

Serum Lipid, Steatosis and Fibrosis in Patients with Chronic Hepatitis C Genotype 4

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ABSTRACT:

Background/Aim: Alterations of lipid metabolism are commonly observed in Chronic Hepatitis C. Steatosis is present on liver biopsy in approximately 50% of patients with hepatitis C and its association with stage of fibrosis has been reported. Relations of serum lipid, steatosis and fibrosis to HCV genotype 4 are unknown. The aim of this work is to study the relation between serum lipid, steatosis and fibrosis and hepatitis C genotype 4.

Patients & Methods: We studied 47 patients (31 males, 16 females, mean age 41.8 ± 17.58 years) with chronic HCV infection. Serum lipid profile was determined in all participants after an overnight fast of 12 h. Hepatitis C virus RNA was detected in patients' sera by reverse transcriptase-polymerase chain reaction (RT-PCR). Liver biopsies were taken to evaluate steatosis and fibrosis.

Results: Serum Total cholesterol ($p < 0.001$) and Low-density lipoprotein-cholesterol ($p < 0.001$), were significantly lower in chronic hepatitis C patients with genotype 4. Aspartate aminotransferases (AST), alanine aminotransferase (ALT) ($p < 0.001$), were significantly higher in chronic hepatitis C patients compared with controls. There was a significant difference between chronic hepatitis subgroups (as regard degree of steatosis) grading and staging ($p < 0.001$).

Conclusions: HCV-genotype 4 infection is associated with clinically significant lower cholesterol levels (TC, and LDL) than those of normal subjects. We have confirmed that steatosis is associated with increased fibrosis & necroinflammation in chronic HCV biopsies.

INTRODUCTION

The hepatitis C virus (HCV) is a major cause of chronic liver disease with an estimated 170 million people infected worldwide. The spectrum of severity of the liver disease associated with HCV varies widely from nonspecific, minimal inflammatory changes to cirrhosis and hepatocellular carcinoma [1].

It is well known that liver plays a key role in serum lipoprotein synthesis and metabolism, and an impaired lipid metabolism is often found in patients with chronic liver diseases [2].

Decreasing levels of serum cholesterol, mainly low-density lipoprotein-cholesterol (LDL-C) has been related to increasing severity of liver disease [3]. Lower total cholesterol (TC) and LDL-C levels were described in hepatitis C virus (HCV)-infected patients soon after viral diagnosis. These lower levels are associated with HCV infection regardless of the degree of hepatic fibrosis [4]. Moreover, patients with chronic hepatitis C were found to have lower TC levels when compared with those with chronic

hepatitis B [9]. In addition, an association between HCV infection and lipid metabolism has been reported. Particles of HCV exist in binding form with beta-lipoproteins [LDL and very lowdensity lipoproteins (VLDL)] and immunoglobulins in the sera of patients with chronic hepatitis C [6,7]. Complexing of the virus to VLDL or LDL could promote endocytosis of HCV via the LDL receptor [8]. These findings suggest that lipoproteins play an important role in the process of HCV infection.

Since the discovery of hepatitis C, there have been several investigations of the role of biopsy histology in determining the severity of chronic hepatitis and progression of disease [9-13]. Most of these studies used histological scoring systems for chronic hepatitis that did not include the assessment of steatosis. The extent of fibrosis and architectural disturbance (stage of disease) increases with time, but at a rate that varies widely between individuals, with some progressing to cirrhosis within 10 years of viral acquisition, and others showing only mild fibrosis after 30 years [12]. Clinical factors associated with increasing fibrosis include older age at viral acquisition, male sex, alcohol consumption, and co-infection with hepatitis B virus or human immunodeficiency virus [14]. Steatosis is seen in 30-70% of liver biopsies from patients with chronic hepatitis C [15,16], more frequently than is seen in other causes of chronic hepatitis [17], and in a high proportion of patients no other cause of fatty liver (such as high alcohol intake or high body mass index (BMI) can be identified [18,19]. Steatosis is thought to be a specific cytopathic effect of the hepatitis C virus (HCV) [20], and may be particularly associated with the type 3 genotype [15,18]. Some studies have shown an association between steatosis and the stage of fibrosis on liver biopsy [15,16, 21-25], but others have not [11, 8]. If such an association exists, this suggests that steatosis may be a factor predicting increased risk of progression of fibrosis; alternatively, steatosis could be acquired during the progression of chronic hepatitis C.

