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# Hepatitis C virus infection and liver steatosis

Fernando Ramalho

*Liver Unit, Medical School of Lisbon, Av. Grão Vasco, 34-6° D, 1500-338 Lisboa, Portugal*

**Abstract**

The mechanism by which the hepatitis C virus (HCV) causes chronic, progressive liver damage is unknown. Factors other than the virus itself have been implicated. The role of liver steatosis has been recently studied. Hepatic steatosis is a common histological finding occurring in more 50% of patients with chronic hepatitis C. Both host and viral factors have been demonstrated to play an important role in its development. In those patients infected with genotype 1, steatosis appears to be due to the co-existence of Non-Alchoholic SteatoHepatitis (NASH) with HCV and associated with an increased body mass index (BMI). Some recent observations suggest that steatosis may be of viral origin and related to genotype 3. This fact raises the possibility of a direct effect of specific viral sequences on the pathogenesis of lipid accumulation. Furthermore, hepatic steatosis attributed to genotype 3 correlates directly with serum and intrahepatic titters of HCV RNA. The resolution of steatosis after successful antiviral therapy as well as steatosis being a sign of recurrent HCV infection in patients with genotype 3 add convincing evidence that steatosis is viral related. The pathogenic mechanism induced by genotype 3 is speculative. A correlation between steatosis, intrahepatic HCV RNA and core protein expression suggest a direct effect. Further support is provided by the finding that HCV core protein induces steatosis in transgenic mice. Another possibility relates to interaction with hepatic triglyceride turnover. In conclusion, for patients infected with genotype 1, BMI has a role in the pathogenesis of steatosis while in those infected with genotype 3, steatosis may be due to a virus-specific cytopathic effect. Regardless of etiology, the contribution of both to liver fibrosis progression seems accepted.


*Keywords:* Steatosis; HCV infection; Genotype 1; Genotype 3; BMI; Liver fibrosis

The mechanisms by which hepatitis C virus (HCV) causes chronic and progressive liver disease are not well known. Only about 30% of patients infected with HCV for 20–30 years will progress to cirrhosis (Niederau et al., 1998), suggesting that factors other than the virus accelerate the hepatotoxicity and fibrogenic capacity of the HCV. Age at infection (Ramalho et al., 2000), gender (Poynard et al., 1997), hepatic iron content (Haque et al., 1996), and HCV genotype (Silini et al., 1995; Mangia et al., 1997) are all implicated as co-factors in the development of cirrhosis. The lack of correlation between intrahepatic HCV RNA level and microinflammation in chronic hepatitis C suggests that the HCV—associated liver damage is mostly immunomediated (Negro et al., 1999). Another contributing factor is alcohol intake (Ostapowicz et al., 1998). The contribution of steatosis to hepatitic fibrosis has only recently been studied.

Hepatic steatosis is a common histopathologic feature demonstrable in patients with chronic hepatitis C (Goodman and Ishak, 1995; Fischer et al., 1996). The main causes of liver steatosis may be related to concomitant infections, obesity, drugs, dyslipemia, alcohol, diabetes type 2 and even Non-Alcoholic SteatoHepatitis (NASH). However, when these causes are carefully excluded, a significant number of patients with chronic hepatitis C still have fatty liver suggesting a virus-specific cytopathic effect.

Previous work has elucidated some aspects of the relationship between HCV and steatosis. HCV infected patients with steatosis are more likely to have risk factors for NASH, particularly higher body mass index (BMI) and elevated cholesterol (Czaja et al., 1998). In many patients, particularly those infected with viral genotype 1, steatosis appears to be due to the co-existence of NASH with HCV infection. In these patients, the steatosis is associated with both subsinusoidal fibrosis and increased BMI (Clouston et al., 2001). Hourigan et al. (1999) showed a relationship between BMI, steatosis and fibrosis in 148 patients, suggesting a role of steatosis in the progression of hepatitis C. This association may have important prognostic and therapeutic implications.

Several lines of evidence indicate that the association between HCV and steatosis is not spurious. The association with the genotype 3 (Mihm et al., 1997) was subsequently confirmed (Rubbia-Brandt et al., 2000). Subsequently, Adinolfi et al. (2001) showed a significant association

*E-mail address:* f-ramalho@netcabo.pt (F. Ramalho).

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between steatosis and BMI in genotype 1 and with the level of HCV RNA in genotype 3 in 221 patients. The data obtained from patients with known duration of infection confirm that steatosis grade 3-4 was associated with higher rate of fibrosis progression.

