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Evaluation of the lipid profile between individuals with hepatitis C

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ABSTRACT

Metabolic profiles correlate with hepatitis C virus (HCV) infection and are prognostic for the viral response. However, little is known about the association between lipid profiles and viral load in chronic patients carrying HCV genotypes 1, 2 and 3. The aim of this study was to investigate the influence of the viremia and viral genotype on lipid metabolism by observing the variations in serum lipoprotein and apolipoprotein B, to assess whether HCV predisposes individuals to lipid imbalance and favors the appearance of vascular complications. A sample group of 150 chronic HCV patients with viral genotypes 1, 2 or 3 and a control group of 20 healthy adults (10 men and 10 women), all aged from 20 to 50 years were studied. The serum lipid profile of the chronic patients was analyzed and compared to that of the control group. The high-density lipoprotein (HDL), very low-density lipoprotein (VLDL) and triglyceride levels of the sample group were lower than those of the control group, while the low-density lipoprotein (LDL) and apolipoprotein B levels of the patients were higher. These differences were more significant in patients carrying genotype 3a. There was a positive correlation between the viremia and the changes in apolipoprotein B levels in patients carrying genotype 1b. It was inferred that the risk of developing vascular complications raised in HCV patients. As 90% of LDL protein is composed of apolipoprotein B, the plasmatic concentration of the latter indicates the number of potentially atherogenic particles. Therefore, the lipid profile monitoring may aid in the diagnosis of hepatic infection severity and equally act as a good prognostic marker.

Keywords: Genotypes. Hepatitis C vírus. Viremia. Lipoproteins.

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INTRODUCTION

More than 20 years after the discovery of the hepatitis C virus (HCV), it is now established as a major health problem in all countries. Currently, there is an estimated prevalence of 2.35%, affecting 160 million chronically infected individuals (Lavanchy, 2011).

Chronic hepatitis C has been linked to the development of hepatocellular carcinoma (HCC) in many parts of the world. Of the more than 500 000 new cases of liver cancer that occur each year, 22% (>100 000) are attributable to HCV infection (WHO, 1996). Prospective studies have shown that 80% of all cases of acute hepatitis C progress to chronic infection; 10-20% of these will develop complications of chronic liver disease, such as liver cirrhosis, within two to three decades of onset, and 1-5% will develop liver cancer, making HCV a health problem of global importance (The Global burden of Hepatitis C working Group, 2004).

More than twenty years after the discovery of HCV, the assessment is far from complete and little progress has been made in the past 10 years in many countries. In some countries, significant increases in prevalence have been reported, and this may also apply to countries were insufficient data exist. There is an urgent need for more accurate information on the long-term outcome of the HCV infection, with its consequences for, and costs and burden to society (Lavanchy, 2011).

Lipids, which exist as free molecules, are an essential component of biological membranes and can be metabolic regulators that control cell function and homeostasis (Chiang, 2005). The liver plays a vital role in lipid metabolism and is the principal site of lipoprotein formation and clearance. Thus, in severe liver disease, lipid metabolism is profoundly disturbed. Ramcharran et al. (2011) found associations between lipid serum profiles and both HCV level and liver disease severity and Malavazi et al. (2004) reported an association between viral infection and abnormal lipid metabolism in the liver.

HCV circulating particles exhibit a heterogeneous density that might reflect binding of the virus to very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). Published evidence supports the hypothesis that lipoproteins could provide affinity enhancement for

certain human serum components (Meunier et al., 2005). Association between HCV and LDL in human serum has been reported (Thomssen et al., 1992) and subsequently an interaction between HCV and the cellular low-density lipoprotein receptor (LDLr) was demonstrated.

Recent work has demonstrated an association between HCV infection and alterations in the lipoprotein serum levels (Siagris et al., 2006). An increase in LDL concentrations and total cholesterol is related to an increased risk of cardiovascular diseases (CVD), whereas a raised high-density lipoprotein concentration (HDL) acts as a protective factor against CVD (Williams, 1996; Krauss, 2004). LDL can pass through the endothelial wall to penetrate the artery wall and may suffer oxidation in the inner layer, resulting in atheromatous plaque formation and development of CVD (Damaso, 2001).

