Factors associated with liver steatosis and fibrosis in chronic hepatitis C patients

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SUMMARY
Liver steatosis is a common finding in patients infected with hepatitis C virus (HCV). Host and viral factors have been associated with steatosis, but their relative contributions have not been clearly addressed. It has been suggested that steatosis plays a role in the progression of liver fibrosis.

Aims — To assess: a) factors associated with steatosis in patients infected with hepatitis C virus; b) their impact on liver fibrosis.

Patients and methods — Three hundred and fourteen untreated infected patients were included. Lifetime alcohol consumption was estimated. Liver fibrosis, inflammation and necrosis were assessed using the METAVIR score. Body mass index (BMI) was determined. The scoring system for steatosis was as follows: 0, no steatosis; 1, less than 10%; 2, 10% to 30%; 3, 30% to 70%; 4, more than 70% of hepatocytes affected.

Results — In univariate analysis, steatosis was associated with elevated BMI (P = 0.001), excessive alcohol intake (P = 0.005), genotype 3 (P < 0.001) and moderate to severe histological activity (P = 0.001). Multivariate analysis showed that steatosis correlated with two independent factors: genotype 3a (OR = 60.7; 95% CI: 7.6-483.4) (P < 0.001) and BMI (OR = 4.86; 95% CI: 1.8-13.13) (P = 0.002).

Conclusions — In patients with chronic hepatitis C, steatosis is significantly associated with genotype 3 infection and high BMI. Steatosis is an independent risk factor associated with severe fibrosis. These results have major implications for the management of patients with chronic hepatitis C.

The full text of this article is available in English free of charge, on the web on: www.e2med.com/gcb.

RÉSUMÉ
Facteurs associés à la stéatose et à la fibrose au cours de l’hépatite chronique C
Franck CHOLET, Jean-Baptiste NOUSBAUM, Martial RICHECŒUR, Emmanuel OGER, Jean-Michel CAUVIN, Nicole LAGARDE, Michel ROBASZKIEWICZ, Hervé GOUÉROU

(Gastroenterol Clin Biol 2004;28:272-278)
Une stéatose est fréquente chez les malades infectés par le virus de l’hépatite C. Des facteurs liés à l’hôte et au virus ont été suggérés à l’origine de cette stéatose, mais leur part respective est mal définie. Le rôle de la stéatose dans la progression de la fibrose a également été suggéré.

Buts — Déterminer : a) les facteurs associés à la stéatose chez des malades infectés par le virus de l’hépatite C ; b) les impacts respectifs de ces facteurs sur la fibrose extensive.

Malades et méthodes — Trois cent quatorze malades non traités ont été inclus. La consommation d’alcool a été évaluée sur l’ensemble de l’existence. Le génotype était connu chez 118 malades. L’évaluation histopathologique a été faite selon la grille METAVIR, et la stéatose a été définie en 5 degrés (absence, <10 %, entre 10 et 30 %, entre 30 et 70 %, supérieure à 70 %).

Résultats — En analyse univariée, la stéatose était associée au surpoids (P = 0.001), à la consommation d’alcool (P = 0.005), au génotype 3a (P < 0.001) et à un score d’activité nécro-inflammatoire modéré à sévère (P = 0.01). L’analyse multivariée a isolé 2 facteurs de risque indépendants associés à la stéatose : le génotype 3a (OR = 60.7 ; IC 95 % : 7.6-483.4) (P < 0.001) et l’indice de masse corporelle (OR = 4.86 ; IC 95 % : 1.8-13.13) (P = 0.002). En analyse univariée, la fibrose extensive (F2-F3-F4) était associée à l’âge (P < 10⁻⁵), au sexe masculin (P = 0.001), à la durée présumée d’évolution (P < 0.004), à l’indice de masse corporelle (P < 10⁻⁷), à la consommation d’alcool (P < 10⁻⁴), à la sévérité du score d’activité (P < 10⁻⁵) et à la stéatose (P < 10⁻⁴). L’analyse multivariée isolait 3 facteurs de risque indépendants de fibrose extensive : une durée présumée d’évolution supérieure à 10 ans (P = 3.17 ; IC 95 % : 0.65-15.4) (P = 0.015), la présence de stéatose (OR = 3.17 ; IC 95 % : 1-9.99) (P < 0.049) et le génotype 3a (OR = 5.56 ; IC 95 % : 1.4-22.1) (P = 0.015).

