Daily Cannabis Use: A Novel Risk Factor of Steatosis Severity in Patients With Chronic Hepatitis C

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Background & Aims: **Steatosis is highly prevalent in patients with chronic hepatitis C (CHC) and has been reported to increase fibrosis and reduce the rate of viral eradication. Two recent studies indicate that endocannabinoids promote experimental steatosis via activation of hepatic CB1 receptors. We therefore investigated the impact of cannabis smoking on steatosis severity during CHC.** ***Methods:*** **A total of 315 consecutive patients with untreated CHC undergoing liver biopsy were included. Detailed histories of recent cannabis, alcohol, and tobacco use were recorded. Steatosis, activity, and fibrosis stage were assessed by 2 pathologists according to METAVIR. Marked steatosis was defined as ≥30%. Patients were categorized as cannabis nonusers (63.5%), occasional cannabis smokers (12.4%), or daily cannabis smokers (24.1%).** ***Results:*** **Multivariate analysis identified 6 predictors of marked steatosis: daily cannabis use (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.01–4.5]), activity grade ≥A2 (OR, 2.1; 95% CI, 1.0–4.3), genotype 3 (OR, 5.4; 95% CI, 2.6–11.3), hyperglycemia or diabetes (OR, 5.1; 95% CI, 1.8–15.0), body mass index >27 kg/m^2 (OR, 2.1; 95% CI, 1.0–4.3), and serum HCV RNA load (OR, 1.7; 95% CI, 1.0–2.9). Upon adjustment of HCV genotype (3 vs non-3) or alcohol intake (<30 g/day vs ≥30 g/day), marked steatosis was more frequent in daily cannabis users compared with occasional users and nonusers (P = .03 and P = .008, respectively).** ***Conclusions:*** **Our results identify daily cannabis smoking as a novel independent predictor of steatosis severity during CHC and strongly argue for a steatogenic role of the cannabinoid system. Cannabis use should be discouraged in patients with CHC.**

Steatosis is a common histologic finding in patients with chronic hepatitis C (CHC), with a prevalence ranging between 40% and 80% in infected patients.[1,2] A number of cross-sectional and longitudinal studies suggest that steatosis is associated with more rapid progression of fibrosis and negatively affects the rate of viral eradication following antiviral treatment.[3–15] These findings stimulated efforts to delineate mechanisms governing steatogenesis during CHC. Current evidence indicates that multiple factors independently underlie fatty liver in CHC. Indeed, hepatitis C virus (HCV)-induced steatosis, a cytopathic lesion related to viral replication into cells, frequently occurs in patients infected with genotype 3 due to direct interactions between unidentified HCV proteins and lipid metabolism[1] and disappears upon successful antiviral therapy.[8,10,11] As well, features of the metabolic syndrome and insulin resistance such as obesity, diabetes, and hyperlipemia are strongly associated with steatosis in CHC as a sole cause in non–genotype 3—infected patients or combined with HCV-induced steatosis in patients infected with genotype 3.[1,2]

Marijuana (*Cannabis sativa*), the most widely used recreational drug worldwide, holds a long-standing history of medical use, with several records of powerful analgesic properties as early as 3000 years BC.[16] Following identification of endocannabinoids and their receptors CB1 and CB2 in the late 1980s, intensive research in the field unraveled a large variety of ubiquitous functions of cannabinoids in health and diseases.[16–21] CB2 receptors are primarily expressed in immune cells and play a central role in regulation of inflammation, whereas CB1 receptors predominate in the central nervous system and mediate psychoactive and appetite stimulant properties of phytocannabinoids and endocannabinoids.[16,18–21] Aside from their high central expression, CB1 receptors are widely distributed, particularly in organs that control energy balance. A number of clinical and experimental studies have established that obesity is associated with an increased CB1-dependent cannabinoid tone, leading to excess food intake, increased lipogenesis, and reduced energy expenditure in peripheral organs.[16,18,19,21,22] These findings led to the development of rimonabant, the first

Abbreviations used in this paper: BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; OR, odds ratio.