The aim of this study was to determine the serum lipid profile in patients with chronic HCV infection, to explore the relation between steatosis, fibrosis, and other histological features

in a series of biopsies from patients with hepatitis C, and to detect if there is any correlation between serum lipid levels and viral load, HCV genotype or liver histology.

MATERIAL & METHODS

We studied 47 patients (31 males, 16 females, mean age 41.8 ± 17.58 years) with chronic HCV infection, which were being regularly followed up at the Tanta University Hospital (Group I). Chronic HCV infection was defined by the presence of HCV-RNA in serum for >6 months.

Patients with other causes of liver dysfunction (e.g. chronic hepatitis B), and under current treatment with IFN and ribavirin were excluded. In addition, patients infected with other than genotype 4 or had clinical signs of cirrhosis and/or definite cirrhosis (stage 6 on liver biopsy) was excluded.

The control group (Group II) was made up of 50 normal subjects, matched for age and sex (35 males, 15 females, mean age 38.4 ± 6.7 years) from the volunteer blood donor programme of our hospital. Each individual had indicated the absence of significant illness. Physical examination, normal liver function test results and absence of hepatitis B surface antigen (HbsAg) and anti-HCV antibodies in their serum, excluded liver diseases in these controls.

None of the enrolled subjects in these two groups had a history of alcoholism, diabetes mellitus or exposure to drugs influencing lipid metabolism (lipid-lowering agents, corticosteroids, non-steroid anti-inflammatory drugs).

Serum lipid profile was determined in all participants after an overnight fast of 12 h. TC, triglyceride (TG), and HDL-C were measured enzymatically with commercial kits by the use of an automated analyzer. LDL-C was calculated according to the formula of Friedewald et al. [26]. The body mass index (BMI) was calculated in accordance with the formula of weight (kg) divided by height² (m²). Patients had BMI ≥ 30 were excluded.

Hepatitis C virus RNA was detected in patients' sera by reverse transcriptase-polymerase chain reaction (RT-PCR). Quantification of serum

HCV-RNA was performed by the branched DNA method. HCV genotype 4 is widespread in East Africa and Egypt [28]. We performed HCV genotyping in some patients by a second-generation, lineprobe assay & confirmed presence of genotype 4.

We studied liver biopsies from patients with chronic hepatitis C with adequate liver biopsies (>1 cm, >4 portal tracts).

Biopsies were routinely processed; 3 mm thick sections were then stained for reticulin and using haematoxylin and eosin, van Gieson, and periodic acid Schiff + diastase. Necro-inflammatory activity is graded on a scale of 0-18 (modified HAI grading) and the staging for liver fibrosis and architectural disturbances is performed using a scale of 0-6 (modified staging).

Fatty change was estimated subjectively and scored as absent (0), or present in < 30% hepatocytes (1+), 30-60% hepatocytes (2+), or > 60% hepatocytes (3+) according to it, group I was classified into four subgroups Ia, Ib, Ic, and Id respectively.

Statistical analysis was done with MINITAB STATISTICAL SOFTWARE™ (MINITAB Release 13.1). Clinical data were analyzed by the unpaired *t* test (for age) and Fisher's exact test (for sex). Differences with *p* values < 0.05 were considered to be statistically significant.

RESULTS

The main clinical and laboratory data are summarized in Table 1. Patients were comparable with controls according to age, sex and BMI.