Conclusion — La stéatose observée chez les malades atteints d’hépatite chronique virale C semble être influencée par le génotype 3 et le surpoids. La présence d’une stéatose est associée à une augmentation du risque de fibrose extensive.

Hepatitis C virus (HCV) infection is characterized by a high rate of developing chronic disease (observed in 70-85% of patients) and exposes the patient to the risk of chronic active hepatitis with progression to cirrhosis and hepatocellular carcinoma [1, 2]. Cirrhosis develops in about one-quarter of patients [3-5]. There are three main factors favoring cirrhosis: duration of viral infection (> 20 years), age at contamination (> 40 years), and excessive alcohol intake (> 40 g/d) [6]. Liver steatosis was recently identified as a risk factor for progression to extensive fibrosis [7]. Pathology studies show that from 31% to 72% of HCV-infected patients will develop...
liver steatosis [8-10]. The underlying pathophysiological mechanisms remain a subject of discussion. Several studies have demonstrated a significant relationship between steatosis and elevated body mass index (BMI) [11-13] in HCV-infected patients. When patients with risk factors for steatosis such as obesity, alcohol, diabetes, dyslipidemia, or drugs are excluded, the high prevalence of steatosis persists [7, 12], suggesting HCV itself may be a risk factor. Recent work has suggested that the prevalence of steatosis is higher in patients infected with genotype 3a [7, 14, 15].

The purpose of this work was to ascertain the respective roles of clinical, biological and viral factors associated with steatosis and fibrosis in a large population of patients with hepatitis C virus infection.

Material and methods

Patients

Between January 1992 and March 2001, 420 consecutive patients with HCV were treated at the Brest University Hospital hepatogastroenterology unit. Positive diagnosis of HCV infection was established with 2nd or 3rd generation ELISA for anti-HCV antibodies (before and after 1992 respectively) and polymerase chain reaction (PCR) to detect HCV RNA in serum (positive threshold 1000 copies/ml before 1998 then 50 IU/mL ~ 100 copies/mL after 1998) [AmpliCor Monitor® HCV assay, Roche]. In addition to HCV infection, inclusion criteria for the study cohort were absence of prior treatment and known liver histology. Exclusion criteria were prior treatment with interferon alpha, hepatitis B or human immunodeficiency virus (HIV) co-infection, other cause of chronic liver disease, organ transplantation, or immunosuppressor treatment. The study cohort included 314 patients. The following clinical variables were recorded: age at time of liver biopsy, mode of contamination, age at time of contamination, body mass index (BMI), lifetime alcohol consumption. The duration of HCV infection was estimated for patients with a history of blood transfusion or intravenous drug abuse taking the day of transfusion (the first in the event of several transfusions) or the first injection with a shared syringe as the date of contamination. Patients were divided into three groups defined by duration of infection: < 10 years, 10-20 years, > 20 years. Patients were considered normal, overweight, or obese according to their BMI (< 24.9 kg/m², 25-29.9 kg/m² and >30 kg/m², respectively). Alcohol intake was recorded in g/d (or g/wk for patients with irregular drinking habits). The level of alcohol intake, established prospectively during several consultations, was plotted against age (3 year periods) to chart consumption and define four groups of patients: low intake (< 20 g/d), moderate intake (20-80 g/d), excessive intake (80-180 g/d) and very excessive intake (> 80 g/d). To establish a lifetime mean, the period starting from initial management as well as earlier periods of very high intake were considered. None of the patients were taking drugs with known steatosis-inducing effects.