Apolipoprotein B (apo B) is the main functional protein responsible for carrying cholesterol to peripheral cells (Rifai et al., 1999), and about 90% of the protein in LDL consists of apo B (Walldius & Jungner, 2006). LDL and VLDL particles have an apo B molecule in their structure, and, as a result, the plasma concentration of apo B indicates the total number of potentially atherogenic particles, being correlated with the cholesterol non-HDL level (Walldius & Jungner, 2006).

The purpose of this study was to assess the influence of HCV viremia and genotypes on lipid metabolism by observing the variations in serum lipoproteins (total cholesterol, LDL, HDL, VLDL and triglycerides) and apo B levels in chronic HCV patients.

MATERIAL AND METHODS

Patients and samples

Serum samples were taken from HCV-infected patients (n=150) attending the State Viral Hepatitis Program and from healthy blood donors (n=20) at Araraquara Regional Blood Center by the Clinical Analysis and Hemotherapy Service of the Community Health Outreach Unit of the Pharmaceutical Sciences School, São Paulo State University (UNESP) at Araraquara (SP, Brazil), in the period between August 2007 and August 2008. Although the number of control samples was small, dyslipidemia was defined in accordance with the 4th Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention (SBC, 2007), as any of the following: LDLc < 130 mg/dL, HDLc > 40 mg/dL, TC < 200 mg/dL or TG < 150 mg/dL.

Apo B reference values (Dati et al., 1989):
- Men: 60-138 mg/dL
- Women: 52-129 mg/dL

Inclusion criteria

Hepatitis Group: HCV carrier, proved by serological anti-HCV test, not treated, as specified by the State Viral Hepatitis Program, and to be under medical supervision with a request for viral analysis of the serum.

Control Group: negative for all the serological tests defined for blood donation (Hepatitis B and C, Chagas' disease, HIV, HTLV, syphilis) and carried out by the Araraquara Regional Blood Center – NAC/FCF/UNESP.

Exclusion criteria

Hepatitis Group: all patients who showed an inconclusive or negative serological test for hepatitis C.

Control Group: all the individuals who showed inconclusive or positive results in any blood bank serological test were excluded.

All serum samples were subjected to serological or molecular tests for HCV infection or serologically selected from blood donors at the Laboratory of Clinical Immunology and Molecular Biology of the school. The blood samples were collected and centrifuged at 1200xg for 15 min. The resultant sera were frozen to -80ºC and stored for up to 6 months, or until the lipids were analyzed.

Viral markers

HCV RNA was detected in patients' sera by reverse transcriptase-polymerase chain reaction (RT-PCR) (AMPLICOR HCV Monitor Test, version 2.0; Roche Molecular Systems, Branchburg, NJ, USA). The quantity of HCV-RNA in serum was assayed by the branched DNA method [HCV RNA 3.0 Assay (b-dna); Versant-Bayer, New York, USA]. The detection limit of this assay is 600IU/mL. HCV genotyping was performed by a second-generation line probe assay (INNO-LiPA HCV II; Innogenetics, Zwijndrecht, Belgium) that allows discrimination of types 1 to 6 and subtypes 1a, 1b, 2a/c, 2b, 2d, 2i, 3a-c, 4a-h, 5a, 6a and 10a. Prevalence of the various HCV genotypes varies with geographic region (Ramia & Eid-Fares, 2006; Zein, 2000).

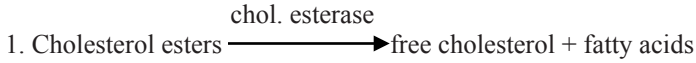
Serum lipoprotein assay

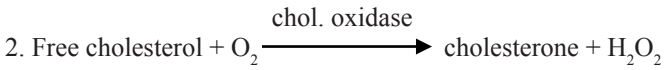
Cholesterol, HDL and triglyceride levels in test samples from HCV patients were analyzed. The HCV patients were subdivided by sex (116 men and 34 women), age (mean 45 $\pm$ 10.24) and virus genotype (1, 1a, 1b, 1a/b and 3a). Control samples from healthy donors were tested and used for comparison (10 men and 10 women).

