Comparative study of lipid profile between chronic hepatitis C Egyptian patients and normal controls and its levels pre and post Treatment

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Abstract: Background: Hepatitis C is a common infection in the Egyptian population, specially genotype 4 .It is well recognized in many studies that hepatitis C chronic infection is associated with hypolipidemia ,so in our study we compare the lipid profile between 150 patients with chronic hepatitis C and 150 normal persons with comparable age, sex and body mass index (BMI). The fasting cholesterol ,low density lipoprotein(LDL),high density lipoprotein(HDL),and triglyceride were compared .Then 36 patients of them received treatment in the form of pegylated interferon and ribavirin and then the patients who achieved viral clearance were reevaluated as regard the lipid profile versus the patients who did not achieve viral clearance and the relpsers. In our study we found that patients with chronic hepatitis C had significant lower LDL, cholesterol, and triglycerides than normal persons with comparable age, sex and BMI .The treated patients with sustained virological response showed increased LDL, cholesterol, and triglycerides from baseline compared to patients without viral clearance and even 2of them had increased LDL more than 130 mg/dl and had increased in cholesterol level more than 200 mg/dl which necessate treatment for dyslipidemia in order to prevent the risk of coronary heart disease. Conclusion : patients with chronic hepatitis C had low levels of LDL, cholesterol, and triglycerides than non infected persons and after viral clearance a significant number of patients showed LDL, cholesterol, and triglycerides rebound even to levels may be associated with increased risk for coronary heart disease, so lipids should be carefully followed up after successful clearance of hepatitis C infection. [Report and Opinion. 2010;2(5):45-51]. (ISSN: 1553-9873).

Key words: HCV infection,lipids profile ,pre and post treatment.

1. Introduction:

Hepatitis C virus is a major public health problem in Egypt specially genotype 4. Egypt has the highest prevalence of HCV in the world (overall prevalence of HCV antibody is 12% among the general population and reaches 40% in persons 40 years of age and above in rural areas whom at higher risk for coronary heart disease.(Habib et al, 2001) (Medhat et al, 2002). The available therapy uptill now is the combination of pegylated interferon and ribavirin, which result in sustained virological response in only half of patients (Armstrong et al, 2006).

Interactions between chronic hepatitis C virus (HCV) and lipid metabolism are strongly noticed. (Fabris et al, 1997) (Serfaty et al, 2001). Several important lipid –HCV interactions have recently been found .First ,host serum lipid play a role in hepatitis C virion circulating and hepatocyte entery.A proportion of circulating hepatits C viral particles are complexed with host triacyl glycerol-rich lipoproteins, known as lipo-viroparticles. (Diaz et al, 2006). Lipo-viroparticles use LDL receptors on hepatocytes as points of entery and are associated with high rate of infectivity(Andre et al, 2002).Once hepatitis C virions have enter the hepatocytes their replication is again dependant on host lipid interactions . New hepatitis C virion formation requires viral binding to either an endoplasmic reticulum phospholipid membrane or to an endoplasmic reticulum –associated membranous web (Dubuisson et al, 2002).

Also HCV replication may produce effects similar to those observed with HMGR inhibitors. HCV replication could decrease intrahepatic cholesterol synthesis through two possible pathways; first, it may shunt geranylpyrophosphate, out of the mevalonate pathway, decreasing the quantity of this necessary intermediate available for cholesterol synthesis. Second, it may divert cholesterol to the synthesis of intracellular membranes that are necessary for the viral replication complex. The net effect of these diversions is the decrease of available cholesterol for physiologic intracellular processes and for peripheral delivery via VLDL, ultimately resulting in decreased serum cholesterol levels. The decrease in available intracellular cholesterol may also lead to an increase in LDL receptors and intrahepatic LDL. This increase in LDL uptake may account for the decreased serum LDL levels in HCV infection. (Dubuisson et al, 2002).