Laboratory tests and liver biopsy histology

The following results were recorded: serum ALT, G-GT, glucose, and triglycerides. Viral genotype was determined for 118 patients with Inno-Lipa® (Innogenetics, Gand, Belgium) through December 1999 then by sequencing (Genekit® HCV SYN Assay) after December 1999. The METAVIR score [14] was established: absence of fibrosis (F0), portal fibrosis with septa (F1), portal fibrosis with a few septa (F2), portal fibrosis with numerous septa (F3), constituted cirrhosis (F4). Good quality biopsies, measuring at least 10 mm and including at least six portal spaces, were obtained. Biopsy specimens were immersed in Bouin solution then embedded in paraffin prior to hematoxylin-eosin-safranin, Masson trichrome, and reticulin staining. All slides were read by two pathologists to limit interobserver variation. The degree of steatosis was noted as the percent of affected hepatocytes using a 5-degree scale: degree 0 (no steatosis), degree 1 (minimal steatosis, 1-10%), degree 2 (moderate steatosis, 11-30%), degree 3 (severe steatosis, 31-70%), degree 4 (very severe steatosis, 71-100%).

Statistical analysis

Clinical, biological and histological variables were compared with degree of steatosis and METAVIR score using univariate analysis. The chi-square test was applied for qualitative variables and Mann-Whitney or Kruskall-Wallis non-parametric tests for quantitative variables. Statistical tests were considered significant for an alpha risk less than 5%. For logistic regression multivariate analysis (SPSS version 11.5 SPSS Inc., Chicago), degree of steatosis was the first dependent variable and extent of fibrosis (two classes F0-F1 and F2-F3-F4) the second for comparison with the following independent variables: age, gender, disease duration, BMI, alcohol intake, viral genotype, histology, and steatosis.

Results

Study population (table I)

The study cohort included 314 patients (196 men and 118 women). The mode of contamination was intravenous drug injection in 129 patients (41%), blood transfusion in 106 (34%), and unknown in 79 (25%). Age at contamination could be reasonably estimated for 235 patients, giving a mean duration of disease of 13.7 ± 7.1 years (range: 1-40). Mean BMI was 23.4 ± 3.4 kg/m² (range: 17.6-36.7). Thirteen patients (4%) were obese, 75 (24%) were overweight, and 226 (72%) had a normal BMI. Patients who drank alcohol were mainly men (91%). Mean of smokers was 41 ± 11.7 years (range: 21-71) and was not significantly different from that of non-smokers (40 ± 13.1 years, range: 6-75) (P = 0.17). Eight patients had diabetes and 13 patients had hypertriglyceridermia. Metabolic parameters (blood glucose, lipid levels) were not retained for statistical analysis due to small number of patients involved. Viral genotype was known for 118 patients (table I). Forty-six patients (15%) had cirrhosis, 42 (13%) had F3 fibrosis, 82 (26%) F2 fibrosis, and 144 (46%) F1 or no (F0) fibrosis. Steatosis was observed in 182 patients (58%); distribution by degree of steatosis is presented in table I. Due to the small number of patients with degree 3 and 4 steatosis, these two degrees were grouped together for the statistical analysis. None of the patients with steatosis had histological signs suggestive of steatohepatitis (polymorphonuclear neutrophil infiltration or acidophilic necrosis).

Univariate analysis

STEATOSIS VERSUS CLINICAL FEATURES

There was no significant correlation between degree of steatosis and age at biopsy, gender, mode of contamination, age at contamination or disease duration. The highest degree of steatosis was observed more often in men (80%) than women (20%) (table II). Due to the small number of obese patients (n = 13), obese and overweight patients were grouped together for the statistical analysis. Steatosis was correlated with BMI: 64/88 patients with BMI > 25 kg/m² had steatosis versus 118/226 patients with BMI < 25 kg/m² (P < 0.001) [OR 2.44; 95% CI 1.37-4.35]. Steatosis was significantly correlated with alcohol intake (Spearman coefficient, r = 0.2; P < 0.001).

