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Short Communication

Factors associated with steatosis in liver biopsies of individuals with chronic hepatitis C infection in southern Brazil

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ABSTRACT

Background and study aims: Infection by the hepatitis C virus (HCV) is associated with various metabolic disorders that are collectively referred to as dysmetabolic syndrome associated with HCV. Hepatic steatosis is a common finding in chronic HCV infection and has been reported in 30–70% of patients. Here, we determine the prevalence of steatosis in patients with HCV, identify the characteristics associated with the presence of steatosis in liver biopsies and assess the association between steatosis and the severity of liver disease.

Patients and methods: This analytic cross-sectional study evaluated HCV carriers (adults) at the Gastroenterology and Hepatology Outpatient Clinic of a public university hospital between July 2013 and June 2014 using retrospective data collection. The patients were divided into two groups according to the presence or absence of steatosis in their liver biopsies. The groups were compared for the presence of risk factors for steatosis and clinical, laboratory, virological and histological characteristics.

Results: One hundred and four patients aged 49.5 ± 9.3 years were included in the study; 56.0% of the patients were men. Steatosis was observed in 65.4% of the liver biopsies. When comparing individuals with and without steatosis, patients with steatosis exhibited a higher proportion of non-1 genotype (43.9 vs. 20.7%; $p = 0.034$), higher median triglyceride levels (101.0 vs. 75.0; $p = 0.034$), ferritin levels (333.0 vs. 193.5; $p = 0.025$) and gamma glutamyl transferase levels (2.92 xULN vs. 1.87; $p = 0.030$). Multivariate analysis demonstrated that triglyceride levels were independently associated with the presence of steatosis (OR = 1.016; 95% CI 1.002–1.031; $p = 0.026$).

Conclusions: Hepatic steatosis was observed in 65.4% of individuals with HCV. We observed that elevated triglyceride levels were associated independently with the presence of hepatic steatosis; we did not demonstrate an association between hepatic steatosis and histological severity.

Introduction

Liver steatosis is a generic term that refers to the accumulation of triglycerides within the cytoplasm of the hepatocytes [1]. Liver steatosis may occur due to chronic alcohol ingestion, metabolic syndrome, diabetes, obesity and/or chronic hepatitis C virus (HCV) infection. It is estimated that 200 million people worldwide are chronically infected with HCV [1]. Hepatic steatosis is a common histological finding in chronic HCV infection and is described in 40–86% of patients [1,2]. HCV infection is associated with several metabolic disorders that are collectively referred to as dysmetabolic syndrome associated with HCV [3]. HCV patients may present liver steatosis due to insulin resistance induced by HCV infection and also alcohol ingestion, metabolic syndrome, diabetes and obesity, irrespective of the presence of the virus.

Our objective is to determine the prevalence of steatosis in individuals with chronic HCV hepatitis, identify the characteristics associated with the presence of steatosis in liver biopsies and elucidate the association between steatosis and the severity of liver disease.

Patients and methods

This analytic cross-sectional study evaluated HCV carriers (adults) at the Gastroenterology and Hepatology Outpatient

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Clinic of a public university hospital in Florianópolis, Brazil between July 2013 and June 2014 using retrospective data collection. We excluded patients from our study for the following reasons: insufficient registration of clinical data, refusal to participate in the study, absence of a liver biopsy, co-infection with the human immunodeficiency virus (HIV), previous liver transplant, or previous antiviral treatment.

Subjects were invited to participate in the study during a routine outpatient visit; they were asked to sign an informed consent form. Clinical, laboratory and histological data were collected from records on medical charts. HCV patients were defined as individuals with HCV ribonucleic acid (RNA) detectable by polymerase chain reaction (PCR) via a Biomolecular Technical Ribonucleic Acid (Qualitative Test). The patients were analysed for clinical, epidemiological and laboratory variables that we then investigated. Patients infected with HCV genotypes 2 and/or 3 were defined as having the "non-1 genotype." The biochemical tests were expressed in absolute values. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) were expressed as a multiple of the upper limit of normal (xULN), and the cutoff was 19 U/L, 26 U/L and 19 U/L for women and 30 U/L, 32 U/L and 31 U/L for men. HOMA-IR was calculated using the formula: HOMA-IR = [glucose (nmol/L) * insulin (μU/mL)/22.5], using fasting values.

