

STEATOSIS AND HEPATITIS C

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Steatosis is frequently found in patients with chronic hepatitis C with a prevalence that can range from 30% to 70%, being more frequent in patients with genotype 3⁽¹⁾. In those carrying this genotype, the presence of steatosis is associated to higher viral load and with reduction of serum cholesterol values. Characteristically, this steatosis tends to recede with viral eradication. These facts suggest that, in these cases, steatosis derives from direct cytopathologic action by the virus. It has been proposed that hepatitis C virus would be capable of inducing hypobetalipoproteinemia, promoting interference in the release of hepatic triglycerides into the blood stream in the form of VLDL^(1,2).

Conversely, in the other genotypes (non-3 genotypes), steatosis tends to persist after treatment and is associated with other factors more connected with the host such as alcoholism, hypothyroidism, and, in special, with insulin resistance⁽³⁾. These patients frequently have central obesity, hypertriglyceridemia and diabetes or glucose intolerance. These characteristics place such patients closer to patients with nonalcoholic fatty liver disease (NAFLD).

As part of an investigation of oxidative stress serum markers in HCV infection (Oliveira AC et al, submitted), 187 chronic hepatitis C carriers were divided according to their genotype [genotypes 1, 2, and 4 (n=131) and genotype-3 (n=56)], and presence or absence of steatosis in the liver biopsy. In these patients, BMI and the serum levels of liver enzymes, ferritin, glucose, insulin, triglycerides, total and HDL-cholesterol, were assessed, together with viral load, and degree of steatosis, inflammation and fibrosis in liver biopsy. The overall prevalence of steatosis in these patients was 60%, being 71% among patients carrying non-3 genotype HCV and 52% in those with genotype 3. The former patients with steatosis (n=71) showed significantly higher values of BMI, HOMA-IR, triglycerides, and ALT, when compared with those patients with no steatosis. Patients with genotype 3 and liver steatosis (n=40) showed significantly higher values of ALT and viral load, and lower total cholesterol levels, with no difference regarding the parameters related to insulin resistance or metabolic syndrome. Linear regression analysis found HOMA-IR (p=0.036) and triglycerides (p=0.035) were independent predictors for steatosis in non-3 genotype, and ALT

(p=0.006), BMI (p=0.036) and HCV-RNA load (p=0.041) for steatosis in genotype 3 infected patients. These findings confirm the diversity of the physiopathogenic mechanisms involved in the establishment of steatosis in chronic hepatitis C.

Several factors have been recognized to be associated with worsening of fibrosis in chronic C hepatitis. During these last few years, the presence of steatosis has also been associated with a faster progression of the disease, regardless of viral genotype^(4,5) and also it could also be associated to a lower response to interferon and ribavirin treatment, mainly in patients infected with non 3 genotype virus⁽¹⁾.

Steatosis has been related with disease progression in hepatitis C infected patients in several papers, but this find has been challenged in a recent analysis on the database of 892 to 699 patients participating in a hepatitis C long-term treatment against cirrhosis (HALT-C trial) with serial liver biopsies taken at the beginning of the trial, 1.5 and/or 3.5 years after randomization⁽⁶⁾. At enrollment most patients had HCV genotype 1 infection (94%), 39% had cirrhosis and 61% had bridging fibrosis on liver biopsy. A decreased in steatosis score of at least 1 point was observed in 30% of patients. Progression of the disease and improvement in metabolic parameters (HOMA, triglycerides concentration, BMI) and alcohol intake were associated with this finding. Such improvement in steatosis was seen with higher baseline BMI, waist circumference, triglycerides concentration and HOMA, higher inflammatory scores and the presence of Mallory bodies, confirming that improvement in metabolic parameters and alcohol intake ameliorate hepatic steatosis and inflammation score. On the other hand, the demonstration that decrease in steatosis was associated with worsening liver disease (cirrhosis, esophageal varices and deterioration in liver function) do not seems to reflect only increased fibrous tissue in the liver and reduction in the number of hepatocytes susceptible to become steatotic, since in these patients a clear demonstration of increased portal pressure could be found in endoscopic and laboratory data. According to the authors these two pathways by which steatosis recedes appears to operate independently, but this has to be proven in additional researchs.

In the last few years, IR that has recognized as one of the main factors leading to therapeutic failure in patients treated with pegylated interferon and ribavirin. A sustained virological response in genotype 1 infected patients with a homeostasis model index (HOMA-IR) higher than 4 was only one third of the response obtained in patients with HOMA-IR \leq 2 after antiviral treatment⁽⁷⁾.

IR has also been independently associated to liver fibrosis

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progression. Several published papers have found that in genotypes 1 and 4 there is a significant association between fibrosis and IR regardless of the presence of steatosis⁽⁸⁾ and, more surprisingly, Bugianesi *et al.*⁽⁹⁾ also found that even in patients with genotype 3 infection the progression of the disease was associated with the presence of IR and not with steatosis.

By analogy with nonalcoholic fatty liver disease (NAFLD) where oxidative stress is related to the progression of the fatty liver to NASH, in non-3 genotype HC carriers, where steatosis and IR are important features of the disease, oxidative stress could be associated with liver fibrosis progression, through the release of cytokines or through lipid peroxidation byproducts (such as malondialdehyde), capable of activating stellate cells.

Increase in oxidative stress serum markers in non-3 genotype chronic hepatitis has been associated with both insulin resistance⁽¹⁰⁾ and with steatosis⁽⁴⁾.

More extensive and longitudinal studies are needed in order to help us gaining better understanding on the correlations observed between IR, steatosis, oxidative stress and chronic hepatitis C progression.

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