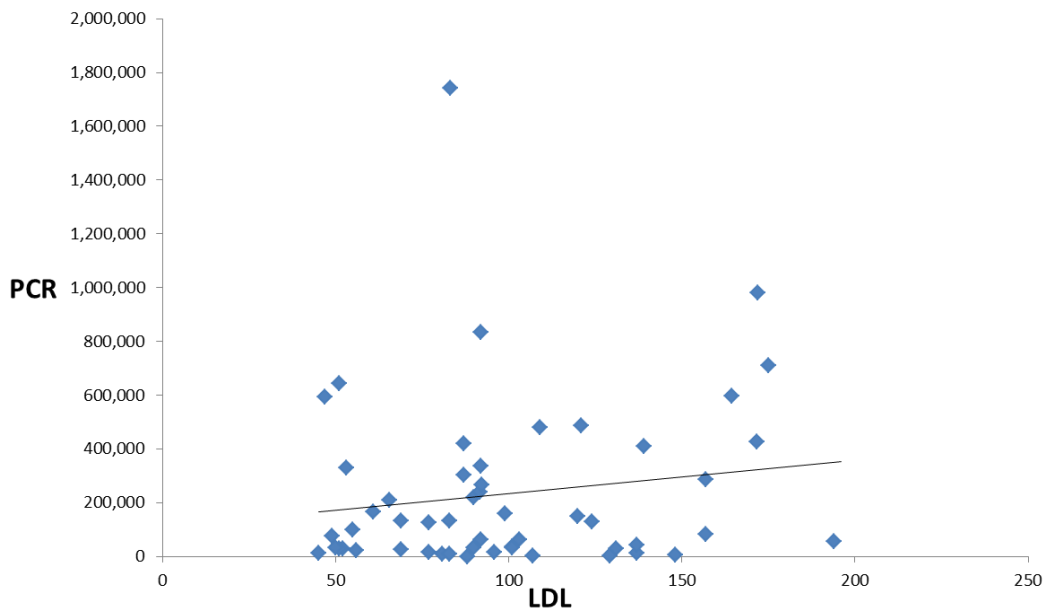


Figure (2): correlation between LDL and PCR.

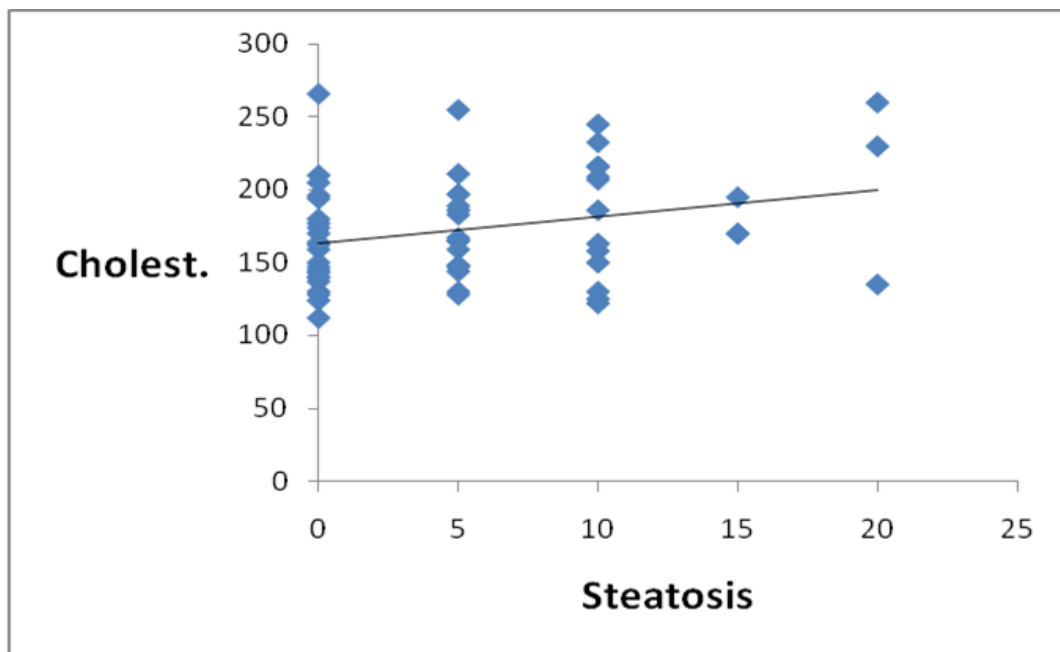


Figure (3): Correlation between cholesterol and steatosis in group 1.