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generation of CB1 receptor antagonists, and to its approval in Europe for the treatment of obesity and overweight associated to cardiovascular risk factors.[23,24] Interestingly, 2 recent reports indicate that in experimental models of nonalcoholic fatty liver disease, CB1 receptors are steatogenic and CB1 antagonism suppresses liver steatosis, even in the presence of a continued high caloric intake.[25,26]

In the present study, we therefore evaluated whether CB1-dependent steatogenic effects reported in experimental models are relevant to human liver disease and investigated the relationship between cannabis use and steatosis grade in patients with CHC.

Materials and Methods

Patients

Consecutive patients were recruited in a single tertiary care center between May 2003 and June 2006 if they met the following criteria: (1) HCV infection defined by a positive test for anti-HCV antibodies (Ortho HCV 3.0 ELISA test system; Ortho Clinical Diagnostics, Raritan, NJ) with detectable serum HCV RNA (Amplicor HCV 2.0 PCR test system; Roche Molecular Systems, Pleasanton, CA) documented for at least 6 months, (2) available liver biopsy specimen (15 mm or greater, with at least 6 portal spaces) consistent with CHC, and (3) serum fasting glucose, triglyceride, and cholesterol levels determined at the time of liver biopsy. Patients with concomitant infection with hepatitis B virus (serum hepatitis B surface antigen positive) or human immunodeficiency virus or with a past history of immunosuppression were excluded, as well as those previously treated for CHC or with ongoing use of illicit drugs other than cannabis at the time of the study. The protocol was approved by the local institutional review board, and all patients gave written informed consent for the study.

Data Collection

Demographic, epidemiologic, environmental, virologic, and metabolic data were collected at the time of liver biopsy, including sex, age, body mass index (BMI), source of contamination (intravenous drug use, blood transfusion before 1990, other nosocomial source, or unknown route of transmission), maintenance treatment by methadone or buprenorphine, and finally alcohol, tobacco, and cannabis consumption during the 6 months preceding liver biopsy. The daily number of drinks equivalent to 10 g of pure ethanol was recorded separately for beer, wine, and spirits, on weekdays and during weekends, taking into account potential variations over time, and was expressed as the average amount of alcohol intake in grams per day. Ongoing alcohol abusers were defined as patients with an average alcohol consumption $\geq$30 g/day.[15] Tobacco smoking was estimated as the mean daily number of cigarettes smoked. Cannabis smoking was recorded at the time of liver biopsy using a standard instrument, as previously reported.[27] Subjects were asked about the frequency of their current (within 6 months of liver biopsy) consumption according to a 5-point scale: no use, use less than once monthly, use at least 1–3 times a month, use 1–6 times a week, and use on a daily basis. The number of cannabis cigarettes used per smoking session was quantified and averaged over the period considered. Patients were classified as follows: (1) nonsmokers were defined as nonusers of cannabis, (2) occasional users smoked less than one daily cannabis cigarette, and (3) daily users smoked at least one cannabis cigarette per day.

Quantitative serum HCV RNA, glycemia, triglyceride, and cholesterol levels were measured at the time of liver biopsy after overnight fasting. Hyperglycemia was defined by a fasting serum glucose level greater than 6.1 mmol/L or a history of diabetes,[28] and hyperlipemia was defined as a triglyceride or cholesterol level greater than 1.7 mmol/L and 6.1 mmol/L, respectively. HCV genotype was determined by a second-generation reverse-hybridization line probe assay (INNO-LiPA HCV II; Innogenetics, Zwijnaarde, Belgium). HCV RNA load was assayed by means of a third-generation branched DNA–based assay (Versant HCV RNA 3.0 Quantitative Assay; Bayer Diagnostics, Tarrytown, NY) with a lower limit of detection of 615 IU/mL. Results were expressed as $\log_{10}$ IU/mL.

