Steatosis in Hepatitis C Virus Infection. Response to Anti-Viral Therapy

Paula Szanto[1], Mircea Grigorescu[1], Iuliana Dumitra[2], Alexandru Serban[2]

1)3rd Medical Clinic, University of Medicine and Pharmacy. 2) Department of Morphopathology, 3rd Medical Clinic, Cluj-Napoca

Abstract

Background. Steatosis is a frequent feature of hepatitis-C-virus (HCV) infection. Steatosis may be an important cofactor in both accelerating fibrosis and increasing liver necroinflammatory activity in chronic hepatitis C. Several studies suggested that steatosis induces resistance to interferon and ribavirin combination treatment. **Aim:** to assess the prevalence of steatosis in chronic HCV-infection and the host factors associated with steatosis, to estimate the impact of steatosis on liver fibrosis, and to evaluate the response to antiviral therapy in patients with HCV-infection and steatosis. **Material and Method.** A retrospective study was performed on 37 patients with chronic active HCV-infection treated with interferon and ribavirin: 21 women and 16 men, mean age 46.97 years. Presence of metabolic syndrome was assessed according to the ATPIII criteria. Cobas Amplicor HCV-Test was used to detect HCV-RNA. Steatosis was graded using the Brunt system. **Results.** Prior to the antiviral treatment, steatosis was present in 26 out of 37 patients (70%). Patients with steatosis were older, especially those with associated metabolic syndrome. Fibrosis stage was significantly advanced in patients with steatosis. Lower baseline viremia correlated with sustained response both in patients with and without steatosis. Absence of baseline steatosis was associated with higher biochemical and virological sustained response. None of the patients with metabolic syndrome had a sustained response to antiviral therapy. In all patients, the stage of fibrosis did not significantly improve 6 months after cessation of the antiviral treatment. **Conclusion.** Steatosis is a frequently encountered histological feature in chronic HCV-infection. It is associated with older age, lower virologic response and worsening fibrosis irrespective of antiviral treatment.

J Gastrointestin Liver Dis
June 2006 Vol.15 No.2, 117-124
Address for correspondence: Paula Szanto, MD
3rd Medical Clinic
Croitorilor str. 19-21
Cluj-Napoca, Romania

Key words

Chronic hepatitis C- steatosis –advanced age- fibrosis - treatment

Rezumat

Premize. Steatoza reprezintă o constatare frecventă în infecția cu virus hepatitic C(VHC). Steatoza poate fi un important cofactor atât în accelerarea fibrozei cât şi în creşterea activității necroinflamatorii în hepatita cronică viralăC. Diverse studii sugerează faptul că steatoza induce rezistanță la tratamentul antiviral combinat. **Scop:** de a evalua prevalența steatozei în infecția cronică-VHC, să estimeze factorii legați de gazdă care se asociază steatozei, precum şi impactul pe care steatoza îl are asupra evoluției fibrozei şi a răspunsului la terapia antivirală, la pacienții cu infecție-VHC şi steatoză. **Material şi Metodă.** S-a efectuat un studiu retrospectiv pe 37 de bolnavi cu infecție cronică activă-VHC, tratați cu IFN şi ribavirină: 21 femei şi 16 bărbați, cu vârsta medie 46,97 ani. Prezența sindromului metabolic a fost evaluată conform criteriilor ATPIII. Pentru detectarea viremiei s-a utilizat testul Cobas-Amplicor. Steatoza a fost evaluată utilizând clasificarea Brunt. **Rezultate.** Inainte de începerea tratamentului, steatoza a fost prezentă la 26 din 37 pacienți (70%). Pacienții cu steatoză au fost mai vârstnici, în special cei cu sindrom metabolic asociat . Corelația cu stadiul fibrozei a fost semnificativ mai mare la bolnavii cu steatoză .Pacienții fără steatoză au avut un răspuns biochimic şi virusologic susținut semnificativ mai mare.Niciunul dintre bolnavii cu sindrom metabolic asociat steatozei nu a avut răspuns susținut la tratamentul antiviral. La niciunul dintre bolnavi, fibroza nu a fost semnificativ influențată de tratament. **Concluzie**. Steatoza reprezintă o constatare histologică frecventă în infecția cronică-VHC. Steatoza s-a asociat cu vârsta mai avansată, răspunsul virusologic scăzut la tratament, fibroza progresivă, ce nu a fost influențată de tratamentul antiviral.

Introduction

Acute infection with hepatitis C virus is followed by chronic infection in 50 to 80% of infected individuals (1, 2).

Chronic infection is associated with multiple clinical conditions, ranging from steatosis, acute and chronic hepatitis, slowly progressive hepatic fibrosis, cirrhosis to hepatocellular carcinoma (HCC), or extrahepatic diseases (3).