Also the metabolic processes which is associated with viral replication may be associated with a drop in triglycerides levels. (Perlemuter et al, 2002), (Marzouk et al, 2007).

So chronic HCV infection by interrupting cholesterol synthesis and using host lipids for replication ,decreasing circulating lipids, and clearance of the virus results in rebound increase of lipid levels.

The purpose of this study was to study the effect of chronic HCV infection on the lipids profile among Egyptian patients and if the lipids values is affected after HCV treatment and comparing lipids values between patients with sustained virological response, nonresponders, and relapsers, and if the post HCV treatment lipid rebound in patients with sustained virological response reached levels that are associated with increased risk of development of coronary heart disease and necessate treatment per the National Cholesterol Education Program Guidelines(NCEP).

Patient and methods:

This study was carried out in the Gasteroenterology and Hepatology clinics at Ain Shams University Hospitals .

The study was conducted on two groups with comparable age, sex and body mass index (BMI).

Group 1: 150 patients with chronic HCV hepatitis who did not receive treatment for HCV before.

Group 2: 150 normal persons as a control group.

All patients and controls in this study were subjected to:

1. Full medical history and medical examination.
2. Liver functions tests (total plasma proteins, serum albumin, SGOT, SGPT, total and direct serum bilirubin, alkaline phosphatase and prothrombin time).
3. Lipid profile: fasting cholesterol, low density lipoprotein(LDL),high density lipoprotein(HDL), and triglycerides.
4. Kidney functions tests (serum creatinine, blood urea nitrogen (BUN) and uric acid).
5. Random blood glucose level.
6. Complete blood count.
7. HCV Antibody for both groups and HCV PCR quantitative for patients only.
8. Thyroid function test for patients only.
9. Body mass index (BMI) (weight in kilogram/height in cubic meter) for both groups.
10. Abdominal Ultrasonography.
11. Liver biopsy for 22 patients from the 36 patients who received treatment.

A written consent was taken from all the sharers in this study.

Exclusion criteria for patients group :

1. Patients with biopsy proved or clinical evidence of cirrhosis (Ishak stage 5-6 fibrosis on biopsy or presence of portal hypertension manifestation in the form of esophageal or gastric varices ,ascites or splenomegaly, or evidence of synthetic dysfunction on laboratory evaluation) .
2. Patients with hepatitis B infection or any other chronic liver diseases.
3. Patients on lipid lowering medications .
4. Recipients of solid organ transplantations .

Exclusion criteria for control group :

1. Patients with HCV, or HBV infection or any other chronic liver diseases.
2. Patients on lipid lowering medications .
3. Recipients of solid organ transplantations.

From the patients group 36 patients received treatment in the form of pegylated interferon and ribavirin, in this group of patients lipid profile is reevaluated after the 24 weeks after stoppage of treatment in the SVR group patients and in non responders group and after 24 weeks after relapse in relapsers group to evaluate and compare the results between patients with sustained virologic response (SVR)(undetectable HCV RNA six months following completion of therapy), non responders (failure to clear HCV RNA during therapy), and relapsers (initial clearance of HCV RNA at the end of treatment but detectable HCV RNA following cessation of treatment),and to detect any change in lipids profile and if any of these patients lipids levels reaches the levels which needs treatment according to National Cholesterol Education Program Adult Treatment Plan Guideline III (NCEP ATP-III) which recommends that patients with coronary heart disease (CHD) or CHD equivalents be treated for a LDL>100 mg/dL (National heart, lung and blood institute, 2004). Patients with two or more major CHD risk factors (including cigarette smoking, hypertension, HDL<40, family history of premature CHD or age greater than 45 in men or 55 in women) should be treated for a LDL>130 mg/dL. Patients without CHD, CHD equivalents or two or more major CHD risk factors require treatment for LDL>160 mg/dL. Total cholesterol level is also a known risk factor for the development of coronary heart disease. (Stamler et al, 1986). Total cholesterol level of 200 mg/dL or less is considered desirable by the NCEP-ATP III and levels above 200 mg/dL carry a 44% increased risk of CHD when compared to levels below 200 mg/dL (National heart, lung and blood institute 2004) (Stamler et al, 1986).