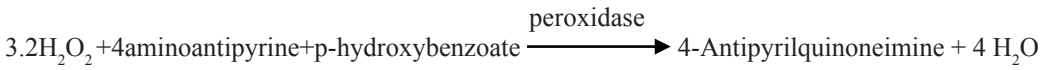
Lipid profiles were analyzed in a Cobas Mira Plus analyzer (Roche Diagnostics) in accordance with the reagent manufacturer's instructions, using specific enzymatic kits for cholesterol, HDL and triglycerides (Biotécnica Comércio e Indústria Ltda, Varginha, Brasil). The LDL and VLDL levels were calculated by the Friedewald equation, which was used for samples containing below 400 mg/dL triglycerides (Friedewald et al., 1972).

Cholesterol assay

The cholesterol in the serum was subjected to the following enzymatic reactions:







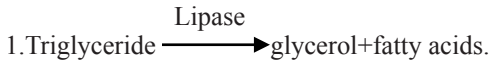
The product formed by oxidation of 4-aminoantipyrine (4-antipyrilquinoneimine) is a red dye and its color intensity is directly proportional to the cholesterol concentration in the serum. The red color was measured in a spectrophotometer in 510nm.

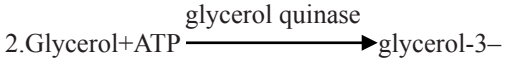
HDL assay

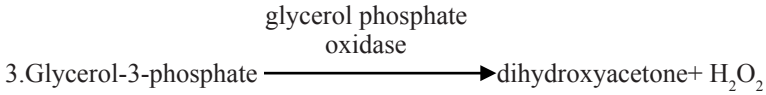
The technique for HDL determination is based on the selective precipitation of the LDL and VLDL fractions by buffered polyethylene glycol (PEG). In the supernatant only the HDL fraction remains, which can be determined as above.

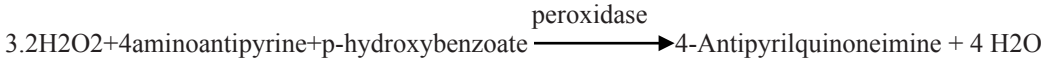
Triglyceride assay

The serum triglyceride is processed by the following enzymatic reactions:









The concentration of the 4- antipyrilquinoneimine dye is proportional to that of the triglyceride and was measured as in the cholesterol assay.

Apo B assay

The apo B concentration in test and control samples was determined by the turbidimetric immunoassay method, using specific enzymatic kits, in a Cobas Mira Plus automatic analyzer (ROCHE DIAGNOSTICS).

The anti-Apo B antibodies react with Apo B to form insoluble composites in the presence of a macro-molecule (PEG), causing turbidity proportional to its concentration in the sample. This is measured photometrically.

STATISTICAL ANALYSIS

The results were subjected to the two-level nested analysis of variance, where significance was accepted when $p<0.05$, followed by the Mann-Whitney test. Pearson correlation analysis was used to determine the correlation between the viral load and lipoprotein levels in HCV carriers.

RESULTS

The lipid profiles of HCV genotype 1a carriers were analyzed. Male carriers showed a significant fall in the HDL level (29%) and an increase in the VLDL level (27%) relative to the control group, and the lipid profile of female carriers of the same HCV genotype showed a similar fall in the HDL levels (27%) and rise in the LDL levels (26%), relative to the control group (Figures 1A and 1B).