Serum Total cholesterol ($p < 0.001$) and Low-density lipoprotein-cholesterol ($p < 0.001$), were significantly lower in chronic hepatitis C patients compared with controls, whereas triglyceride, and high-density lipoprotein-cholesterol levels were similar in the two groups.

Aspartate aminotransferases (AST), alanine aminotransferase (ALT) ($p < 0.001$), were significantly higher in chronic hepatitis C patients compared with controls.

Table 2 shows the mean grading score of four chronic hepatitis subgroups Ia, Ib, Ic, and Id were 5.01 ± 2.31 , 7.45 ± 1.89 , 12.48 ± 4.67 , and 11.02 ± 3.59 respectively. The mean staging score of four chronic hepatitis subgroups Ia, Ib, Ic, and Id were 2.14 ± 0.15 , 3.67 ± 0.38 , 5.07 ± 1.01 , and 5.17 ± 1.16 respectively. There was a significant difference between chronic hepatitis subgroups grading and staging ($p < 0.001$) by ANOVA. There was not a significant difference between chronic hepatitis subgroups according to HCV-RNA levels.

Table [1]: Demographic and serum lipid data in chronic hepatitis patients: comparison with healthy donors

	Group I Chronic hepatitis [n=47]	Group II Control [n=50]	p-value
Age	41.8 ± 17.58	38.4 ± 6.7	p > 0.05 ^o
Sex [M/F]	31 / 16	35 / 15	p > 0.05 ^o
BMI	25.91 ± 1.04	26.02 ± 0.87	p > 0.05 ^o
Total cholesterol	194.14 ± 13.08	223.45 ± 34.59	P < 0.001 #
Triglyceride	133.56 ± 14.59	128.08 ± 15.69	p > 0.05 ^o
High-density lipoprotein cholesterol	41.51 ± 6.03	43.18 ± 5.19	p > 0.05 ^o
Low-density lipoprotein cholesterol	110.96 ± 40.02	155.78 ± 37.43	P < 0.001 #
ALT	88.45 ± 43.10	22.01 ± 15.98	P < 0.001 #
AST	74.09 ± 39.45	20.98 ± 11.07	P < 0.001 #

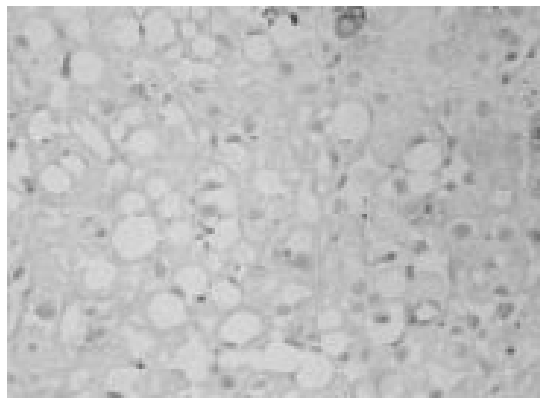
^oNon-significance, # Significant

Normal levels: total cholesterol 125-200 mg/dL; triglycerides 40- 150 mg/dL; high-density lipoprotein cholesterol > 35 mg/dL; low-density lipoprotein cholesterol 150-190 mg/dL; aspartate aminotransferases (AST) < 40 IU/L; alanine aminotransferase (ALT) < 40 IU/L.

Table [2]: Comparison of grading, staging, and HCV-RAN level in chronic hepatitis subgroups by ANOVA.

	Group I Chronic hepatitis				p-value
	Group Ia [n=26]	Group Ib [n=11]	Group Ic [n=6]	Group Id [n=4]	
Grade [0-18]	5.01 ± 2.31	7.45 ± 1.89	12.48 ± 4.67	11.02 ± 3.59	P < 0.001 #
Stage [0-6]	2.14 ± 0.15	3.67 ± 0.38	5.07 ± 1.01	5.17 ± 1.16	P < 0.001 #
HCV-RNA level	1,800,000 ± 1,950,000	2,700,000 ± 850,000	1,900,000 ± 1,400,000	3,100,000 ± 900,000	p > 0.05 ^o

^oNon-significance, # Significant

**Fig1: Sever HCV-induced steatosis (group Id)**

DISCUSSION

Circulating HCV is extremely heterogeneous [27]. HCV genotype 4 is widespread in East Africa and Egypt [28]. Both prevalence and extent of HCV-related steatosis are genotype-dependent, with the highest prevalence and accumulation of steatosis being observed in HCV genotype 3 infection [29].