Data Management:

After tabulation, all data were analyzed statistically using SPSS statistical package version 16 & the following tests were done:

1. Mean =X
2. Standard Deviation=SD.

3. Student t test. $p<0.05$ indicated statistical significance.

Results:

This study was carried out on 150 chronic HCV infected patients and 150 normal persons as control group, both groups are comparable as regard age which was 38.7(±3.15) and 38.1(±3.11) respectively, with no significant difference between both groups, as regard sex men/women were 103/47 in both groups, and as regard BMI there was no significant difference between both groups which was 29.8(±2.43) in patients group and was 30.1(±2.45) among controls (Table 1). Liver biopsy was done in 22 patient of the 150 patients included in this study, the Median Ishak Hepatic Activity Index was 6 (range was 0-11) and Ishak fibrosis stage was from stage 0-2 in 14 patients (63.63%) and from stage 3-4 in 8 patients (36.37%). (Table 1).

Patients in the HCV group had significantly lower total cholesterol levels, (mean 162.44 mg/dl) than the uninfected control group (mean 208.76mg/dl). ($P < 0.0001$). Patients in the HCV group also had significantly lower total LDL levels when compared to the uninfected control group ,(mean 95.2mg/dL) versus (mean117.9mg/dL); ($P < 0.0001$). Patients in the HCV group also had significantly lower trigtlycerides levels when compared to the uninfected control group (mean 114.9mg/dL) versus (mean164.3mg/dL); $P < 0.0001$). (Table 1, fig 1). HDL levels were not statistically significant between the HCV group and uninfected controls. (Table 1, fig 1).

From the patients group 36 patients received treatment in the form of pegylated interferon and ribavirin, 16 patients achieved SVR, 14 were nonresponders and 6 relapsed after an initial response to therapy. Because of the small numbers of relapsers, relapsers and nonresponders were combined into a single group.

In this group of patients lipid profile is reevaluated after the 24 weeks after stoppage of treatment for SVR patients and non responders and after 24 for weeks after relapse in relpsers to evaluate and compare the results between responders ,non responders and relapsers group.

The mean pretreatment cholesterol, LDL, HDL and triglycerides levels did not differ significantly between the responder and nonresponder/relapser groups (Table 2, fig 2). The mean values of cholesterol, LDL and triglycerides are below the recommended levels for treatment with lipid lowering medications based on NCEP guidelines for primary prevention of atherosclerosis. A significant changes were seen in circulating lipid levels post treatment between responders group and nonresponders/relapsers group. Responders had significantly higher mean post treatment cholesterol levels than nonresponders (206.5 versus 156.4, P=<0.001) as well as significantly higher LDL levels (114.37 versus 96.35, P=<0.05), also responders had significantly higher triglycerides levels than nonresponders (148.8 versus 1111.95, P=< 0.001). The mean LDL in patients who achieved sustained virologic response was 114.37 mg/dL. This level of LDL requires lipid lowering therapy in patients with coronary heart disease (CHD) or CHD equivalents. None of our patients had previously diagnosed CAD and non required lipid lowering treatment prior to HCV therapy. However, 2 of the 16 patients (2.5%)who had SVR had LDL increases to greater than 130 mg/dL, one of them was131 mg/dl and the other was 136 mg/dl both were cigarette smokers and one of them was hypertensive which necessate treatment for dyslipidemia.

