



SERUM LIPOPROTEINS AND CHRONIC HEPATITIS C INFECTION; IMPORTANCE OF INVERSE RELATIONSHIP

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INTRODUCTION

HCV is a unique virus targeted towards liver cells and HCV closely interacts with host lipoprotein metabolism^{1,2}. Very low density lipoproteins "VLDL" synthesized and secreted from liver cells play a critical role in the generation and secretion of Hapatitis C virus³. The sero prevalence rate is 1% in Western Europe and North America, 3-4% in some Mediterranean and Asian countries up to 10-20% in parts of central Africa and Egypt⁴. The incidence found higher in Eastern Europe as compare to Western Europe.

Present standard of treatment of combination pegylated interferon (PEG-IFN) alfa and ribavirin is

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ABSTRACT... Objectives: To determine the serum lipid profile in patients with chronic HCV infection and correlation between serum lipid levels and liver histology. **Material and methods:** Descriptive study was carried out in Medical Unit I of Liaquat University Hospital Jamshoro Hyderabad, from September 2007 to August 2009. Convenience sampling was used and 30 patients were selected. Positive PCR test for HCV, non diabetic patients and non cirrhotic patients were included in this study. All the patients were selected from the medical OPD. Clinical examination performed and then blood tests were done. Serum lipid profile were determined in all participants after an overnight fast of 12 h. TC, TG, and HDL-C was measured enzymatically with commercial kits (Olympus System Reagent, Hamburg, Germany) by the use of an automated analyzer. The body mass index (BMI) was calculated in accordance with the formula of weight (kg) divided by height² (m²). Selected patients were called in the ward and biopsy was done via Trucut needle and the specimen was fixed in formalin. The biopsies were used to calculate the degree of steatosis (0-3) and fibrosis by METAVIR score. **Results:** A total of 30 patients were selected for this study. Out of these 19 were males and 11 females. The patients were divided in three groups. Patients with chronic HCV infection were found to have significantly lower levels of serum TC, HDL-C and LDL-C than normal adults values. Steatosis was present in significant number of patients (36.67%). However, steatosis was not correlating with fibrosis ($p > 0.005$). **Conclusions:** Hypolipoproteinemia and steatosis are important factors which are associated with chronic hepatitis C.

Key words: Chronic hepatitis C – steatosis – fibrosis – hypolipoproteinemia

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not completely effective in patients with hepatitis C genotype 1, the predominant viral type in the US with approximately 46% people achieving sustained virological response (SVR)⁵. Furthermore, there is a racial difference in response with African Americans (AAs) having a significantly lower response to combination treatment compared to Caucasian Americans (CAs)⁶. Factors that give details the racial disparity in efficacy are mostly unknown⁶.

Changes in serum lipid levels throughout interferon therapy have been reported, although the results are incompatible and vary by HCV genotype. Interferon therapy has been associated

with increases in total cholesterol (TC) and triglyceride (TG) levels, with TC levels remaining significantly higher and TG levels returning to pretreatment levels after stopping therapy⁷. Other work has found significant increases in TG levels, and no significant change in TC levels⁸. Compared with pretreatment, significant increases in TC have been reported in a subgroup with HCV genotype 3, but not genotype 1 during therapy,⁹ whereas another study reported higher TG levels during therapy in a group with genotype 1, but not in non genotype 1¹⁰. Recent studies further suggest that pretreatment serum lipid measures may be important predictors of treatment response. Several studies indicate that high pretreatment low-density lipoprotein cholesterol (LDLc) and TC levels are associated with higher rates of SVR in multivariable analyses¹⁰.

In addition, higher pretreatment TG levels have also been reported among virological responders compared with nonresponders⁷. These studies further suggest that associations between lipid measures and virological response may be specific to HCV genotype 1 and possibly genotype 2. Little is known about the association between changes in lipid measures while on therapy and treatment response. Observations from *in vitro* studies suggest relationships between lipoproteins and HCV that are important for mechanisms of viral entry into hepatocytes, viral replication, and secretion. Several studies suggest that HCV may combine with lipoproteins in the serum, possibly obscuring the virus from the host immune response, which may in turn help in viral entry into the hepatocytes¹¹.