Many published researches focus on genotypes 3, and 1 in discussing HCV-induced steatosis. In this study, we tried to spot light on genotype 4.

In our study, patients with chronic HCV infection were found to have significantly lower levels of serum total cholesterol, and Low-density lipoprotein-cholesterol than normal adults matched for age and sex. 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 disease [30]. The mechanism by which HCV infection may lower serum cholesterol is not known. Liver disease resulting from HCV infection might impair VLDL synthesis in hepatocytes [6]. It is well established that chronic inflammation causes hypocholesterolaemia through a reduction of LDL, and, to some extent, HDL [31]. Cytokines, endogenously produced, have been related to change in blood lipid composition and to the outcome of infections [32]. The relationship between lipids and cytokines appears to change according to the kind of viral infection involved (HCV or HBV) [3]. Binding of the HCV to lipoproteins LDL, VLDL, and HDL in plasma has been reported in many studies [6,7,33]. Thomssen et al. [34] described that heterogeneities in the density of hepatitis C virus RNA-carrying material found in human sera are attributed to the binding of low-density lipoproteins and/or of IgG. It has been postulated that the LDL may protect the virus from inactivation by antibodies [35].

Kono et al. [43] showed that there is an apparent difference in the lipoprotein-binding rate between different genotypes. He found that genotype 2a/2b HCV had a higher LDL binding rate and also a striking higher HDL binding rate than of genotype 1b HCV. Moreover, Moriya et al. [44] showed that genotype 1b HCV patients

had lower serum cholesterol levels than those infected with genotype 2a.

Results emerging from this study revealed that patients with genotype 4 have the nearly serum lipid changes as other genotypes with little differences. It is possible that this difference in serum lipid levels between genotypes may be connected to the different lipoprotein-binding rate between them.

As expected, there was a significant difference of liver enzyme (serum aspartate aminotransferases, and alanine aminotransferase) between both groups.

The quantitative association between steatosis and hepatic HCV RNA, the loss of steatosis after viral eradication, and the development of steatosis by transgenic mouse and in vitro cell line models of HCV infection are cited as evidence that steatosis is a direct cytopathic effect of HCV [29]. This interacts with factors predisposing to steatosis in the host, particularly high BMI, to result in the expression of steatosis in a proportion of HCV positive patients [19]. Recent evidence that weight reduction in patients who are mildly overweight results in improvement in steatosis, and in some also in the degree of fibrosis [19,42], suggests both the reversibility of steatosis in patients with chronic hepatitis C, and also the direct importance of steatosis in the development of fibrosis.

The presence of steatosis in patients with hepatitis C is dependent on a complex interaction of viral and host related factors [20]. Steatosis in patients without hepatitis C is related to alcohol consumption, obesity, high BMI, type II diabetes, and hyperlipidaemia [36]. These factors are also important in patients with hepatitis C, but a proportion of patients with hepatitis C have no other risk factor for steatosis.

Our study showed that steatosis was present in about 45 % of liver biopsies from patients with chronic hepatitis C genotype 4, which is in consistent with other studies which concluded steatosis is seen in 30-70 % of liver biopsies from patients with chronic hepatitis C [15,16]. It has been shown that HCV genotype 3 is

independently associated with hepatocellular steatosis with highest incidence in patients with chronic hepatitis C [21,45]. This can clear relatively low incidence of steatosis in our patients.