Moreover the patients who achieved SVR also had a mean post treatment cholesterol of 206.5 mg/dL. The two patients with LDL increases to greater than 130 mg/dL,both of them had total cholesterol levels far above 200, one of them was223 mg/dl and the other was 231 mg/dl, which also necessate treatment for dyslipidemia

Table 1 : General characters and lipids values for HCV group and contol group

Characteristics	HCV group	Control group	P value
Number	150	150	
Sex(men/women)	103/47	103/47	
Mean age(SD)	38.7(±3.15)	38.1(±3.11)	1.66 NS
BMI Mean(SD)	29.8(±2.43)	30.1(±2.45)	1.06 NS
Medain Ishak Hepatic Activity Index(Range)	6(0-11)	_	_
Ishak fibrosis stage Stage 0-2 Stage 3-4	 14(63.63%) 8(36.37%)	_	_
Cholesterol(SD)	162.44(±13.26)	208.76(±17.04)	26.27(<0.0001)
LDL(SD)	95.2(±7.77)	117.9(±9.6)	22.5 (<0.0001)
HDL(SD)	46.93(±3.83)	46.96(±3.83)	0.06 NS
Triglycerides(SD)	114.9(±9.38)	164.3(±13.41)	36.9 (<0.0001)

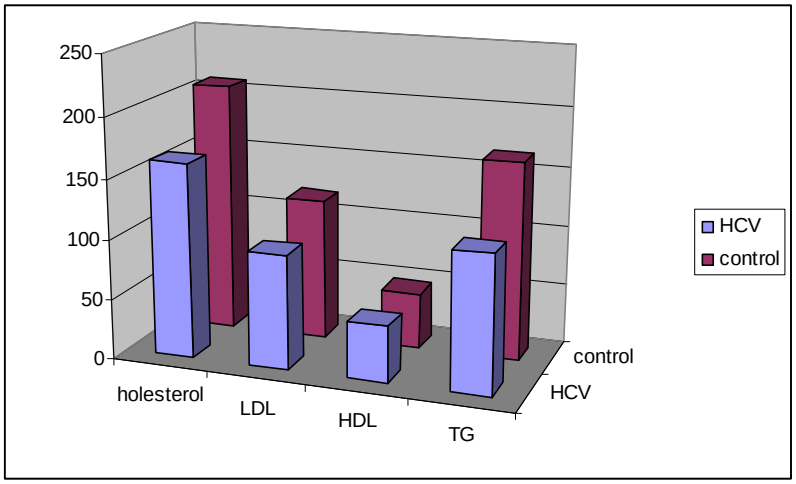

Fig 1: lipids profile among HCV patients versus control group

Table 2. Mean pretreatment and post treatment lipid levels for responders and nonresponder /relapsers

	Sustained virologic response		Norespnder/relapsers		P value	
	Pretreatment	posttreatment	Pretreatment	post treatmen	Pretreatment	Posttreatment
Cholesterol	165.25(±39.06)	206.5(±51.6)	156.3(±34.9)	156.4(±33.8)	0.71 NS	3.35 (<0.001)
LDL	98.8(±24.7)	114.37(±28.4)	97.2(±21.7)	96.35(±21.5)	0.2 NS	2.1 (<0.05)
TG	111.93(±27.9)	148.8(±37.2)	111.1(±24.8)	111.95(±25.1)	0.09 NS	3.39 (< 0.001)
HDL	45.88(±11.46)	46.18(±11.5)	45.91(±11.5)	46.03(±11.45)	0.07 NS	0.04 NS

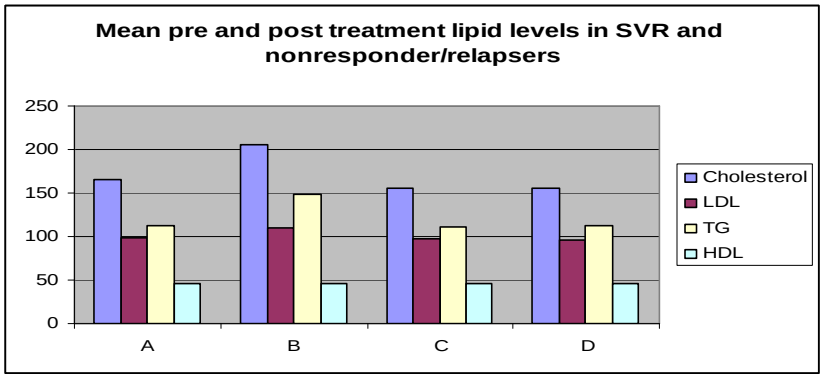

Fig 2 Mean pretreatment and post treatment lipid levels for responders and nonresponder /relapsers
A=SVR Pretreatment B=SVR Post treatment
C=Nonresponders/relapsers pretreatment
D=Nonresponders/relapsers posttreatment