The prevalence of steatosis among HCV genotypes varies significantly. Our results (Serejo et al., 2001) from 106 consecutive patients with chronic HCV, in which obesity, alcohol intake, dyslipemia, and diabetes were excluded, compared those with and without steatosis has demonstrated a significantly higher prevalence of steatosis with genotypes 3 and 2 infection as compared to genotype 1 (80.1% and 88.9% versus 37%; $P = 0.0001$). In addition, the results of Rubbia-Brandt et al. (2000) in type 3 infection demonstrate that the degree of liver steatosis correlates with the levels of intrahepatic HCV replication.

On the whole, the data suggest that steatosis in patients with genotype 3, and perhaps in those with type 2a/c, is in part related to HCV. The data published by Kumar et al. (2002) add convincing evidence that in genotype 3, steatosis is virus related. In 52 chronically infected patients, those with HCV genotype 1 infection, there was no change in hepatitic steatosis after treatment irrespective of outcome. In contrast, genotype 3 infected patients who achieved a sustained virological response (SVR) had significantly reduced steatosis. Those patients who failed to achieve a SVR had no change in steatosis.

The question raised by this study, then, is: what is the pathogenic mechanism of steatosis induced by genotype 3? A correlation between extent of steatosis (grade) and intrahepatic HCV RNA levels as well as intrahepatic core protein expression in genotype 3 chronic hepatitis C suggests a direct viral effect (Fujie et al., 1999; Rubbia-Brandt et al., 2000). Moreover, genotype 3 core protein expression has been shown in vitro to be associated with lipid droplets (Abid et al., 2002). Similarly, HCV core protein expression can induce steatosis in transgenic mouse model (Moriya et al., 1997).

The observation that patients chronically infected with HCV have decreased levels of β lipoproteins (Serfaty et al., 2001) suggests an interference with the assembly of very low-density lipoprotein (VLDL). An interference with the VLDL assembly is also consistent with the observation that HCV core protein reduces the activity of the Microsomal Triglycerides Transfer Protein and modifies hepatic VLDL secretion with subsequent steatosis. Steatosis can be associated with hepatic inflammatory changes and fibrosis. A number of studies have now demonstrated a significant relationship between hepatic fibrosis and steatosis in chronic hepatitis C (Czaja et al., 1998; Adinolfi et al., 2001; Ong et al., 2001).

Otherwise our study (Emerit et al., 2000), as others (DeMaria et al., 1996), has shown the occurrence of oxidation stress and lipid peroxidation in chronic hepatitis C patients. Lipid peroxidation is associated to stellate-cell activation and synthesis of collagen type I (Lee et al., 1995) and we formulate the hypothesis that in chronic HCV infection, steatosis is an important cofactor in accelerating the development of liver fibrosis and that both host (visceral obesity) and viral factors (genotype 3 and/or genotype 2) play a role in the pathogenesis of steatosis in chronic hepatitis C.

In conclusion, steatosis of the liver is a frequent occurrence in chronic HCV infection and the pathogenesis may be metabolic or even directly HCV related. Whatever the etiology its contribution to liver disease progression seems accepted.

## References


Abid, K., Rossi, C., Latorre, P., Rubbia-Brandt, L., Hhadengue, A., Negro, F., 2002. The core protein of HCV genotype 3a, 3b and 1b induces lipid accumulation in Huh 7 cells. In: Proceedings of the 9th International Meeting on HCV and Related Viruses, San Diego, July 7–11.

Adinolfi, L., Gambardella, M., Andreana, A.A.A., Tripodi, M., Utili, R., Ruggiero, G., 2001. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotypes and visceral obesity. Hepatology 33, 1558–1564.

Clouston, A.D., Jonssom, J.R., Purdie, D.M., Macdonald, G.A., Pandeya, N., Shorthouse, C., Powell, E.E., 2001. Steatosis and chronic hepatitis C: analysis of fibrosis and stellate cell activation. J. Hepatol. 34, 314–320.

Czaja, A.J., Carpenter, H.A., Santrach, P.J., Moore, S.R., 1998. Host and disease specific factors affecting steatosis in chronic hepatitis C. J. Hepatol. 29, 198–206.

DeMaria, N., Calantroni, A., Faginoli, S., Guang-Jun, L., Rogers, B.K., Farinati, F., Van Thiel, D.H., Floyd, R.A., 1996. Association between reactive oxygen species and disease activity in chronic hepatitis C. Free Radic. Biol. Med. 21, 291–295.

Emerit, I., Serejo, F., Filipe, P., Alaoui Youseefi, A., Fernandez, A., Costa, A., Freitas, J., Ramalho, F., Bapista, A., Carneiro de Mura, A., 2000. Clastogenic factors as biomarkers of oxidative stress in chronic hepatitis C. Digestion 62, 200–207.

Fischer, H.P., Willsch, E., Bierhoff, E., Pfeifer, U., 1996. Histopathologic finding in chronic hepatitis C. J. Hepatol. 24, 35–42.