We conducted a liver biopsy on all patients with positive hepatitis C virus-ribonucleic acid (HCV RNA), regardless of ALT levels. Hepatitis C liver disease was classified according to Scheuer's classification [4]. Fibrosis was ranked as follows: 0 = no fibrosis; 1 = enlarged, fibrotic portal tracts; 2 = periportal or portal–portal septa but intact architecture; 3 = fibrosis with architectural distortion but no obvious cirrhosis; 4 = probable or definite cirrhosis. Portal/periportal necroinflammatory activity was graded on a scale of 0–4: 0 = none or minimal; 1 = portal inflammation; 2 = mild limiting plate necrosis; 3 = moderate limiting plate necrosis; 4 = severe limiting plate necrosis. Advanced fibrosis was defined as stages 3 or 4, and severe periportal activity was defined as grades 3 or 4. We analysed hepatic steatosis in all biopsies and rated it as present (in any number) or absent for comparative analysis. Steatohepatitis was defined by the presence of steatosis, perisinusoidal fibrosis, Mallory's corpuscles and/or ballooning.

Numerical variables with a normal distribution were expressed as a mean and standard deviation and compared using the Student's *t*-test. We used the Kolmogorov–Smirnov test to test the normality of the sample. Numerical variables with a non-normal distribution were expressed as a median and interquartile range and compared using the Mann–Whitney test. We represented qualitative variables by frequency (%), and we analysed them using a chi-squared test or Fisher's exact test, when necessary. *p* values less than 0.05 were considered to be statistically significant.

We performed bivariate analysis to identify the variables associated with the presence of hepatic steatosis. Variables with *p* values less than 0.20 were included in the multivariate analysis. We performed forward-stepwise (conditional) analysis to identify variables independently associated with the presence of steatosis in liver biopsies. All of the tests were performed using the IBM Statistical Package for Social Sciences software, version 17.0 (SPSS Statistics, Chicago, Illinois, USA). Our study protocol adheres to the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee (number 301465).

Results

From July 2013 until June 2014, 148 patients with chronic HCV were evaluated for inclusion in the study. We excluded 44 patients, 3 patients with previous treatment, 8 HIV carriers, 2 transplant patients and 31 patients who did not undergo a liver biopsy.

The study included 104 individuals with HCV with a mean age and standard deviation of 49.5 ± 9.3 years; the median age of the cohort was 50.5 years. Over half of the participants (53.8%) were men and 96.7% declared themselves to be Caucasian. Amongst 34 individuals who had a body mass index (BMI) measurement, overweight individuals constituted 42.9% of individuals with steatosis and 14.3% of those without. Clinical characteristics of the included patients are listed in Table 1. Virus genotyping was available in 86 patients and was distributed as follows: genotype 1 = 64% genotype 2 = 7% and genotype 3 = 29%. The patients exhibited means and standard deviations (medians) of the following laboratory characteristics: ALT, 4.6 ± 3.3 (3.7) xULN; AST, 2.3 ± 1.7 (1.7) xULN; GGT, 3.8 ± 3.2 (2.8) xULN; albumin, 3.8 ± 0.5 (3.8) g/dL, prothrombin activity (PA), 84.5 ± 13.7 (84.9)% and platelets, 199267.3 ± 57493.3 (204000.0) mm^{-3}. Liver biochemistries, lipid profiles and glycemic profiles are listed in Table 2. In the liver biopsy, 9.7% of patients had liver cirrhosis, steatosis was observed in 65.4% of the patients and steatohepatitis was seen in 5.8% of the sample.

Individuals with liver steatosis had a mean age of 49.5 ± 8.4 years, and 51.5% were men. Amongst the 34 individuals with BMI measurements, 54.5% of patients were overweight and 9.1% were obese. Approximately one twentieth of the patients (6.7%) presented a total cholesterol over 200 mg/dL, 59.3% exhibited an HDL cholesterol less than 50 (60) for women (men) and 36.2% demonstrated an LDL higher than 100 mg/dL. Fasting glucose levels higher than 100 g/L were observed in 42.2% of cases.