It has been estimated that 2.2% of the world's population (approximately 130 million individuals) are infected with hepatitis C virus (4). The majority have been infected via parenteral exposure with contaminated injections, either related to intravenous drug use or contaminated injections or transfusion with blood products.

The importance of steatosis in the diagnosis of hepatitis C virus (HCV) infection has been established. Liver steatosis is found with an overall prevalence of 50%, varying between 35 to 80% in chronic hepatitis C (5- 8). Among patients with HCV genotype 1 infection, the grade of steatosis was correlated with host-related factors, mainly with the presence of the metabolic syndrome (MS) - metabolic steatosis (9). In fact, body mass index (BMI) and visceral obesity play a major role in the development of HCV-associated steatosis. However, approximately 40% of patients with steatosis lack conventional risk factors such as obesity, diabetes mellitus, alcohol abuse and drugs (3). The mechanisms by which HCV causes liver damage are poorly understood. Specific HCV sequences may be implicated in the pathogenesis of steatosis. It has been suggested that at least genotype 3 infection is directly responsible for steatosis through a cytopathic effect (3, 10, 11). The grade and the extent of steatosis are significantly associated with genotype 3 infection (6).

The severity of fat accumulation correlates with activation of hepatic stellate cells, thus steatosis *per se* may activate fibrogenesis. Most published papers report a significant relationship between the grade of steatosis and fibrosis within the context of HCV infection (3, 8, 9).

Since the combination of interferon (IFN) and ribavirin has been introduced, the treatment of chronic hepatitis C has significantly improved. However, lack of response to the current therapies remains common, especially among patients with genotype 1 infection (12). Several factors have been shown to influence response: these include viral factors (particularly genotype) and host factors: HLA type, cytokine polymorphism, sex, age, presence of cirrhosis and race (13). The degree of hepatic steatosis may be an important cofactor in both accelerating fibrosis and increasing liver necroinflammatory activity in chronic hepatitis C (14). In genotype 3 HCV infection, steatosis disappeared with the clearance of the virus after successful antiviral treatment. In other HCV genotypes there are arguments that steatosis worsens the response to IFN therapy (3, 8).

The aim of this study was to assess the prevalence of steatosis in chronic HCV infection and the host factors associated with steatosis, to estimate the impact of steatosis on liver fibrosis, and to evaluate the response to antiviral therapy in patients with chronic HCV infection and steatosis.

Patients and methods

A retrospective study of 37 patients with chronic hepatitis C, given antiviral therapy between 2003 and 2005, was conducted. Inclusion criteria for treatment were as follows: persistently elevated alanine aminotransferase (ALT) levels (>1.5 times upper normal limit), a liver biopsy consistent with chronic hepatitis, a hemoglobin level greater than 12 g/dL in female patients or greater than 13 g/dL in male patients, a white blood cell count greater than 3,000/mm3, a neutrophil count greater 1,500/mm3, and serum bilirubin, albumin, and creatinine levels all within normal limits. Patients also needed to have HCV-RNA detectable in the serum by polymerase chain reaction (PCR). Exclusion criteria for treatment were: age more than 65, decompensated liver disease, persistently normal ALT levels, autoimmune disorders, ingestion of more than 20 g/day of alcohol within the previous 6 months, history of uncontrolled depression or psychosis, uncontrolled cardiac disease, women who were pregnant in the following year, or any other debilitating medical condition.

Patients were treated with a combination of standard IFN α-2a or α-2b 3MU 3 times weekly and ribavirin 1,000-1,200 mg daily, or with pegylated IFN-α2a 180 μg weekly respectively IFN-α2b 100-120 μg weekly and ribavirin 1,000-1,000 mg daily. Only those individuals who completed 12 weeks or more of treatment and 80% of the intended doses of antiviral therapy were included in the study.

Presence of MS was assessed according to the ATP III criteria (two or more of the following: abdominal obesity and BMI > 28 kg/m^2, hypertriglyceridemia > 150 mg/dL, low HDL level, diabetes mellitus/insulin resistance, hypertension) (9).

A baseline biopsy was performed in all patients, and a second one at six months after cessation of therapy in 55% of cases. Liver biopsy specimens were processed using standard techniques with hematoxylin-eosin-stained sections for necroinflammatory grading and Masson trichrome-stained sections for assessment of fibrosis. The presence of hepatocytes containing large-droplet fat was evaluated. Steatosis was scored using the Brunt grading system (15) in which steatosis is graded 0 to 3 based on percentage of hepatocytes involved (grade 0-none involved; grade 1<33%; grade 2≥33-66%; grade 3>66%). Necroinflammatory activity was assessed by means of Knodell hepatitis activity index (16) and was ≥ 6 for each patient. For assessment of fibrosis, the METAVIR system was used (17). Fibrosis was scored in 4 grades: F0 no definite fibrosis; F1 minimal fibrosis (portal fibrosis without septa), F2 mild fibrosis (occasional septa), F3 moderate fibrosis (moderate septa without cirrhosis), F4 cirrhosis.