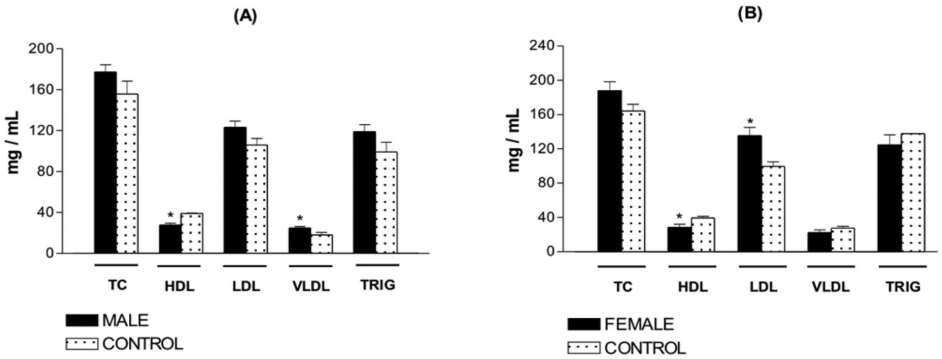
In the lipid profile of male HCV genotype 1b carriers, the HDL level was lower (23%) and the triglyceride level higher (26%) than in the control group. The lipid profile of female HCV genotype 1b carriers also showed lower HDL level (21%), and higher LDL level (27%) than in the control group (Figures 2A and 2B).

The lipid profile of male HCV genotype 1a/1b carriers showed a lower HDL level (36%) higher LDL level (25%), than the control group.

The lipid profile of male HCV genotype 3a carriers showed a lower HDL level (41%) in comparison with the control group, whereas in the women carrying the same

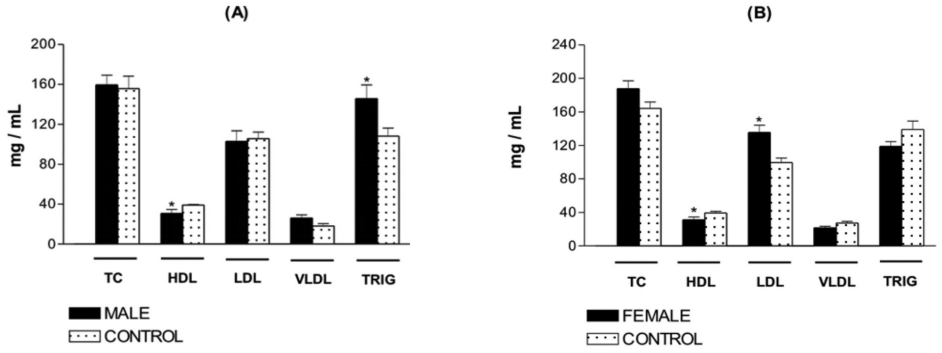
genotype, all parts of the lipid profile were changed. There were reductions in the HDL (21%) and VLDL levels (25%) and an increase in the LDL (20%) and triglycerides levels (27%), relative to the control group (Figures 4A and 4B).

To correlate the viral load with the lipid profile, two groups were analyzed, the first consisting of HCV genotype 1a carriers (n = 23) and the second of HCV genotype 1b carriers (n = 10), both groups consisting with male and female adult patients. The viral load from each group was tested for correlation with the LDL, HDL and apo B values, these being the lipoproteins and proteins those suffered the most significant alterations. It was found that significant correlations occurred only between viral load and LDL and apo B in genotype 1b carriers (Figures 7 and 8). These results are consistent with this viral type, which has proved to be refractory to treatment with ribavirin and interferon. In the other results, it is clearly observed that there was no correlation between the viral load and HDL or LDL levels for genotype 1a carriers (data not shown).