Table 1
Clinical characteristics of 104 individuals with chronic HCV infection according to the presence of steatosis in liver biopsies.

Characteristics	All *n* = 104 (100%)	With steatosis *n* = 68 (65.4%)	Without steatosis *n* = 36 (34.6%)	*p*
Male sex (*n*, %)	56 (53.8)	35 (51.5)	21 (58.3)	0.504[x]
Age (years)[b]	49.5 ± 9.3	49.5 ± 8.4	49.5 ± 10.9	0.984[t]
White ethnicity (*n*, %)	89 (96.7)	57 (95.0)	31 (100)	0.548[f]
Hypothyroidism (*n*, %)	7 (7.4)	5 (8.2)	2 (5.9)	1.000[f]
Hypertension (*n*, %)	21 (22.1)	15 (24.6)	6 (17.6)	0.434[x]
DM (*n*, %)	11 (11.6)	7 (11.5)	4 (11.8)	1.000[f]
Dyslipidemia (*n*, %)	3 (3.2)	3 (4.9)	0 (0)	0.550[f]
Alcohol consumption (*n*, %)	43 (56.6)	30 (60.0)	13 (50.0)	0.404[x]
Risk factors for HCV transmission				
IV drug use (*n*, %)	24 (47.1)	15 (42.9)	9 (56.3)	0.374[x]
Blood transfusion (*n*, %)	20 (38.5)	11 (32.4)	9 (50.0)	0.213[x]
BMI (kg/m^2)[a,c]	27.3 (23.5–28.6)	27.6 (23.9–28.3)	24.1 (20.2–31.7)	0.259[m]

DM: diabetes mellitus; HCV: hepatitis C virus; IV: intravenous; BMI: body mass index. x: Chi-square test; t: Student's *t* test; f: Fisher's exact test; m: Mann–Whitney test.
[a] Available in 34 individuals.
[b] Mean ± standard deviation.
[c] Median (interquartil range).

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Table 2
Laboratory characteristics of 104 individuals with chronic HCV infection according to the presence of steatosis in liver biopsies.

Characteristics	All $n = 104$ (100%)	With steatosis $n = 68$ (65.4%)	Without steatosis $n = 36$ (34.6%)	p
Creatinine (mg/dL)[f]	0.9 (0.8–1.0)	0.7 (0.8–1.0)	0.4 (0.8–1.0)	0.887[m]
Haemoglobin (g/dL)[g]	14.5 ± 1.6	14.6 ± 1.7	14.3 ± 1.2	0.465[t]
Platelets (/mm^3)[g]	199267.3 ± 57493.3	199058.9 ± 61220.4	199.697.0 ± 49.820.6	0.959[t]
Ferritin (ng/mL)[f,a]	266.5 (116.0–470.5)	337.0 (153.0–546.0)	193.5 (76.4–342.0)	0.025[m]
Total cholesterol (mg/dL)[f]	159.0 (139.5–183.0)	162.0 (136.0–181.8)	158.0 (141.5–194.0)	0.536[m]
HDL (mg/dL)[f]	49.3 ± 14.4	47.6 ± 14.5	52.7 ± 13.9	0.096[t]
LDL (mg/dL)[f]	88.0 (68.5–111.5)	89.5 (66.5–112.0)	87.9 (76.0–106.0)	0.725[m]
Triglycerides (mg/dL)[f]	93.0 (60.8–123.5)	101.0 (69.0–128.0)	75.0 (56.0–106.0)	0.034[m]
Fasting glucose (mg/dL)[f]	98.0 (89.8–107.3)	98.0 (92.0–106.8)	97.0 (85.5–108.3)	0.317[m]
Fasting insulin (U/mL)[f,b]	10.3 (6.8–14.1)	11.2 (7.2–14.1)	9.6 (3.4–16.9)	0.637[m]
HOMA-IR[b]	2.7 (1.6–3.9)	3.0 (1.7–4.2)	2.4 (0.9–4.2)	0.516[m]
ALT xULN[f]	3.7 (2.9–8.4)	3.6 (3.0–7.7)	2.9 (2.8–8.8)	0.957[m]
AST xULN[f]	1.7 (1.0–3.1)	1.7 (1.1–3.0)	1.8 (1.0–3.5)	0.862[m]
GGT xULN[f]	2.8 (1.6–4.5)	2.92 (1.8–4.8)	1.87 (1.3–3.5)	0.030[m]
Direct bilirubin (mg/dL)[f]	0.2 ± 0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.7 (0.1–0.2)	0.355[m]
Albumin (g/dL)[g,c]	3.8 ± 0.5	3.9 ± 0.4	3.7 ± 0.5	0.089[t]
PA (%)[g]	84.5 ± 13.7	85.8 ± 15.0	82.2 ± 10.4	0.171[t]
Viral load (UI/mL)[f]	857,000 (277,000–2,630,864)	915,000 (313,000–2,514,728)	846,000 (274,000–3,990,000)	0.795[m]
Non-1 genotype (n, %)[d]	31 (36.0)	25 (43.9)	6 (20.7)	0.034[x]
Anti-HBc (n, %)[e]	52 (30.1)	14 (30.4)	8 (29.6)	0.942[x]