HCV genotyping was not performed in our patients, but a recent multicenter study in Romania revealed that 95.54% of the HCV infected population has HCV genotype 1 infection (18). Cobas Amplicor HCV Test was used to detect HCV RNA, and a sustained response was defined as either undetectable HCV RNA (< 500 IU/mL) and/or normal ALT

levels (only in those treated before availability of HCV RNA testing) at the end of treatment, and at the end of 6 months of follow-up following the cessation of antiviral therapy. Non-responders were considered those patients with detectable HCV RNA at 3 months of therapy, and incomplete responders those with detectable HCV RNA at the end of 48 weeks of combined therapy.

Statistical analysis

Descriptive statistical analysis was used, and distributions of categorical variables were compared using chi square or Fisher tests. Continuous data were expressed as means, medians and standard deviation (SD). Comparisons between qualitative and quantitative variables were performed using the Student *t*-test and Anova test. Mann Whitney U test was used to compare differences in variables such as fibrosis stage and steatosis grade. A value of $p < 0.05$ was considered as statistically significant.

Results

A total of 37 patients with a baseline biopsy and treated with combined antiviral therapy were included in our study. There were 21 women and 16 men (Table I). The mean age of patients was 46.97 years (ranges 29-64 years).

Table I Characteristics of the patients

Characteristics	
No. of patients	37
Males/females	16/21
Mean age (limits) years	46.97 (29-64)
Patients without steatosis (M/F)	11 (6/5)
Patients with steatosis (M/F)	26 (10/16)
Patients with metabolic syndrome (M/F)	9 (4/5)
-obesity + HTG (M/F)	-4 (2/2)
-obesity + DM (M/F)	-3 (1/2)
-DM + HTG (M/F)	-2 (1/1)
Median fibrosis stage	3 (25% = 0; 75% =3)
Median steatosis grade	1 (25% = 0; 75% =1)
Patients with sustained response	15 (40.54%)
Patients with incomplete response+ non response	22 (59.45%)

M/F- male/female; HTG-hypertriglyceridemia; DM- diabetes mellitus type 2

Steatosis and associated factors. Prior to antiviral treatment, steatosis was present on liver biopsy specimens in 26 patients (70%), more often but not significantly in women. Metabolic syndrome (BMI> 28 kg/m^2 or abdominal obesity, diabetes mellitus ± hypertriglyceridemia) was present in 9 patients (24.32%), all with histological signs of steatosis. Among the patients with histological signs of steatosis, those with type 2 diabetes mellitus, obesity and/or hypertriglyceridemia were approximately one third (34.6%).

Patients with steatosis, especially those having MS were significantly older than those without steatosis (Table II).

Grade of steatosis was 1 or 2 in most patients according to Brunt grading system (Table III). There were no significant differences concerning the grade of steatosis between patients with isolated steatosis and those with associated MS, but the mean value was greater in those without metabolic syndrome. Histological pattern of steatosis was mixed (micro-macro vesicular) in 17 patients, microvesicular in 7 patients and macrovesicular in 2 patients. Mallory's bodies were not seen in histological samples without steatosis nor in those with steatosis and MS.

Table II Mean age of the patients

Patients	No	Mean age ± SD (yrs)	p
Without steatosis	11	40.27 ± 7.66	
Steatosis without MS	17	47.88 ± 8.51	<.02
Steatosis and MS	9	53.22 ± 6.85	<.0003

SD-standard deviation; MS-metabolic syndrome

Table III Distribution of grade of steatosis (Brunt grading system) in patients with and without metabolic syndrome

Patients (no)	Steatosis grade 1	2	3	Mean value ± SD
Without MS (17)	10	6	1	1.47 ± 0.62
With MS (9)	6	3	0	1.22 ± 0.44
Total (26)	16	9	1	1.38 ± 0.57

p value NS (<.3); MS-metabolic syndrome

Because none of the patients without steatosis had MS, it results in the fact that patients with MS had the highest grade of steatosis in the whole studied group (Table IV).

Table IV Distribution of steatosis and metabolic syndrome in studied group (Chi square test: $p > 0.041$)

		Steatosis Present	Absent
Metabolic syndrome	Present	9(34.6%)	0(0%)
	Absent	17(65.3%)	0(0%)

Baseline steatosis and fibrosis. Patients with baseline steatosis in comparison with patients without steatosis were with significantly extended fibrosis irrespective of the presence or absence of MS. There was a significant correlation ($p < .05$) between the presence of steatosis and advanced fibrosis stage (Fig 1). None of the studied patients had fibrosis stage F2.