Discussion:

Hepatitis C virus is a major public health problem in Egypt specially genotype 4 . Egypt has the highest prevalence of HCV in the world (overall prevalence of HCV antibody is 12% among the general population and reaches 40% in persons 40 years of age and above in rural areas whom at higher risk for coronary heart disease.(Habib et al,2001),(Medhat et al, 2002).

The origin of the HCV epidemic in Egypt has been attributed to intravenous schistosomiasis treatment in rural areas in the 1960s–70s.(Frank et al, 2000).

Interactions between chronic hepatitis C virus (HCV) infection and lipid metabolism have been

described in some studies, (Thomson et al,1993), (Maggi et al,1996) , (Cicognani et al, 1997), (Fabris et al, 1997),), (Serfaty et al, 2001). Some studies have reported a higher prevalence of hypocholesterolemia and low LDL levels in HCV-infected patients compared to control groups (Maggi et al, 1996), (Fabris et al, 1997) (Serfaty et al, 2001). Other studies showed decrease levels of triglycerides among chronic HCV patients, (marzouk et al, 2007). Although changed serum lipid is commonly found in patients with chronic liver disease of any etiology, the relationship between HCV and lipid metabolism seems to be more specific: binding of HCV particles to human high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) has been described (Thomson et al,1993). Moreover the LDL receptors could permit the entry of HCV in hepatocytes, (Agnello et al, 1999, and(Monazahian et al,1999). Also HCV replication could decrease intrahepatic cholesterol synthesis. The decrease in available intracellular cholesterol may also lead to an increase in LDL receptors and intrahepatic LDL. This increase in LDL uptake may account for the decreased serum LDL levels in HCV infection(Monazahian et al,1999).

The purpose of this study was to study the effect of chronic HCV infection on the lipid profile among Egyptian patients and if the lipids values is affected after HCV treatment and comparing lipids values between patients with sustained virological response, nonresponders, and relapsers, and if the post HCV treatment lipid rebound in patients with sustained virological response reached levels that are associated with increased risk of development of coronary heart disease and necessate treatment per the National Cholesterol Education Program Guidelines(NCEP).

This study was conducted on two groups with comparable age, sex and body mass index (BMI), (table 1) ,group 1 was 150 patients with chronic HCV hepatitis who did not receive treatment for HCV before, group 2 was150 normal persons as a control group, we excluded patients with biopsy proved or clinical evidence of cirrhosis, (Ishak stage 5-6 fibrosis on biopsy or presence of portal hypertension manifestation in the form of esophageal or gastric varices ,ascites or splenomegaly, or evidence of synthetic dysfunction on laboratory evaluation) ,Patients or controls with any other chronic liver diseases (other than chronic HCV in the patients group) ,patients on lipid lowering medications ,and recipients of solid organ transplantations .

Patients in the HCV Group had significantly lower total cholesterol levels than the uninfected control group, ($P < 0.0001$). Patients in the HCV Group also had significantly lower total LDL levels when compared to the uninfected control group (95.2mg/dL versus 117.9mg/dL; $P < 0.0001$). These results agree with (Fabris et al, 1997), (Serfaty et al, 2001), (Floris-Moore et al, 2007), (Marzouk et al, 2007) and (Corey et al, 2009), who observed that frequency of hypocholesterolemia in noncirrhotic HCV-infected patients was five times higher than in their reference population. Also patients in the HCV group had significantly lower trigtlycerides levels when compared to the uninfected control group , ($P < 0.0001$) ,(table 2, fig 2). These results agree with Perlemuter et al, 2002 and Marzouk et al, 2007, which refers this drop to the metabolic processes associated with viral replication .But these results disagree with Corey et al, 2009 who did not found significant difference as regard triglycerides between patients and controls.