Various receptors involved in lipoprotein-viral particle entry into hepatocytes are posited, including the scavenger receptor B1 (SR-B1) and LDL receptor¹.

Direct entry of free HCV (i.e., not associated with lipoproteins) is also proposed to occur through binding of the HCV envelope glycoprotein E2 with SR-B1 or its human analogue CD81¹³.

Within the hepatocyte endoplasmic reticulum,

studies indicate that HCV replication may be reliant on cholesterol metabolism and a secretion process consisting of HCV and very low-density lipoprotein conglomerate particles¹⁴⁻¹⁵. Recent work suggests that interferon therapy leads to down-regulation of SR-B1 expression¹⁶. This supports the notion that decreased lipoprotein expression may in turn impact serum lipoprotein and lipid profile measures. Therefore, associations between the serum lipids and treatment response are supported by biologically plausible mechanisms. This study has been conducted to determine the serum lipid profile in patients with chronic HCV infection and correlation between serum lipid levels and liver histology at out institutions.

METHODOLOGY

This case series, descriptive study was conducted at Medical Unit IV, Department of Medicine, Liaquat University Hospital Jamshoro from September 2007 to August 2009. Non probability convenience variety of sampling was used to select 30 patients. Patients were included if they had a positive PCR (qualitative) for HCV, were aged between 20 to 70 years, non diabetic and non cirrhotics. The patients were excluded if they were diagnosed with other causes of liver dysfunction (chronic hepatitis B, primary biliary cirrhosis, autoimmune hepatitis, continued alcohol abuse), if they had autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome) or if they were receiving anti-tuberculous treatment.

All the patients were selected from the medical OPD of LUMHS Jamshoro, which were further classified as outpatients or inpatients (if they are admitted in the medical unit). Specific questionnaire forms were filled, clinical examination performed and then blood tests were done. Serum lipid profile were determined in all patients after a fast of 12 h. TC, TG, and HDL-C were measured with commercial kits (Olympus System) by the use of an analyzer. The body mass index (BMI) was calculated in accordance with the formula of weight (kg) divided by height² (m²).

Selected patients were called in the ward and biopsy was done via Trucut needle and the specimen were fixed in formalin. The biopsies were used to calculate the degree of steatosis (0-3) and fibrosis by METAVIR score.

RESULTS

A total of 30 patients were selected for this study. Out of these 19 were males and 11 females. The patients were divided in three groups, 15-30 years, 31-50 years, and 51-70 years. Two, 25 and three patients were present in each group respectively. Table I shows the continuous variables which were studied in this study. Mean age ± SD was 42.1±7.6 years. The remaining variables are shown in Table I.

	Mean ± Standard Deviation
Age	42.13 ± 7.615
Random Blood Sugar	158.80 ± 18.37
Total Cholesterol	158.00 ± 12.63
Triglycerides	134.80 ± 35.13
LDL*	114.70 ± 19.72
HDL**	43.90 ± 2.67
AST***	43.60 ± 12.43
ALT ****	53.50 ± 19.28
GGT*****	41.30 ± 4.85

Table-I. Descriptive statistics (n = 30)

* LDL: Low density lipoprotein, ** HDL: High density lipoprotein, *** AST: Aspartate aminotransferase, **** ALT: Alanine aminotransferase, ***** GGT: Gamma Glutamyl transferase

Figure 1 and 2 show the age groups, sex distribution, total cholesterol <160 mg/dl, proportion of triglycerides <150 mg/dl, LDL <110 mg/dl, HDL <45 mg/dl, AST >40 IU/ml, ALT >40 IU/ml, presence of steatosis, microvesicular steatosis, grades of steatosis and hepatic fibrosis respectively.