Our study showed that no significant difference between severity of steatosis as regard HCV RNA load. This is in agreement with Hezode et al., who concluded that, the severity of steatosis in these patients is directly related to the burden of the HCV RNA load. This relationship between the HCV viral load and the magnitude of steatosis was not observed in other HCV genotypes [46].

We found a significant association between steatosis and stage of fibrosis in non-cirrhotic biopsies, as has previously been demonstrated in several [15, 16, 21-25], but not all, studies [11, 18] where this has been examined. However, most of the studies examining histological factors predicting the progression of hepatitis C cited in clinical guidelines for patient management [12, 13] did not include an assessment of the importance of steatosis. Histopathology scoring systems used in studies of hepatitis C [37-40] do not include steatosis, and so the prognostic importance of steatosis has received little attention. Furthermore, recognition and grading of steatosis by histopathologists is much more reproducible than the scoring of interface hepatitis and lobular necroinflammation, currently used in the clinical management of patients with hepatitis C [41]. Consequently, we recommend the assessment of steatosis should be included in the evaluation of biopsies for clinical and research purposes.

In conclusion, HCV-genotype 4 infection is associated with clinically significant lower cholesterol levels (TC, and LDL) than those of normal subjects. We have confirmed that steatosis is associated with increased fibrosis & necroinflammation in chronic HCV biopsies.

Some key questions remain unanswered: why some HCV [genotype 4] infected patients develop steatosis & other don't? Is this related to host or viral factors? Is HCV induced steatosis is linked to high incidence of hepatocellular carcinoma in Egypt? We suggest that these issues should be guidelines for further research.

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الملخص العربي

دهون المصل وتدهن الكبد والتليف الكبدي في مرضى التهاب الكبد المزمن ج النمط الجيني أربع .
أيمن الجندي وأمانى ابو العيدين وحسين غرابية
من أقسام طب المناطق الحارة والباثولوجيا الاكلينيكية والباثولوجي - كلية الطب - جامعة طنطا

يلاحظ تغير تمثيل الدهون في التهاب الكبد المزمن ج ، وفي خمسين من المائة من الحالات مرضى التهاب الكبد ج يتبين وجود التدهن في الخزعة الكبدية . وقد تبين ارتباطها بدرجة التليف الكبدي . وما زالت علاقة دهون المصل والتدهن والتليف بالنمط الجيني أربعة للفيروس الكبدي ج غير معروف .
هدف هذا البحث إلى دراسة العلاقة بين مستوى الدهون والتدهن والتليف مع التهاب الكبد ج لنمط الرابع .

قمنا بدراسة سبعة وأربعين مريضاً ، ٣١ ذكراً و١٦ أنثى مصابين بالتهاب الكبد لمزمن ج . تم تحديد صورة الدهون في كل المشاركين بعد صيام ١٢ ساعة . تم العثور على الحمض النووي ر ن أ في المصل باستخدام تفاعل سلسلة البوليمير ترانس كربتيز العكسي . تم أخذ خزعات كبدية لتقييم التدهن والتليف .

كان الكوليسترول الكلي والدهون البروتونية قليلة الكثافة أقل بشكل ذي دلالة إحصائية في مرضى التهاب الكبد المزمن ج . تبين أن أنزيم الكبد (أس ت) و (أل ت) أعلى بشكل ذي دلالة إحصائية في مرضى التهاب الكبد المزمن ج مقارنة بالمجموعة القياسية . كان هناك فارق ذو دلالة إحصائية بين المجموعات الفرعية لالتهاب الكبد المزمن فيما يخص درجة لتدهن والتصنيف والفرز .

يرتبط لنمط الجيني الرابع لالتهاب الكبد ج بنسبة كوليسترول أقل (الكوليسترول الكلي والدهون البروتونية قليلة الكثافة) عن الأشخاص الطبيعيين وقد ثبتنا أن التدهن يرتبط بزيادة التليف والالتهاب في خزعات التهاب الكبد المزمن ج .