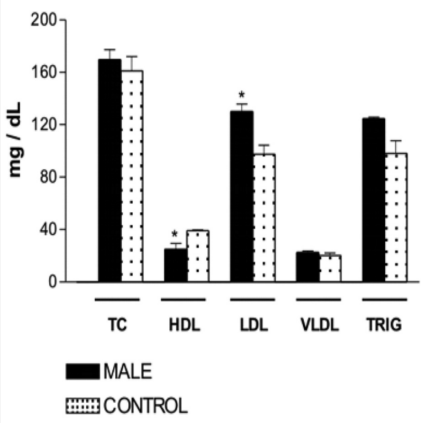
Lipid profiles of HCV genotype 1a patients and respective controls (A) serum samples of adult male (n=47) and (B) female (n=8) patients carrying HCV genotype 1a group were analyzed.
*Lipid profile of each group is shown significantly different from control by the Mann-Whitney test (p> 0.05).

Figure 1 - Lipid profile of HCV genotype 1a patients



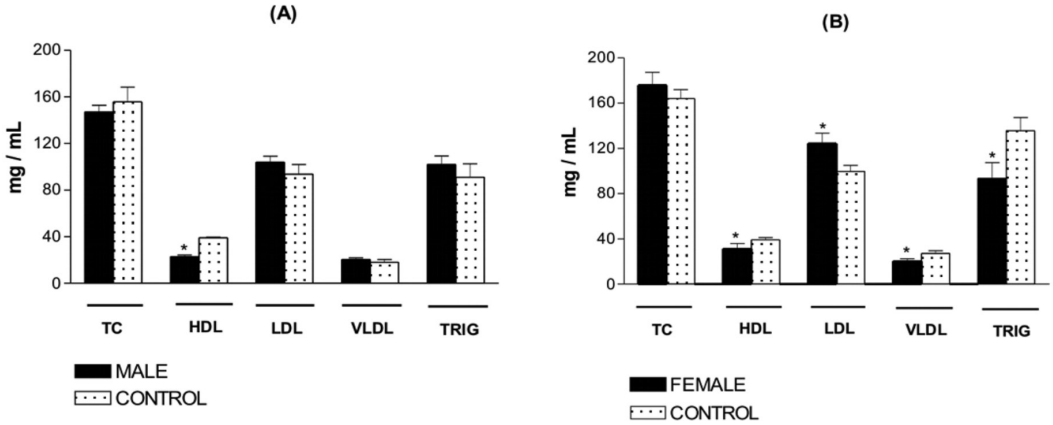
Lipid profiles of HCV genotype 1b patients. Serum samples of adult (A) male (n=16) and (B) female (n=12) patients and respective controls were analyzed.
*Lipid profile of each group is shown significantly different from the control group by the Mann-Whitney test (p> 0.05).

Figure 2 - Lipid profile of HCV genotype 1b patients



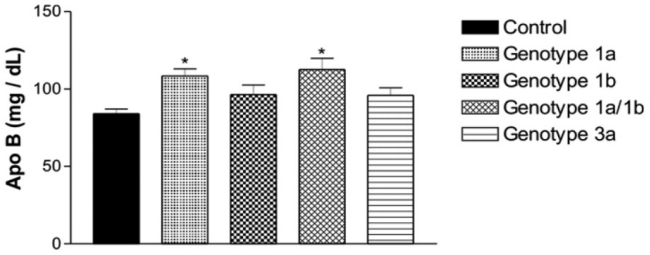
Lipid profiles of adult male patients (n=6) carrying the HCV genotype 1a/1b.
*Different from the control group by the Mann-Whitney test (p>0.05).

Figure 3 - Lipid profile of HCV genotype 1a/1b patients



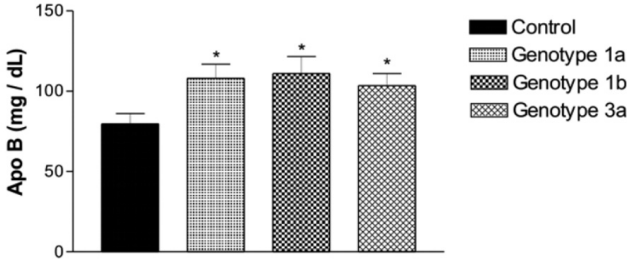
Lipid profiles of HCV genotype 3a patients. Serum samples of adult (A) male (n=41) and (B) female (n=10) patients and respective controls were analyzed.
*Different from the control group by the Mann-Whitney test (p> 0.05).