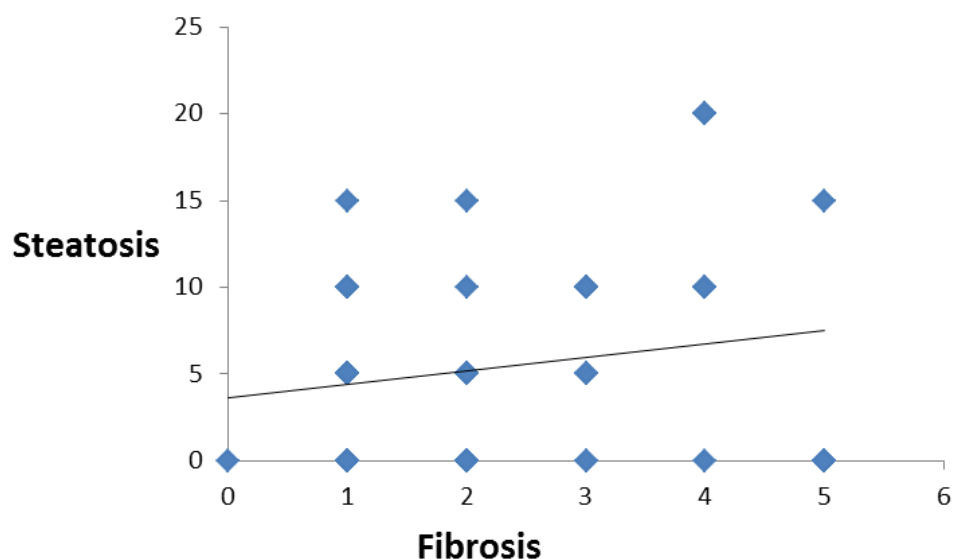


Figure (4): Correlation between degree of steatosis and stage of hepatic fibrosis

Discussion

The prevalence of steatosis in hepatitis C varies between 40% and 80%, depending on the occurrence of alcohol abuse, overweight / obesity, type II DM and other cause of fatty liver (12). When all common factors of fatty liver have been excluded, steatosis still occurs in about 40% of chronic hepatitis C cases, which is up to twice as many compared to chronic hepatitis B (7). This suggests that both host and viral factors concur to fatty liver in HCV-infected persons (13).

The hepatitis C virus (HCV) genotype 3 is more commonly associated with steatosis with frequency estimated to be 73% compared to 50% in non-genotype 3 patients (14). Currently, there is no clear evidence of exact percentage of steatosis in HCV genotype 4 (15).

In the present work, there was no significant difference between both groups as regard lipid profile but with lower levels in HCV infected group. This is in agreement with *Corey et al.* who did not found significant difference between CHC patients and control as regards TG level (16), and with the results of *Nashaat* who found no significant difference as regards serum level of HDL (17). On the contrary, *Nashaat* found that patients with HCV had significant lower LDL, cholesterol and TG than control (17). *Fabris et al.* and *Serfaty et al. (2001)* reported a higher prevalence of hypocholesteremia, low LDL level in HCV infected persons compared to control (18)(19). *Marzouk et al.* showed decreased level of TG among HCV patients (20). *Jarmay et al.* reported that triglyceride and cholesterol levels were significantly lower in patients with chronic HCV (with and without steatosis), compared to NAFLD patients and to the virus-free control groups (21).

Hypolipidemia is more marked in cases suffering from hepatitis C virus and this abnormality is directly related to viral load and viral response (9). Lower total cholesterol and low density lipoprotein levels were described in hepatitis C virus infected patients soon after viral diagnosis. These lower levels are associated with HCV infection regardless of degree of hepatic fibrosis (22). *Siagris et al.* found more marked hypolipidemia in cases suffering from hepatitis C virus especially genotype 3a and this abnormality is directly related to viral load and viral response (9).

HCV replication could decrease intrahepatic cholesterol synthesis, and it may divert cholesterol to the synthesis of intracellular membranes that are necessary for the viral replication complex. The decrease in available intracellular cholesterol may also lead to an increase of LDL receptors and intra-hepatic LDL. This increase in LDL uptake may

account for the decreased serum LDL level in HCV infection (23)(24). Also the metabolic processes which are associated with viral replication may be associated with a drop in triglycerides level (20)(25).