Genotype 3a was strongly correlated with presence of steatosis [OR 40.2; 95% CI 5.9-844.5]. Among the 34 patients with genotype 3a infection, 33 had steatosis. The genotype was known for 12 of the 35 patients with > 30% steatosis; 11 of these 12 patients had genotype 3a.

STEATOSIS VERSUS LABORATORY RESULTS

Serum ALT and serum G-GT were often elevated in patients with steatosis, with an increasing trend with increasing degree of
steatosis (table II). Serum ALT was elevated in all patients with >30% steatosis.

STEATOSIS VERSUS HISTOLOGY RESULTS

The prevalence of steatosis was 73% among patients with extensive fibrosis (F2-F3-F4) versus 40% for those with moderate or no fibrosis (F0-F1) (figure 1) (P < 10⁻⁶). The mean METAVIR score was higher in patients with steatosis (1.5 ± 0.7) than in patients free of steatosis (1.3 ± 0.6), both for degree 2 (P = 0.02) and for degree 3-4 (P = 0.003). The mean METAVIR score for degree 1 steatosis (1.4 ± 0.6) was higher than for degree 0 (1.3 ± 0.6), but not significantly (P = 0.28).

FACTORS AFFECTING EXTENSIVE FIBROSIS (F2-F3-F4) (table III)

Extensive fibrosis was more frequent in men (71%) than women (29%) (P = 0.001). Patients with extensive fibrosis were older than those with minimal or no fibrosis. Severity of fibrosis was not correlated with mean age at contamination or mode of contamination (transfusion, intravenous drugs, unknown). Mean disease duration, which could be estimated for 235 patients, was significantly shorter (12.2 ± 6. years) for patients with extensive fibrosis (F0-F1) than in those with extensive fibrosis (15.7 ± 6. years) (P < 0.006). Sixty-four of the 88 patients with BMI > 25 kg/m² had extensive fibrosis versus 106/226 with a normal BMI (P < 10⁻⁶). The prevalence of extensive fibrosis was higher in drinkers (56%) than in non-drinkers (44%) (P < 10⁻⁶), the difference being significant for moderate intake (P = 0.004), excessive intake (P = 0.0007) and very excessive intake (P < 0.001) (OR 5.45; 95% CI 2.93-10.21). Conversely, there was no significant difference in prevalence of extensive fibrosis between different groups defined by alcohol intake (P = 0.19). Although the number of patients in the subgroups was small, a higher prevalence of genotype 3a was found in patients with extensive fibrosis than in the others. The prevalence of extensive fibrosis was higher among patients with steatosis (P < 10⁻⁶), the significant difference being found for degrees 1, 2 and 3 (P < 0.0001 for each degree) (OR 14.44; 95% CI 3.27-73.47). Patients with extensive fibrosis had a higher METAVIR score (1.55 ± 0.5) than those with little or no fibrosis (1.2 ± 0.6 (P < 10⁻⁶) (OR 4.13; 95% CI 1.32-13.26).

Multivariate analysis

FACTORS ASSOCIATED WITH STEATOSIS

Two independent risk factors were associated with steatosis: genotype 3a (OR 60.7) (P < 0.001) and BMI (or 4.86) (P = 0.002) (table IV).

FACTORS ASSOCIATED WITH SEVERE FIBROSIS

Three independent risk factors were associated with severe fibrosis (F2-F3-F4): disease duration greater than 10 years (OR 3.17; 95% CI 0.65-15.4) (P = 0.015), presence of steatosis (OR 3.17; 95% CI 1.9-9.99) (P = 0.049) and genotype 3a (OR 5.56; 95% CI 1.4-22.1) (P = 0.015) (table V).