Steatosis and histological response to treatment. The necroinflammatory activity was significantly reduced ($p < .002$) at the end of the antiviral therapy in the whole group (Fig.2). This improvement ($p = .0167$) was observed also in patients with steatosis (Fig. 3). Patients with baseline steatosis had a higher necroinflammatory index (median 8.66 vs. 7.80) but not statistically significant ($p=.5$).

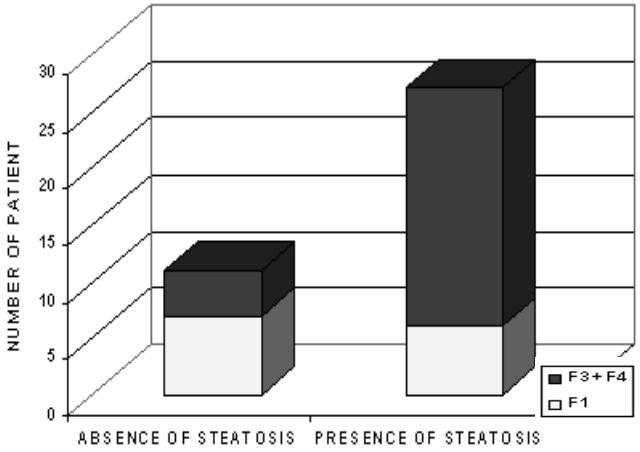

Fig.1 Baseline fibrosis stage and steatosis in our patients. F 1, F 3, F 4- fibrosis stage; p< .05.

Steatosis and histological response to treatment. The necroinflammatory activity was significantly reduced (p< .002) at the end of the antiviral therapy in the whole group (Fig.2). This improvement (p= .0167) was observed also in patients with steatosis (Fig. 3). Patients with baseline steatosis had a higher necroinflammatory index (median 8.66 vs. 7.80) but not statistically significant (p=.5).

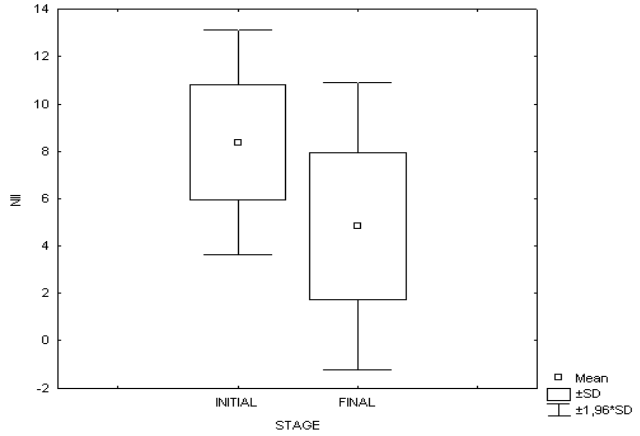

Fig.2 Effect of antiviral therapy on necroinflammatory activity in the entire group with chronic HCV infection. NII – necroinflammatory index; p < .002.

Fibrosis score was not significantly influenced by treatment. In patients with steatosis, fibrosis had a worsening evolution (p< .04) irrespective of the antiviral treatment (Fig. 4).

Baseline steatosis was improved but not significantly reduced by antiviral therapy (p=.13) neither in isolated steatosis nor in steatosis associated with MS.

The disappearance of steatosis was observed in three of four patients with baseline steatosis, sustained response and post-treatment biopsy.

Steatosis and virological response to treatment. Sustained virological response (SR) in all the studied group was 40.54%. The median baseline serum HCV RNA level was significantly higher (1.5 million IU/mL, p< .01) in nonresponders or incomplete responders vs. sustained responders (0.6 million IU/mL) (Fig 5). Patients with steatosis

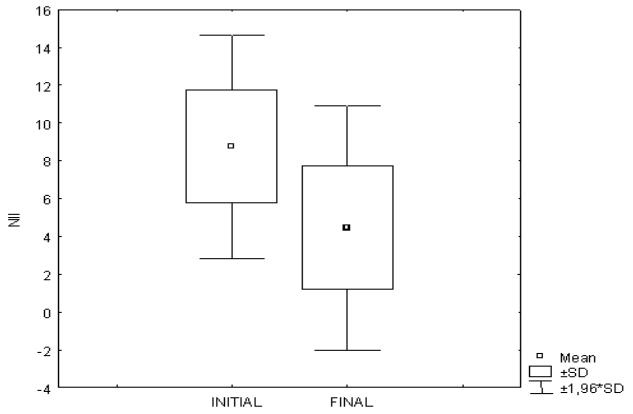

Fig.3 Effect of antiviral therapy on necroinflammatory activity in patients with steatosis. NII- necroinflammatory index; p= .0167.