Liver Histopathology

Liver biopsy specimens were obtained from all patients for diagnostic purposes. Specimens were fixed in formalin, embedded in paraffin, and subsequently stained with H&E and safran, picrosirius red for collagen, and Perls' technique for iron. All liver biopsy specimens were reviewed by 2 pathologists unaware of clinical and biological data except for the presence of chronic infection with HCV. Steatosis, activity grade, and fibrosis stage were determined according to the METAVIR scoring system.[29] Necroinflammatory activity grade was scored on a scale of 0–3 (A0–A3), and fibrosis was staged on a scale of 0–4. Steatosis was defined according to the percentage of hepatocytes containing cytoplasmic fat vacuoles as absent (<5%), mild (5%–10%), moderate (11%–29%), and marked ($\geq$30%).[29]

Statistical Analysis

Descriptive statistics are shown as means and SD, medians and interquartile ranges, or percentages, as appropriate. Comparisons between groups used Kruskal–Wallis test or Mann–Whitney test for quantitative data and χ^2 test or Fisher exact test for qualitative data. All tests were 2-tailed. Factors related to marked steatosis were first identified by univariate analysis; for this purpose, most quantitative data were transformed in qualitative or ordinal variables, based either on clinical relevance or mean value of the parameter. Bivariate analysis was performed using the Mantel–Haenszel statistics.

Stepwise logistic regression analysis was used to explore the independence of factors related to marked steatosis by univariate analysis. All factors with a P value ≤.10 at univariate analysis were tested in the model. Odds ratios (ORs) were estimated from the model and given with their 95% confidence intervals (CIs). P values of less than .05 were considered significant. All analyses were performed using BMDP statistical software (Los Angeles, CA) and Stata (Stata Corp, College Station, TX).

Results

Study Population

Table 1 summarizes baseline characteristics of the overall study population (n = 315). There were 223 men and 92 women with a mean age at liver biopsy of 45.1 ± 10.9 years and an average BMI of 24.8 kg/m^2. Ongoing alcohol abuse was reported by 13.3% of patients. Intravenous drug use was the most common route of transmission (44.1%). Genotype distribution showed a predominance of genotype 1 (62.5%), followed by genotype 3 (21.0%). Activity grade ≥A2 and significant fibrosis (≥F2) were found in 58.7% and 35.6% of cases, respectively. Overall, 144 patients (45.7%) had histologic evidence of steatosis. Steatosis was graded mild, moderate, or marked in 47 (14.9%), 37 (11.8%), and 60 (19.0%) patients, respectively.

Table 1. Baseline Features of 315 Patients With CHC

Male gender, n (%)	223 (70.8)
Age at liver biopsy (*y*), mean (SD)	45.1 (10.9)
Route of transmission, n (%)	
Blood transfusion	95 (30.2)
Intravenous drug use	139 (44.1)
Nosocomial	31 (9.8)
Unknown	50 (15.9)
Tobacco consumption (*cigarettes/day*)[a]	
Median (interquartile range)	10 (0–20)
>10, n (%)	126 (40.0)
Alcohol intake (*g/day*)[a]	
Median (interquartile range)	2 (0–14)
≥30, n (%)	42 (13.3)
Methadone or buprenorphine use, n (%)	23 (7.3)
HCV genotype, n (%)	
1	197 (62.5)
2	21 (6.7)
3	66 (21.0)
4/5/6	31 (9.8)
Serum HCV RNA (log_{10} *IU/mL*), mean (SD)[b]	5.83 (0.68)
Hyperglycemia or diabetes, n (%)	23 (7.3)
Hyperlipemia, n (%)	
Triglyceride level >1.7 mmol/L	25 (7.9)
Cholesterol level >6.1 mmol/L	22 (7.0)
BMI (*kg/m^2*)	
Mean (SD)	24.8 (4.1)
>27, n (%)	80 (25.4)
Steatosis, n (%)	
<5%	171 (54.3)
5%–10%	47 (14.9)
11%–29%	37 (11.8)
≥30%	60 (19.0)
METAVIR activity grade, n (%)	
A0–A1	130 (41.3)
A2	168 (53.3)
A3	17 (5.4)
METAVIR fibrosis stage, n (%)	
F0	14 (4.4)
F1	189 (60.0)
F2	43 (13.7)
F3	28 (8.9)
F4	41 (13.0)

[a]During the 6 months preceding liver biopsy.
[b]Information missing in 6 patients.