Discussion

Fifty-eight percent of our 314 HVC-infected patients had steatosis. This rate is similar to that reported in pathology studies [8-10]. Multivariate analysis demonstrated that steatosis was associated with two independent risk factors, infection by genotype 3a and BMI greater than 25 kg/m². It also showed that severe fibrosis was associated with three independent risk factors: disease duration greater than 10 years, presence of steatosis and genotype 3a.

Our data could have several biases. The real duration of HCV infection depends on the accuracy of the presumed date of contamination. This date was most likely correct for patients who had post-transfusion hepatitis or for those who had had only one transfusion. The HCV status of transfusion products was traced, but information was not available on all donors. For patients who had multiple transfusions, the oldest date was retained as the presumed date of contamination, possibly lengthening disease duration. It was also difficult to establish the date of contamination resulting from intravenous drug injections. Some patients revealed high-risk practices only after several consultations and proof of contamination at one particular time could not be obtained. It is known however that HCV infection occurs early in the course of intravenous drug abuse, 33% of abusers becoming HCV-positive within six months [17]. For alcohol intake, two
physicians conducted independent inquiries, repeating their questions at different consultations, but some patients may have denied or minimized their drinking habits.

Univariate analysis revealed a correlation between the degree of steatosis and BMI. The correlation was present from the first degrees but the level of significance increased greatly for increasingly severe steatosis. There was no significant correlation between BMI and genotype and adjusting for genotype did not affect the BMI-steatosis relationship. In agreement with the findings reported by Hourigan et al. [11] BMI was an independent risk factor for steatosis but not for fibrosis. Adinolfi et al. [7], who studied a group of 180 HCV-infected patients with no confounding risk factors of steatosis, particularly excessive alcohol intake, found a statistically significant relationship between BMI and steatosis solely among patients infected with genotype 1. There was a trend for genotype 2, but no significant relationship with genotype 3. In their cohort however, android obesity, more so than BMI, appeared to be associated with steatosis. Others have also found a relationship between android obesity and steatosis [18, 19]. Android and gynoid obesity could not be distinguished in our retrospective cohort. It has been demonstrated that obesity causes insulin resistance, a crucial factor in the development of non-alcoholic steatotic liver disease [20].

Alcohol consumption was associated with both steatosis and fibrosis at univariate analysis, but multivariate analysis failed to confirm its independent relationship with either. At univariate analysis, even moderate alcohol intake (20-40 g/d) was associated with more frequent severe fibrosis. Conversely, while excessive alcohol intake was associated with steatosis, moderate intake was not. Alcohol consumption is a known independent risk factor for progression to fibrosis in HCV infection [21]. It does not appear to be a predominant risk factor for steatosis in HCV-infected patients unless daily alcohol intake exceeds 80 g/d. In a recent study of 142 patients with known disease duration [14], there was no relationship between steatosis and high-risk drinking habits (> 30 g/d for men and > 20 g/d for women). The authors did however demonstrate that even moderate alcohol intake was an independent risk factor for extensive fibrosis.

Genotype 3a was strongly correlated with steatosis in our small cohort. In patients with the highest degree of steatosis (> 30%) for whom the genotype was known, 12 out of 13 (92%) had genotype 3 infection. At multivariate analysis, genotype 3

<table>
<thead>
<tr>
<th>Degree of steatosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 132)</td>
<td></td>
</tr>
<tr>
<td>1 (n = 90)</td>
<td></td>
</tr>
<tr>
<td>2 (n = 57)</td>
<td></td>
</tr>
<tr>
<td>3/4 (n = 35)</td>
<td></td>
</tr>
</tbody>
</table>

Alcohol intake

None

> 20 g/day

Genotype

1a or 1b (n=71)

3a (n=34)

Others

GGT (% with elevated level)

ALT (% with elevated level)

METAVIR activity score

BMI: body mass index.