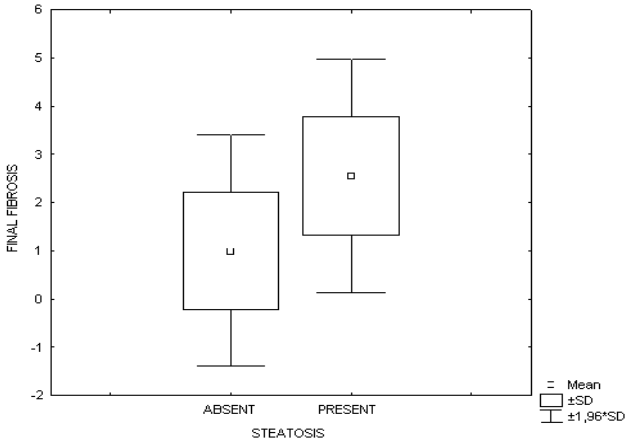

Fig.4 Fibrosis stage after antiviral treatment in patients without or with steatosis. p= .042.

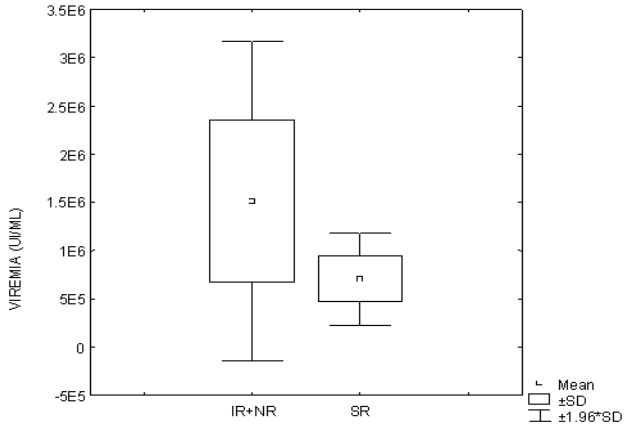

Fig.5 Correlation between baseline viremia and response to antiviral therapy. IR- incomplete response; NR- nonresponder; SR- sustained response;p<.01.

and persistent viremia after cessation of antiviral therapy had a higher mean baseline viremia (1.8 million IU/mL) than those without steatosis.

Correction for age was performed when examining the influence of steatosis and MS on response to therapy.

Among the patients without steatosis, sustained response was 63% vs. those with steatosis without MS

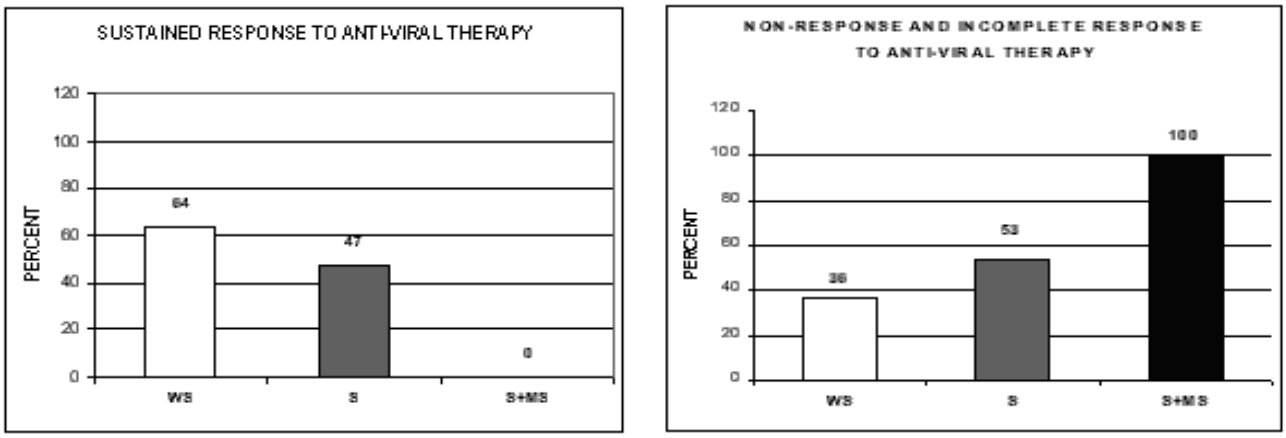

Fig.6 Response to antiviral therapy in patients with and without steatosis and metabolic syndrome. WS- without steatosis; S-steatosis; MS-metabolic syndrome; p<.01.

(47%). Moreover, considering that none of the patients with MS and high BMI had sustained response the difference between the groups with and without steatosis was greater (only 30.76% sustained response in group of all patients with steatosis, p< .01). Absence of baseline steatosis was associated with higher sustained response. The worst group in terms of virologic response was that of patients with steatosis and MS (Fig 6).