Fujie, H., Yotsuyanagi, H., Murya, K., Shintani, Y., Tsutsumi, T., Takayama, T., Makuuchi, M., Matsura, Y., Miyamura, T., Kimura, S., Koike, K., 1999. Steatosis and intrahepatic hepatitis C virus in chronic hepatitis. J. Med. Virol. 59, 141–145.

Goodman, Z.D., Ishak, K.J., 1995. Histopathology of hepatitis C virus infection. Semin. Liver Dis. 15, 70–81.

Haque, S., Chranda, B., Gerber, M., Lok, A., 1996. Iron overload in patients with chronic hepatitis C: a clinicopathological study. Hum. Pathol. 27, 1377–1381.

Hourigan, L.F., MacDonald, G.A., Purdie, D.M., Whitehall, V.H., Shorthouse, C., Clouston, A.D., Powell, E.E., 1999. Ffibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. Hepatology 29, 1215–1219.

Kumar, D., Farrel, G., Fung, C., George, G., 2002. Hepatitis C virus genotype 3 is citophatic to hepatocytes: reversal of hepatic steatosis after sustained therapeutic response. Hepatology 36, 1266–1272.

Lee, K.S., Buck, M., Houglum, K., Chojkier, M., 1995. Activation of hepatic stellate cells by TGF alpha and collagen type I mediated by oxidative stress trough c-myc expression. J. Clin. Invest. 96, 2461–2468.

Mangia, A., Cascavilla, I., Lezzi, G., Spirito, F., Maertens, G., Parlatore, L., Saracco, G., Rizzetto, N., Andriulli, A., 1997. HCV genotypes in patients with liver disease of different stages and severity. J. Hepatol. 26, 1173–1178.

Mihm, S., Fayyazi, A., Hartman, H., Ramadori, G., 1997. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. Hepatology 25, 735–739.

Moriya, K., Yotsuyanagi, H., Shintam, H., Fujie, H., Ishibasha, K., Matsuura, Y., Miyamura, T., Koike, K., 1997. Hepatitis C virus core protein induces steatosis in transgenic mice. J. Gen. Virol. 78, 1527–1531.

Negro, F., Krawczynski, K., Quadri, R., Rubbia-Brandt, L., Mondelli, M., Zarski, J.P., Hadengue, A., 1999. Detection of genomic and minus-strand of hepatitis C virus RNA in the liver of chronic hepatitis C patients by strand-specific semi-quantitative RT-PCR. Hepatology 29, 536–542.

Niederau, C., Lange, S., Heintges, T., Erhadt, A., Buschlamp, M., Hurter, D., Nawrocki, M., Kruska, L., Hensel, F., Petry, W., Haussinger, D., 1998. Progression of chronic hepatitis C: results of a large prospective cohort study. Hepatology 28, 1687–1695.

Ong, J.P., Younossi, Z.M., Speer, C., Olano, A., Gralmich, T., Bopara, N., 2001. Chronic hepatitis C and superimposed non alcoholic fatty liver disease. Liver 21, 266–271.

Ostapowicz, G., Watson, K.J.R., Locarnini, S.A., Desmond, P.V., 1998. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. Hepatology 27, 1730–1735.

Poynard, T., Bedossi, P., Opson, P., 1997. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 349, 825–832.

Ramalho, F., Costa, A., Pires, A., Cabrila, P., Serejo, F., Correia, A.P., Fatela, N., Cloria, H., Lopes, J., Pinto, H.C., Marinho, R., Raimundo, M., Velosa, J., Batista, A., De Moura, M.C., 2000. Correlation of genotypes and route of transmission with histological activity and disease stage in chronic hepatitis C. Dig. Dis. Sci. 45, 182–187.

Rubbia-Brandt, L., Quadri, R., Abid, K., Giostra, E., Male, P.J., Mentha, G., Spahr, L., Zarski, J.P., Borisch, B., Hadengue, A., Negro, F., 2000. Hepatocyte steatosis is a cytopatic effect of hepatitis C virus genotype 3. J. Hepatol. 33, 106–115.

Serejo, F., Costa, A., Ramalho, F., et al., 2001. Liver steatosis and HCV infection. Liver fibrosis. In: Proceedings of Cell Biology to Clinical Targets, Florence, Italy.

Serfaty, L., Andreani, T., Giral, P., Ccarbonnel, N., Chazovillieres, O., Poupon, R., 2001. Hepatic virus induced hypobetaliproteinemia:: a possible mechanism for steatosis in chronic hepatitis C. J. Hepatol. 34, 428–431.

Silini, E., Bono, F., Cividini, A., Cerino, A., Bruno, S., Rossi, S., Belloni, G., Brugnetti, R., Civardi, E., Salvaneschi, L., Mondelli, M.U., 1995. Differential distribution of hepatitis C genotypes in patients with and without liver function abnormalities. Hepatology 2, 285–290.