Figure 4 - Lipid profile of HCV genotype 3a patients



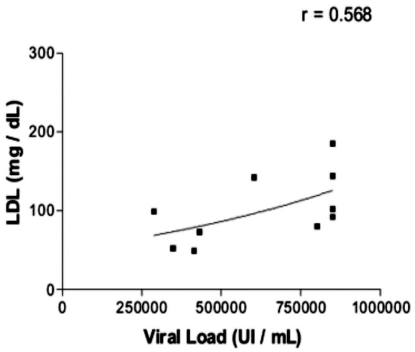
Apo B levels in male patients (n=110) carrying HCV genotypes 1 and 3 (and subtypes). Results analyzed by the Mann-Whitney test (p>0,05), when compared to the control group.
*Significant alterations.

Figure 5 - Apo B levels in male HCV patients



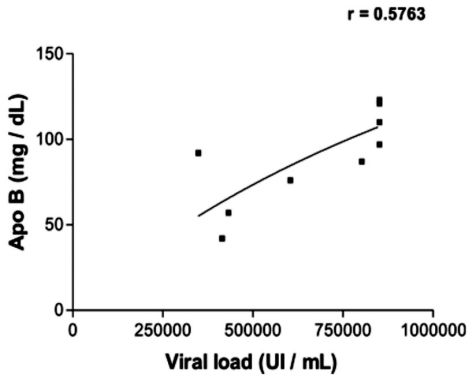
Apo B levels in female patients (n=30) carrying HCV genotypes 1 and 3 (and subtypes). Results analyzed by the Mann-Whitney test (p>0,05), when compared to the control group.
*Significant alterations.

Figure 6 - Apo B levels in female HCV patients



LDL levels of male and female HCV genotype 1b patients plotted against HCV viral load (n=10). r is Pearson's correlation coefficient.

Figure 7 - Correlation between viral load and LDL levels in HCV 1b genotype patients



Correlation between viral load and apo B levels in HCV genotype 1b patients

Figure 8 - Correlation between viral load and apo B levels in HCV genotype 1b patients

DISCUSSION

HCV infection is clinically associated with significant alterations in serum lipoprotein levels (mainly HDL and LDL), compared to the lipid profile of healthy individuals. There are reports in which not only the disturbed metabolism is shown but its significance in chronic liver infection is made clear (Ooi et al., 2005; Rubbia-Brandt et al., 2001).

Ooi and co-authors (2005) studied the dyslipidemia in various liver infections, such as chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma and metastatic hepatic infection. They discovered anomalies in lipid metabolism in several hepatic infections, for example, in chronic hepatitis, cirrhosis and hepatocellular carcinoma the triglycerides and the total cholesterol levels had diminished, while the LDL fraction had increased.

In the present study increased LDL (24.5%) and decreased HDL (28.3%) level were revealed in chronically infected patients that carry mainly the HCV genotype 3a, corroborating the findings of Fernández-Rodriguez et al. (2006). They reported that chronic hepatic infections caused by HCV genotype 3 are associated with changes in the lipid metabolism that can be reversed by a sustained viral response. This interference is related quantitatively to the viral load.

It has been observed that serum lipid levels were low in patients carrying HCV genotype 3a, and this anomaly was more pronounced with greater viral load and sustained viral response (Rubbia-Brandt et al., 2001). Therefore, it is recommended that the lipid profile should be analyzed in all patients that suffer from chronic hepatic infection, especially when it is due to HCV genotype 3a.

Epidemiological and clinical studies have consistently demonstrated that an elevated LDL concentration in the plasma is associated with an increased risk of coronary artery disease (CAD) (Grundy, 2002; Grundy et al., 2004). Increased LDL concentration is a well-established risk factor for CAD and currently recommended as the primary target for lipid-lowering therapy used for the prevention and treatment of cardiovascular disease (Hofer, 2002; Third Report of the National Cholesterol Education Program, 2002). The population analyzed in this study showed an average increase of 24.5% in the LDL levels, in comparison with the control group, which suggests that the risk of HCV patients developing vascular complications is higher (Leon & Sanchez, 2001).