Discussion

Hepatitis C virus infection produces acute and chronic hepatitis, cirrhosis and, eventually, hepatocellular carcinoma. Both immune-mediated mechanisms and direct viral cytotoxicity contribute to the pathologic changes associated with hepatitis C. Steatosis is a frequently occurring feature of HCV infection, more so than in hepatitis B virus infection (19). After exclusion of alcohol and drugs, data of various studies found a large prevalence of steatosis, ranging between 35 and and 80% (3, 5, 6, 8, 20).

In our study, the prevalence of steatosis among patients with chronic active hepatitis C was 70%. This data confirms the high prevalence of steatosis in chronic HCV infection, especially in active forms of chronic disease because all our patients had intense necroinflammatory activity which imposed antiviral therapy. Alcoholic or drug induced steatosis were excluded at the start of treatment, suggesting that the high prevalence of steatosis may be of viral or host related origin.

Because our patients were a selected group, with active forms of HCV infection, the proportion of women was greater (57%). Steatosis respected this proportion, without significant sex differences. Other studies (8) reported a greater prevalence of steatosis in males, but associated with genotype 3 HCV infection which is extremely rare in our country.

Steatosis in HCV infection may be of viral origin mainly in genotype 3 infection, and associated with host related factors, especially obesity, type 2 diabetes mellitus and other metabolic factors that belong to nonalcoholic fatty liver disease, namely in non-3 HCV genotypes (3, 13, 21). In our patients metabolic steatosis was present only in one third of patients with histologic signs of steatosis, suggesting that hepatitis C virus *per se* may be implicated in the pathogenesis of steatosis.

This is an interesting fact, because our patients were presumably almost all genotype 1. The mechanism by which HCV causes liver damage is poorly understood. There are evidences in support of the direct causative roles of both the structural and nonstructural proteins of HCV in oxidative stress, steatosis, and carcinogenesis (22-24). At least two HCV proteins,core and NS5A, have been credited with the ability to alter lipid metabolism in cell culture. These proteins bind to apolipoproteins A1 and A2, which are likely involved in triglyceride accumulation and storage in the liver cells. Both the core and NS5A proteins are localized on surface of lipid droplets. Overexpression of core protein further stimulates the formation of lipid droplets. Both structural and nonstructural proteins contribute to steatosis. There is no doubt that HCV proteins can cause hepatic steatosis in the absence of immune response (22, 24). In addition, core protein causes mitochondrial injury, leading to oxidative stress. Oxidative stress alters lipid metabolism, thus contributing to steatosis and apoptosis, the latter being a standard feature of viral hepatitis (23).

Another host factor related to hepatic steatosis in HCV infection is advanced age. Indeed, our study revealed that steatosis is significantly associated with advanced age, particularly in patients with MS.

In subjects with viral steatosis (as observed in genotype 3) greater degrees of steatosis (more than 50%) may occur directly as a result of HCV infection and do not necessarily indicate the presence of MS (3, 9). Patients in our study had only mild to moderate steatosis, but the grade of steatosis was greater in patients without signs of MS suggesting that virus related steatosis is more important than that observed in host related factors. The pattern of steatosis (micro-, macro-vesicular, or mixed) was not specific.

Hepatic steatosis has recently been identified as a risk factor for progression of hepatic fibrosis. In our patients,

there was an expected significant association between steatosis and fibrosis within the context of HCV infection. Paired-biopsy follow-up studies confirmed that the worsening of steatosis was the only independent factor associated with hepatic fibrosis progression (26). Steatosis is a definite cofactor of chronic hepatitis C which accelerates the progression to end-stage liver disease.

Presence of steatosis also correlated with necroinflammatory activity in nonalcoholic steatohepatitis as well as chronic hepatitis C (3). We found that necroinflammatory index was greater in patients with chronic active hepatitis C and steatosis (including those with MS) vs. patients without steatosis. These results suggest that steatosis correlates with intrahepatic viral replication. Our study revealed that baseline viral load was higher in patients with steatosis and confirmed the fact that HCV replication has a direct steatogenic effect.

Despite improvement in the efficacy of treatment with the recently introduced pegylated IFN-alpha-based regimens, more than 40% of chronic hepatitis C patients fail to achieve a sustained response (27). The probability of sustained virologic response is lower in patients with HCV genotype 1 than 2 or 3, high than low baseline serum HCV RNA levels, heavy than light baseline body weight, older than younger age, and/or with than without bridging fibrosis or cirrhosis (27, 28). The sustained virological response may prevent development of hepatocellular carcinoma and improve liver fibrosis, biochemical markers as well as in quality of life and fatigue (29).