HDL levels were not statistically significant between the HCV group and uninfected controls (table 2, fig 2). These results agree with Corey et al,2009 . From the patients group 36 patients received treatment in the form of pegylated interferon and ribavirin , 16 patients achieved SVR, 14 were nonresponders and 6 relapsed after an initial response to therapy. Because of the small numbers of relapsers, relapsers and nonresponders were combined into a single group.

In this group of patients lipids profile is reevaluated after the 24 weeks after stoppage of treatment for SVR patients and non responders and after 24 weeks after relapse in relapsers to evaluate and compare the results between responders ,non responders and relapsers group ,and this was the first time according to my knowledge that follow up lipids profile pre and post treatment in chronic HCV patients was evaluated prospectively, as the other studies were retrospective studies which depend on patients filings.

The mean pretreatment cholesterol, LDL, HDL and triglycerides levels did not differ significantly between the responder and nonresponder/relapser groups (table 2, and fig 2). The mean values of cholesterol, LDL and triglycerides were below the recommended levels for treatment with lipid lowering medications based on NCEP guidelines for primary prevention of atherosclerosis.

A significant changes was seen in circulating lipids levels post treatment between responders and nonresponders/relapsers. Responders had significantly higher mean post treatment cholesterol levels than nonresponders ,as well as significantly higher LDL levels, our findings are consistent with (Corey et al, 2009), also responders had significantly higher triglycerides levels than nonresponders ,and this findings are consistent with (Marzouk et al, 2007)(table 2, fig 2).

The mean LDL in patients who achieved sustained virologic response was 114.37 mg/dL. This level of LDL requires lipid lowering therapy in patients

with coronary heart disease (CHD) or CHD equivalents. None of our patients had previously diagnosed CAD and none required lipid lowering treatment prior to HCV therapy. However, 2 of the 16 patients (2.5%) who achieved SVR had LDL increased to greater than 130 mg/dL, one of them was131 mg/dl and the other was 136 mg/dl, both were cigarette smokers and one of them was hypertensive, which necessate treatment for dyslipidemia. The patients who achieved SVR also had a mean post treatment cholesterol of 206.5 mg/dL. The two patients with LDL increased to greater than 130 mg/dL,both of them had total cholesterol levels far above 200, one of them was 223 mg/dl and the other was 231 mg/dl, which also necessate treatment for dyslipidemia as recommended by the Scandanivian Simvastatin Survival Study (4S) 1994, and NCEP ATP-III 2004, these results were also consistent with (Shepherd et al, 1995) ,and (Corey et al, 2009).

In spite of the small number of these patients but on the bases of the high prevalence of chronic HCV infection in Egypt ,and if we studied older age group it is thought that post treatment elevation of lipids profile will be significant risk for CHD among this group and may warranate proper follow up for lipids profile in treated HCV patients and early recognition and treatment to reduce CHD mortality in this population.

This study has shown several important findings. First, HCV infection is associated with lowering of lipids, providing further evidence of an important interaction between HCV and host lipids, and suggesting a possible novel therapeutic target as some authors suggested that high concentrations of triglycerides at the time of acute infection compete with HCV for binding to the hepatocyte receptors, resulting in lower hepatocyte entry and easier infection clearance among those with high triglyceride levels,(Kenny, 1999), (Wise et al, 2000).

Second, post treatment viral clearance is associated with increased LDL and cholesterol levels, sometimes to levels associated with an increased risk for coronary heart disease, so we suggest that serum lipid levels should be assessed during follow-up among patients undergoing successful antiviral therapy. Further researches are needed to correlate the rise in lipid levels with clinically significant outcomes, such as the development of coronary heart disease.

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