HDL: high density lipoprotein; LDL: low density lipoprotein; ALT: alanine aminotransferase; xULN: times the upper limit of normal; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; PA: prothrombin activity. x: Chi-square test; t: Student's t test; m: Mann–Whitney test.
[a] Available in 72 individuals.
[b] Available in 58 individuals.
[c] Available in 85 individuals.
[d] Available in 86 individuals.
[e] Available in 73 individuals.
[f] Median (interquartile range).
[g] Mean ± standard deviation.

Table 3
Histological characteristics of 104 individuals with chronic HCV infection according to the presence of steatosis in liver biopsies.

Characteristics	All $n = 104$ (100%)	With steatosis $n = 68$ (65.4%)	Without steatosis $n = 36$ (34.6%)	p
Iron overload (n, %)	38 (43.7)	29 (47.5)	9 (34.6)	0.266[x]
Advanced fibrosis (n, %)[a]	19 (18.4)	10 (14.9)	9 (25.0)	0.209[x]
Severe periportal inflammatory activity (n, %)[b]	29 (28.4)	22 (33.3)	7 (19.4)	0.137[x]

x: Chi-square test.
[a] Scheuer's stages 3 or 4.
[b] Scheuer's grades 3 or 4.

When individuals with steatosis in their liver biopsies were compared with patients without steatosis, there was a higher proportion of non-1 genotype (43.9 vs. 20.7%; $p = 0.034$), a higher median triglyceride level (101.0 vs. 75.0; $p = 0.034$), higher ferritin levels (333.0 vs. 193.5; $p = 0.025$) and higher GGT levels (2.92 vs. 1.87 xULN; $p = 0.030$) in patients with liver steatosis. No differences were observed in terms of gender, age, race, hypothyroidism, hypertension, diabetes mellitus, dyslipidemia, BMI transmission mode and habits such as alcohol consumption. Similarly, we did not find any differences in terms of creatinine, haemoglobin, platelets, total cholesterol and fractions, glucose, insulin, ALT, AST, albumin, PA, direct bilirubin, viral load, and anti-HBc.

There was no difference in the prevalence of iron overload, severe parenchymal activity (grades 3 and 4), severe periportal activity (grades 3 and 4) and advanced fibrosis (grades 3 and 4) when we compared individuals with and without steatosis in their liver biopsies (Table 3).

We included the following variables in the multivariate analysis: ferritin, HDL, triglycerides, GGT, albumin and non-1 genotype. The multivariate forward-stepwise (conditional) analysis revealed that triglyceride levels were independently associated with the presence of steatosis in liver biopsies (OR = 1.016; 95% CI 1.002–1.031; $p = 0.026$).

Discussion

With respect to the variables of age, gender, ethnicity and genotype our sample does not differ from other studied samples in both Brazil and elsewhere.