In our study overall prevalence of sustained response was 40.5%. In patients without steatosis the sustained response was significantly higher (63% vs. 30.7%). Baseline serum HCV RNA levels was significantly lower in patients with sustained response, especially in those with baseline steatosis, and confirmed the fact that a high viral load lowers the response rate. Metabolic syndrome, especially high BMI, worsened significantly the response to antiviral treatment. None of our patients with steatosis and MS had sustained responses.

Steatosis is an important cofactor of disease which accelerates the progression to cirrhosis, hepatocellular carcinoma and lowers the response rate to antiviral treatment (3,4,8).Various reasons explain why steatosis worsens the response to IFN. It has been hypothesized that the two intertwined factors obesity and steatosis act independently on viral clearance. Recent data indicates that both fat within hepatocytes and BMI, better still, visceral obesity appear to influence treatment response (3,8,13). At least for genotype 3 infection, a strong argument in favour of a direct effect of HCV in the development of steatosis, is disappearance or reduction of steatosis associated with the clearance of the virus in sustained virologic responders (3, 8, 11). In our patients with sustained response, the small number of patients with non-metabolic steatosis who performed control biopsies confirming disappearance of steatosis does not permit a pertinent conclusion.The response of patients with genotype 3 to antiviral treatment indicates that it cannot be hepatic steatosis alone that decreases the antiviral response (30). In our study, steatosis was not significantly influenced in sustained responders, suggesting that other metabolic factors, gender, age, advanced fibrosis or non-3 genotype HCV, produced a less reversible steatosis.

As expected, our study showed an improvement in histological activity with a significant decrease in inflammatory activity, 6 months after the end of treatment, both in patients presenting or not presenting baseline steatosis. Prior studies showed histological improvement with a significant decrease in both inflammatory activity and fibrosis in sustained virological responders to IFN therapy alone or in combination with ribavirin (31,32).

We found not only a baseline grade of fibrosis significantly advanced in patients with steatosis, but also a significant worsening of fibrosis 6 months after the cessation of therapy, irrespective of antiviral treatment. The proportion of sustained responders among the group with steatosis was low, and we presumed that other associated factors, especially MS, influenced fibrosis progression.

Steatosis has synergistic interaction with even low alcohol consumption as a contributory factor in extensive liver fibrosis. Therefore, all factors susceptible to induce oxidative stress, including alcohol, should be avoided in patients with steatosis (14, 33, 34). An aggressive weight loss programme induced by a combination of dietary modification and exercise has been associated with a reduction in hepatic fat and a reduction in hepatic fibrosis in individuals with hepatitis C (35, 36). Metformin, an insulin sensitizer, protect hepatocytes against reactive oxygen species and must be considered in patients with hepatic steatosis and insulin resistance. Thiazolidinediones exert antioxidative effects by inducing antioxidant enzymes (3, 36). Silymarin improves hepatic steatosis and vitamin E is an antioxidant agent.

Although HCV clearance from serum and liver is the main therapeutic target in chronic hepatitis C, delay in progression of fibrosis may represent a secondary therapeutic target that could be particularly important in patients with advanced fibrosis who fail to achieve sustained virological response. Long term treatment with colchicine versus Peg-IFN is currently under evaluation in cirrhosis (37,38). Besides IFN α, ribavirin, interleukin-10 and IFN-gamma have also been suggested as potential antifibrotic agents in chronic hepatitis C (37,39).

In conclusion, the presence of steatosis dramatically affects the natural history of treated patients with chronic hepatitis C. In the context of HCV infection, steatosis is a distinct disease entity. The prevalence of steatosis in HCV active infection is very high, especially in older patients, and cannot be accounted by the host risk factors (especially MS) even in genotype 1 infection. The mechanisms for the development of steatosis seem to be both host and virus related. Hepatic steatosis is a high risk factor for reduced response to antiviral treatment and for evolution towards fibrosis.The low therapeutical response is associated with

metabolic steatosis. Obesity and fibrosis represent major therapeutic targets, in association with standard antiviral regimes.