This study showed that about 62% of chronic hepatitis C infected patients had steatosis ranging from 5-20%, while 38% of them showed no steatosis. This could reflect the percentage of steatosis in HCV genotype 4 reaching about 60% as 90% of chronic HCV infected Egyptian patients have genotype 4 (4). This is in some similarity with *Khattab et al.*, who found that 44.2% of genotype 4 HCV infected patients had steatosis mainly of mild degree (26).

In this study, there was a significant correlation between serum cholesterol level and steatosis in chronic hepatitis C patients. *Talaat et al.* reported that the degree of steatosis correlated positively with serum triglyceride level (15). *Hsieh et al.* found a strong association between steatosis and TG level in patients with chronic HCV infection genotype 1, 2 in Taiwan (27).

There was significant positive correlation between TG and fibrosis score which is in agreement with *Ramcharran et al.* who found a positive correlation between fibrosis and TG level (28).

In the current study, there was a significant correlation between LDL and PCR. This is in some similarity with *Hsu et al.* who found that high TG and total cholesterol level correlated with higher HCV RNA level in genotype 2 in a study done in Taiwan (29). *Khattab et al.* found that in patients with HCV genotype 4, TG levels were associated with higher HCV RNA level (26). *Ramcharran et al.*, conducted a study on 160 African Americans and 170 Caucasian Americans, and found that TG levels were significantly and directly correlated with HCV levels in patients with HCV genotype 1 infection (28). Host serum lipid plays an important role in hepatitis C virion circulation and hepatocyte entry. A proportion of circulating hepatitis C viral particles are complexed with host triacyl glycerol-rich lipoproteins, known as lipo-viroparticles (30). Lipo-viroparticles use LDL receptors on hepatocytes as points of entry and are associated with high rate of infectivity (31). Once hepatitis C virions have entered the hepatocytes their replication is again dependant on host lipid interactions.

In this work there was a significant correlation between steatosis and BMI specially in overweight and obese patients suggesting that overweight and obesity are the most probable cause of steatosis in HCV-genotype 4-infected patients. This is in agreement with *Hsieh et al.* who reported that BMI is the strongest risk factor associated with hepatic steatosis in chronic HCV infected patients genotype 1 and 2 (27). *Cholet et al.* reported that in patients with chronic hepatitis C, steatosis is significantly associated with genotype 3 infection and high BMI (32). *Gordon et al. and Reddy et al.* reported that there is significant association between BMI and steatosis in HCV patients with genotype 3a (33)(34). *Angulo* reported that more than 90 percent of patients with a BMI greater than 39 have steatosis (35). In another study, *Solis-Herruzo et al.* reported that, while HCV genotype 3 infection and BMI are associated with the presence of steatosis in chronic hepatitis C, BMI is the only factor independently associated with the presence of NASH in these patients, and they suggested that overweight-related factors might induce NASH in chronic HCV patients (36).

On the other hand this study found no correlation between the degree of hepatic steatosis and fibrosis stage. This agrees with the study conducted by *Perumalswami et al.* who suggested that hepatic steatosis was not related to hepatic fibrosis in chronic HCV infection (37). *Leandro et al.* believed that hepatic steatosis is an independent and imported risk factor for developing hepatic fibrosis in chronic infected HCV patients (38). In another study in Taiwan the clinical relevance of hepatic steatosis in patients with chronic hepatitis C included a close correlation with hepatic fibrosis (39). *Talaat et al.* reported that the degree of steatosis had a positive correlation with both fibrosis and necroinflammatory scores in the liver biopsies of chronic HCV genotype 4 (15). Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C (40).

It has been suggested that in HCV infected liver, steatosis could contribute to fibrosis through a steatohepatitis like pathway involving stellate cell activation and perisinusoidal fibrosis (41). Patients with nonalcoholic steatohepatitis, hepatic inflammation and fibrosis develop as a consequence of two hit process, the first being steatosis and the second

oxidative stress with subsequent lipid peroxidation (42). Indeed, it has been shown in the liver of patients with chronic HCV infection that steatosis correlates with lipid peroxidation (43) and active fibrogenesis (44).

Conclusion:

Chronic hepatitis C viral infection is associated with lower levels of serum lipids with significant correlation between LDL and hepatitis C viral load and between TG and hepatic fibrosis. 62% of CHC infected patients had steatosis which correlated positively with BMI.

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