Liver steatosis was found in 65.4% of patients in our study, which is similar to the 61% fraction reported by Hourigan et al. [2]. In subjects with HCV infection, liver steatosis may be associated with BMI; overweight patients have significantly more steatosis than lean individuals, regardless of viral genotype [5]. However, beyond the host characteristics that contribute to the development of steatosis, there are viral factors that induce liver steatosis and do not depend on the patient's weight [2]. In this study, no difference was observed between the median BMI values of individuals with steatosis compared with patients without steatosis, possibly due to the small number of subjects for whom BMI measurements were available.

Patients infected with HCV genotype 3 have a higher prevalence of steatosis than individuals infected with other genotypes [6]. We identified a higher fraction of patients with non-1 genotype amongst patients with liver steatosis in the univariate analysis but not in the multivariate analysis. In individuals with HCV genotype 3, liver steatosis may result from viral cytopathic effects [7] and lead to more serious forms of steatosis and even cirrhosis [6,7].

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Higher median ferritin levels were observed in the group with liver steatosis. Licata et al. suggested that the serum ferritin level is a risk factor for steatosis [8]; liver injury related to HCV is characterised by increased iron stores, which causes a free radical mediated peroxidation and results in steatosis [9]. Serum ferritin is synthesised from intracellular ferritin, which reflects the iron stores of an individual. High levels of serum ferritin may reflect excess iron stored in the tissues; however, hyperferritinemia can also be observed in inflammatory conditions, tissue damage and increased metabolism. As a result, serum ferritin is a sensible but not very specific protein for evaluating the balance of iron [10]. In our present study, a higher median serum ferritin was associated with iron overload in liver biopsies (477.0 vs. 144.5 ng/mL; $p < 0.001$; data not shown), but iron overload was not related to the presence of steatosis. Silva et al. identified an association between elevated serum ferritin and the highest values of liver iron concentration. However, in these authors' final model analysis, serum ferritin was not independently associated with liver iron concentration, suggesting that ferritin is an inadequate marker of hepatic iron content [11].

GGT is a sensitive marker of chronic alcoholism, metabolic syndrome, type 2 diabetes, hypertension, cardiovascular risk, canalicular injury, hepatocellular injury, liver structural lesions and the presence of steatosis [12]. Benini et al. found that increased serum GGT levels in patients with chronic HCV were associated with hepatic steatosis and fibrosis with higher scores [13]. Silva et al. showed an association between high GGT levels and higher fibrosis scores but did not find an association with liver steatosis [14]. We identified higher GGT values in patients with liver steatosis in the univariate analysis but not in the multivariate analysis. Benini et al. demonstrated a correlation between increased serum GGT levels and liver steatosis and fibrosis associated with more advanced stages of liver disease [13], which defines GGT as a marker of liver damage induced metabolically [15].

In this study, multivariate analysis revealed that triglyceride levels were independently associated with the presence of steatosis in liver biopsies. Likewise, Hwang et al. reported significantly higher serum triglyceride levels in patients with liver steatosis [7], and the degree of fatty liver was also correlated with serum triglyceride levels [6].

Some of the possible limitations of this study should be discussed. Although the total number of patients included in the cohort was representative of the general population, we examined possible associations between certain factors and the presence of liver steatosis, which considerably reduced the number of individuals possessing particular combinations of variables and hence the power of the statistical tests. For this reason, these results need to be confirmed in a larger set of patients. Furthermore, the study design was cross sectional with retrospective data collection and did not include longitudinal follow-up. Data on diet quality, exercise routine, waist circumference and waist/hip ratio were not evaluated, so an analysis of the effect of these variables on the presence of steatosis in this population was not possible. As discussed earlier, the number of individuals with BMI values was reduced in the sample, which may have influenced the outcome. Another limitation of this study was the lack of a control group, although our results were similar to previously published data.

In conclusion, in our univariate analysis, non-1 genotype HCV infection and high levels of GGT, ferritin and triglycerides were related to the presence of steatosis in liver biopsies. Furthermore, high triglycerides values were independently associated with the presence of fatty liver disease in individuals with chronic HCV infection; there was no association between fatty liver and histological severity.

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Conflict of interest

The authors declare no conflicts of interest.

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