DISCUSSION

In this study, patients with chronic HCV infection

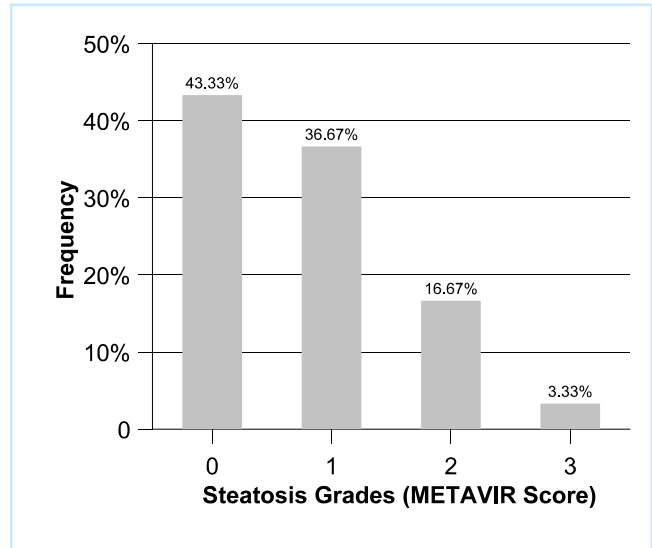


Figure-1. Steatosis Grades (METAVIR Score), n = 30

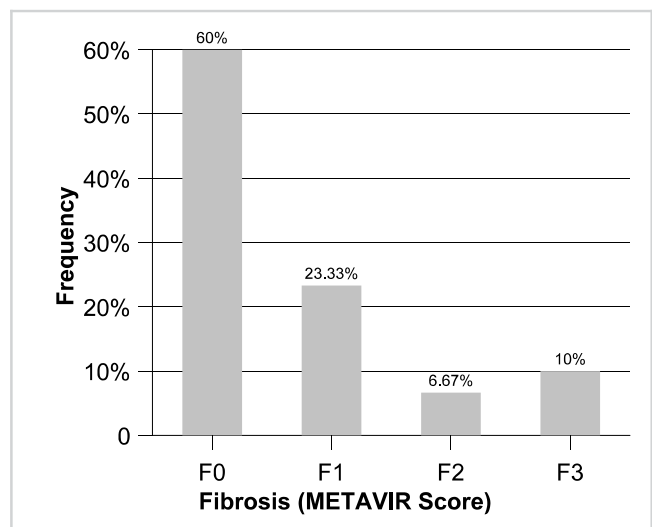


Figure-2. Fibrosis (METAVIR Score), n = 30

were found to have significantly lower levels of serum TC, HDL and LDL than normal adults values. Majority of patients were having genotype 3 (which is independently associated with the presence of steatosis). Relation of HCV infection to low LDL levels may be clinically relevant as it may reduce the risk of diseases associated with hyperlipidaemia, mainly atherosclerotic heart disease¹⁷.

Adinolfi et al¹⁸ reported that disturbed lipoprotein metabolism had significant links with the specific type of HCV genotype. The same results have

been reported in variety of other such significant studies¹⁹. Our study didn't attempt to differentiate between different genotypes but as prior studies in the local populace have concluded that >90% of chronic hepatitis C patients have genotype 3, so it is because of this reason that the close association of this genotype (independently) with steatosis the results would always be doubtful and cannot be extrapolated to the general populace with HCV.

Many theories exist regarding the strange relationship between serum lipids and different forms of HCV but consensus still seem to be lacking so as to the exact modus operandi of this relationship^{20,21}. In our study subjects hypocholesterolaemia was not attributed to the liver hypofunction because all cases of cirrhosis were excluded. Moreover, no correlation was observed between serum cholesterol (TC, HDL-C and LDL-C) and staging score in our study.

However, a positive correlation (and not a negative as it was expected) was found between serum cholesterol (TC and LDL-C) and grading score. This finding is surprising and difficult to explain, as a higher grading score means more severe inflammation, elevated serum levels of cytokines and hypocholesterolaemia.

Our results are in accordance with the report of Serfaty et al²² who suggested that in chronic hepatitis C, hypobetalipoproteinaemia is prevalent and associated with steatosis, especially in patients with genotype 3a. According to the some other studies lipoprotein profiles in the sera of patients with chronic "HCV" infection have been studied with special attention to the association of hepatitis C virus genotype and the response to interferon (IFN) based antiviral therapy^{23,24}. Abnormal lipoprotein profiles are more prominent in hepatitis C virus genotype 3 "G3" than in HCV genotype 1 "G1" infection²⁵.

CONCLUSIONS

In conclusion, we found that hypolipoproteinaemia was definitely present in patients suffering

from chronic hepatitis C infection. Although more such studies are needed to elucidate the exact mechanism behind this association.

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