References

1. Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatology 2000; 31: 1014-1018.
2. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. N Engl J Med 1999; 340: 1228-1233.
3. Lonardo a, Loria P, Adinolfi LE, Ruggiero G, Carulli N. Fat in HCV: does it matter? Monothematic Conference"Non-alcoholic steatohepatitis: from cell biology to clinical practice" EASL (ed), Estoril, 2004: 56-60.
4. Heathcote J, Main J. Treatment of hepatitis C. J Viral Hepat 2005; 12: 223-235.
5. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Host and disease-specific factors affecting steatosis in chronic hepatitis C. J Hepatol 1998; 29: 198-206.
6. Serfaty L, Andreani T, Giral P, Carbonell N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. J Hepatol 2001;34: 428-434.
7. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. Hepatology 2002; 36: 729-736.
8. Poynard T, Ratziu V, McHutchison J et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. Hepatology 2003; 38: 75-85.
9. Ramesh S, Sanyal AJ. Hepatitis C and non-alcoholic fatty liver disease. Sem Liver Dis 2004; 24: 399-413.
10. Rubia-Brandt L, Quadri R, Abid K et al. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype. J Hepatol 2000; 33: 106-115.
11. Kumar D, Farrell GC, Fung C, George J. Hepatitis C virus genotype 3 is cythopathic to hepatocytes. Reversal of hepatic steatosis after sustained therapeutic response. Hepatology 2002; 36: 1266-1272.
12. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004; 39: 1147-1171.
13. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for response to antiviral treatment in chronic hepatitis C. Hepatology 2003; 38: 639-644.
14. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001; 33: 1358-1364.
15. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999; 94: 2467-2474.
16. Knodell RG, Ishak KG, Black WC et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1: 431-435.
17. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology 1994; 20: 15-20.
18. Grigorescu M, Radu C, Pascu O et al. Etiological profile of chronic hepatitis and liver cirrhosis in Romania. A multicenter study. Rom J Gastroenterol 2001; 10: 199-204.
19. Goodman ZD, Ishak KG. Histopathology of hepatitis C virus infection. Semin Liver Dis 1995; 15: 70-81.
20. Rubbia–Brandt L, Leandro G, Spahr L et al. Liver steatosis in chronic hepatitis C: a morphological sign suggesting infection with HCV genotype 3. Histopathology 2001; 39: 119-124.
21. Hui JM, Kench J, Farrell GC et al. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. J Gastroenterol Hepatol 2002; 17: 873-881.
22. Okuda M, Li K, Beard MR et al. Mitochondrial injury, oxidative stress and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 2002; 122: 366-375.
23. Lerat H, Honda M, Beard MK et al. Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus. Gastroenterology 2002; 122: 352-365.
24. Lai MM. Hepatitis C virus proteins: direct link to hepatic oxidative stress, steatosis, carcinogenesis and more. Gastroenterology 2002; 122: 568-571.
25. Moriya K, Yotsuyanagi H, Shintani Y et al. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. J Gen Virol 1997; 78: 1527-1531.
26. Castera L, Hezode C, Roudot-Thoraval F et al. Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. Gut 2003; 52: 288-292.
27. Manns MP, McHutchison JG, Gordon SC et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-965.
28. Papatheodoridis GV, Cholongitas E. Chronic hepatitis C and no response to antiviral therapy: potential current and future therapeutic options. J Viral Hepat 2004; 11: 287-296.
29. Formann E, Steindl-Munda H, Hofer H et al. Long-term follow-up of chronic hepatitis C patients with sustained virological response to various forms of interferon-based antiviral therapy. Aliment Pharmacol Ther 2006; 23: 507-511.
30. Rubia-Brandt L, Giostra E, Mentha G, Quadri R, Negro F. Expression of liver steatosis in hepatitis C virus infection and pattern of response to alpha-interferon. J Hepatol 2001; 35: 307.
31. Reichard O, Glaumann H, Fryden A et al. Two year biochemical, virological, and histological follow-up in patients with chronic hepatitis C responding in a sustained fashion to interferon alfa-2b treatment. Hepatology 1995; 21: 918-922.
32. Marcellin P, Boyer N, Gervais A et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997; 127: 875-881.
33. Serfaty L, Poujol-Robert A, Carbonell N, Chazouilleres O, Poupon RE, Poupon R. Effect of the interaction between steatosis and alcohol intake on liver fibrosis progression in chronic hepatitis C. Am J Gastroenterol 2002; 97: 1807-1812.

34. Vanbiervliet G, Marine-Barjoan E, Gelsi E et al. Evaluation of liver fibrosis with APRI score in patients with chronic alcoholic liver disease. J Hepatol 2005; 42: 255A.
35. Hickman IJ, Clouston AD, MacDonald GA, Purdie DM, Prins JB, Ash S. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. Gut 2002; 51: 89-94.
36. Harano Y, Toyama T, Ito Y et al. Fenofibrate, peroxisome proliferator-activated receptor (PPAR) alpha ligand diminishes hepatic steatosis in fatty liver shionogi via antioxidant effect. Hepatology 2005; 42: 631A.
37. Di Bisceglie AM, McHutchison J, Rice CM. New therapeutic strategies for hepatitis C. Hepatology 2002; 35: 224-231.
38. Afdhal NH, Freilich B, Black M, Levine R, Brass C. The National COPILOT investigators. Comparison of the therapy with Peg-Intron 0.5 mcg/kg versus colchicine 0.6 mg bid in 250 patients with cirrhosis and HCV: interim data from COPILOT. Hepatology 2002; 36: 312A.
39. Pockros PJ. Development in the treatment of chronic hepatitis C. Expert Opin Investig Drugs 2002; 11: 515-528.