An increase of 29% in the apo B levels and a positive correlation between HCV genotype 1b viral load and apo B serum levels ($r = 0.5763$) were observed in the studied population. In the last decade, attention has been drawn back to the determination of the apo B serum concentration, because it represents the number of atherogenic particles more adequately. Apo B is essential for LDL particles to bind to cell receptors, allowing LDL to enter cells; thus, an excess of apo B is a triggering factor for the atherogenic process (Forti & Diament, 2007).

In patients with chronic hepatitis caused by HCV infection, lipid levels have been reported to be lower than in those with hepatitis B infection, which suggests an HCV-specific effect on lipids, resulting either from differential effects on liver function or from a direct interaction with lipid metabolism (Fabris et al., 1997). Some studies suggest that HCV core protein decreases the activity of the microsomal triglycerides transfer protein, leading to decreased hepatic VLDL assembly and secretion (Thomssen et al., 1992; Perlemuter et al., 2002; Wunschmann et al., 2000). In addition, there is evidence that HCV particles associate with LDL and VLDL particles in the plasma and utilize the LDLr for cell binding, possibly leading to increased lipid uptake by cells (Thomssen et al., 1992; Wunschmann et al., 2000). In HCV-infected patients with hepatic steatosis, serum lipid levels have been reported to be lower than in those without steatosis, in particular in association with HCV genotype 3 infection (Third Report of the National Cholesterol Education Program, 2002; Adinolfi et al., 2001).

Lipid profile monitoring may help in the diagnosis of hepatic infection severity and may also act as a good prognostic sign, so it must be analyzed in all advanced hepatic infection cases. However, additional studies are necessary to determine whether the lipid profile manipulation might be capable of improving the response to anti-HCV therapies.

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ETHICAL APPROVAL

According to resolution 15/2008, the study was approved by the Research Ethics Committee of the School of Pharmaceutical Sciences, UNESP, Araraquara, SP, Brazil, in compliance with resolution of the National Health Council of the Ministry of Health.

RESUMO

Avaliação do perfil lipídico entre indivíduos com hepatite C

Perfis metabólicos correlacionam-se com infecção pelo vírus da hepatite C (VHC) e são prognósticos da resposta viral em pacientes crônicos. Porém, pouco se sabe a respeito da associação entre perfis lipídicos e a carga viral entre infecções dos genótipos 1, 2 e 3. O objetivo foi estudar a influência da viremia e dos genótipos virais sobre o metabolismo lipídico através das variações de lipoproteínas séricas e apolipoproteína B em hepatopatas crônicos, avaliando se o vírus predispõe os indivíduos a complicações vasculares. O grupo amostral constituiu-se de 150 pacientes crônicos e grupo controle de 20 indivíduos saudáveis. Níveis séricos de HDL, VLDL e triglicérides mostraram-se diminuídos em relação ao grupo controle, enquanto os níveis de LDL e apolipoproteína B mostraram-se elevados. Observou-se correlação positiva entre a viremia e alterações de LDL e apolipoproteína B nos portadores do genótipo 1b. Assim, foi pressuposto que o risco de pacientes portadores do VHC desenvolverem complicações vasculares é elevado, uma vez que cerca de 90% da proteína na LDL constitui-se de apolipoproteína B, sua concentração plasmática indica o número de partículas aterogênicas. Portanto, o monitoramento do perfil lipídico pode auxiliar no diagnóstico da severidade da infecção hepática causada pelo VHC e atuar como bom sinal prognóstico.

Palavras-chave: Vírus da hepatite C. Genótipos. Viremia. Lipoproteínas.

CONFLICTS OF INTEREST

None declared. We authors did not maintain a relationship with any organization, neither accepted any funding or support that could influence this manuscript.

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