*p = 0.01 vs degree 0 and p = 0.02 vs degree 1

Fig. 1 – Association between liver fibrosis (METAVIR score) and steatosis in chronic hepatitis C patients.

Association entre fibrose (classification METAVIR) et stéatose chez les malades atteints d’hépatite chronique C.
infection was the leading independent risk factor associated with steatosis. Two independent risk factors of steatosis were identified in recent studies, BMI and genotype 3 [14, 22]. The relationship between genotype 3 and steatosis was suggested earlier [15, 23, 24]. Adinolfi et al. demonstrated that steatosis is associated with viral load only in patients with genotype 3a infection [23]. Rubbia-Brandt et al. found that the level of intra-hepatic replication is correlated with steatosis in HCV-infected patients [15]. Since the majority of the patients with genotype 3a infection were former intravenous drug users, it could be hypothesized that alcohol, sometimes consumed as a replacement for drugs, could have been the cause of steatosis. We did not however find any correlation between steatosis and mode of contamination. These findings suggest that, independently of contamination mode,

Table III. – Characteristics of the patients according to the severity of liver fibrosis.  
Caractéristiques de la population en fonction du degré de la fibrose.

<table>
<thead>
<tr>
<th>METAVIR fibrosis score (F)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F1 (( n = 144 ))</td>
<td>F2-F3-F4 (( n = 170 ))</td>
</tr>
<tr>
<td>Mean age (years) 37.0 ± 10.3</td>
<td>44.0 ± 13.2</td>
</tr>
<tr>
<td>Male (( n = 196 )) 76 (53%)</td>
<td>120 (71%)</td>
</tr>
<tr>
<td>Female (( n = 118 )) 68 (47%)</td>
<td>50 (29%)</td>
</tr>
<tr>
<td>Mode of contamination</td>
<td></td>
</tr>
<tr>
<td>transfusion (( n = 108 )) 47 (33%)</td>
<td>59 (35%)</td>
</tr>
<tr>
<td>drug abuse (( n = 131 )) 63 (44%)</td>
<td>66 (39%)</td>
</tr>
<tr>
<td>unknown (( n = 25 )) 34 (23%)</td>
<td>45 (26%)</td>
</tr>
<tr>
<td>Age at contamination 24.7 ± 9.4</td>
<td>28.7 ± 12.8</td>
</tr>
<tr>
<td>Disease duration (years) 12.2 ± 6.0</td>
<td>15.0 ± 7.6</td>
</tr>
<tr>
<td>BMI 22.5 ± 3.0</td>
<td>24.2 ± 3.5</td>
</tr>
<tr>
<td>&lt; 25 kg/m(^2) 120 (83%)</td>
<td>106 (62%)</td>
</tr>
<tr>
<td>≥ 25 kg/m(^2) 24 (17%)</td>
<td>64 (38%)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
</tr>
<tr>
<td>None 109 (76%)</td>
<td>74 (44%)</td>
</tr>
<tr>
<td>&gt; 20 G/day 35 (24%)</td>
<td>96 (56%)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>1a or 1b 35</td>
<td>36</td>
</tr>
<tr>
<td>3a 5</td>
<td>29</td>
</tr>
<tr>
<td>Others 4</td>
<td>8</td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
</tr>
<tr>
<td>Absent 86 (60%)</td>
<td>46 (27%)</td>
</tr>
<tr>
<td>Present 58 (40%)</td>
<td>124 (73%)</td>
</tr>
<tr>
<td>METAVIR activity score 1.2 ± 0.6</td>
<td>1.55 ± 0.5</td>
</tr>
</tbody>
</table>

BMI: body mass index.

Table IV. – Independent factors associated with liver steatosis at multivariate analysis.  
Facteurs indépendants associés à la stéatose en analyse multivariée.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3a</td>
<td>60.7</td>
<td>7.6-483.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>4.86</td>
<td>1.8-13.15</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table V. – Independent factors associated with liver fibrosis at multivariate analysis.  
Facteurs indépendants associés à la stéatose hépatique en analyse multivariée.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive alcohol intake</td>
<td>2.71</td>
<td>0.89-8.3</td>
<td>0.079</td>
</tr>
<tr>
<td>Active liver disease</td>
<td>2.73</td>
<td>0.93-7.99</td>
<td>0.067</td>
</tr>
<tr>
<td>Disease duration &gt; 10 years</td>
<td>3.17</td>
<td>0.65-15.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Steatosis</td>
<td>3.17</td>
<td>1.9-9.99</td>
<td>0.049</td>
</tr>
<tr>
<td>Genotype 3a</td>
<td>5.56</td>
<td>1.4-22.1</td>
<td>0.015</td>
</tr>
</tbody>
</table>
genotype 3a is involved in the development of steatosis during the course of the HCV infection. It has also been demonstrated that steatosis resolves after sustained virological response in patients infected with genotype 3a without any change in BMI, but that steatosis persists in non-responders [25-26].

The results of the present study show that the presence of steatosis is associated with more severe fibrosis (OR = 5.53) and that the relationship is stronger with higher degree of steatosis. The correlation between extensive fibrosis and steatosis remains significant (P = 0.03) after confounding factors such as alcohol, excessive body weight, diabetes, and dyslipidemia have been excluded. The same observation was made by others [7, 11, 12]. The correlation between fibrosis and steatosis has also been demonstrated with a statistical model [27]. More active necroinflammatory liver disease and higher serum transaminase and GGT levels were observed in patients with steatosis. There could be two explanations: steatosis plays a direct role in the course of fibrosis, or another independent factor favors both steatosis and extensive fibrosis. Adinolfi et al. recently demonstrated that perportal necrosis is more pronounced in patients with steatosis and extensive fibrosis than in patients with extensive fibrosis without steatosis [7].

New insight concerning the mechanisms underlying the development of steatosis in patients with chronic HCV infection is now available. It has been demonstrated in vivo that transgenic mice expressing the HCV capsid develop steatosis [28]. In a recently proposed model of virus-induced steatosis, the HCV capsid protein inhibits hepatic secretion of VLDL via reduced activity of the triglyceride transfer protein [29], but always with genotype 1 which is not associated with steatosis in humans. Serfaty et al. [30] demonstrated that HCV infection is associated with hypobetalipoproteinemia via a reduction in serum apolipoprotein b which could cause steatosis. Lipid peroxidation could be the common denominator in this toxicity mechanism leading to steatosis which would thus favor oxidative stress by generating free radicals. Lipid peroxidation is also associated with activation of hepatic stellate cells, which are responsible for synthesis of type 1 collagen, the principal type of hepatic fibrogenetic collagen [31]. The association between lipid peroxidation and liver fibrosis, apart from steatohepatitis, has been demonstrated in other liver diseases such as hemochromatosis, and alcoholic liver disease [32, 33]. As demonstrated by Farinati et al., lipid peroxidation is associated with steatosis during the course of chronic HCV infection [34]. In other work where the link with steatosis was not examined, in situ signs of lipid peroxidation were detected in areas of active liver fibrosis in HCV-infected patients [35].

Conclusion

Several factors are probably involved in the development of steatosis during the course of HCV infection. We found that genotype 3a and high BMI were two independent risk factors of steatosis. Except for patients with very high intake > 80 g/d, alcohol was not an independent risk factor. The presence and the degree of steatosis in HCV-infected patients was associated with more severe fibrosis, particularly in patients with genotype 3a infection. Antiviral treatment and better control of risk factors of steatosis are thus indicated for the often younger drug-user patients infected by genotype 3a HCV. Patients who develop hepatic steatosis should be advised against drinking alcohol which can aggravate pre-existing liver damage.

RÉférences