Table 2 displays the characteristics of patients according to cannabis use during the 6 months preceding liver biopsy. Two hundred patients (63.5%) were nonusers, 39 patients (12.4%) were occasional smokers with a median consumption of 4 cannabis cigarettes/month, and 76 patients (24.1%) were daily cannabis users and smoked a median of 82 cannabis cigarettes/month (P < .001). Young age and male gender were significantly more frequent in cannabis users compared with nonusers. Cannabis users were more likely to have a history of ongoing alcohol abuse or of tobacco smoking ≥10 pack-years. Mean BMI and the prevalence of overweight (BMI >27 kg/m^2) were lower in daily and occasional cannabis users. Intravenous drug use was the predominant route of transmission in cannabis users; accordingly, the prevalence of genotype 3 was significantly higher in these patients compared with nonusers (Table 2). In contrast, there were no statistical differences in the characteristics of daily and occasional cannabis smokers, with the exception of a higher prevalence of ongoing alcohol abuse in daily users (28.9%) compared with occasional smokers (5.1%; P < .001) (Table 2).

Relationship Between Steatosis Severity and Cannabis Use

Univariate analysis. Table 3 shows the results of univariate analysis using marked steatosis as the dependent variable. Marked steatosis was significantly more frequent in daily cannabis smokers (32.9%) compared with occasional users (7.7.0%) and nonusers (16.0%; P = .001). Other factors associated with marked steatosis included infection with HCV genotype 3 (39.4%; P < .001), the presence of hyperglycemia or diabetes (47.8%; P = .001), BMI ≥27 kg/m^2 (28.8%; P = .01), ongoing alcohol abuse (35.7%; P = .003), tobacco smoking (>10 cigarettes/day, 24.6%; P = .04), ongoing maintenance treatment with methadone or buprenorphine (39.1%; P = .02), and a high serum HCV RNA load (P = .058). Marked steatosis was also significantly more common in patients with an activity grade ≥A2 (24.9%; P = .002) or a fibrosis stage ≥F2 (28.6%; P = .001). There was no statistical association between marked steatosis and sex, age at liver biopsy, route of transmission, or hyperlipemia.

Logistic regression analysis. By logistic regression analysis (Table 4), marked steatosis was associated

Table 2. Characteristics of Patients According to Cannabis Use

Cannabis use	None (n = 200)	Occasional (n = 39)	Daily (n = 76)	P[a]
Cannabis use (*cigarettes/mo*), median (interquartile range)[b]	0	4 (4–8)	82 (30–150)	<.001
Sex (male), n (%)	124 (62.0)	31 (79.5)	68 (89.5)	<.001
Age at liver biopsy (y), mean (SD)	49.2 (11.0)	37.5 (6.1)	38.1 (5.9)	<.001
Route of transmission, n (%)				
Blood transfusion	86 (43.0)	4 (10.3)	5 (6.6)	
Intravenous drug use	37 (18.5)	32 (82.0)	70 (92.1)	<.001
Nosocomial exposure	29 (14.5)	2 (5.1)	0 (0)	
Unknown	48 (24.0)	1 (2.6)	1 (1.3)	
Tobacco use >10 cigarettes/day, n (%)[b]	50 (25.0)	23 (59.0)	53 (69.7)	<.001
Alcohol intake (*g/day*)[b]				
Median (interquartile range)	1 (0–10)	3 (0–14)	8.5 (0–34)	<.001
≥30, n (%)	18 (9.0)	2 (5.1)	22 (28.9)	<.001
Methadone or buprenorphine use, n (%)	2 (1.0)	6 (15.4)	15 (19.7)	<.001
HCV genotype, n (%)				
1	36 (68.0)	24 (61.5)	37 (48.7)	
2	19 (9.5)	0 (0%)	2 (2.6)	<.001
3	24 (12.0)	11 (28.2)	31 (40.8)	
4/5/6	21 (10.5)	4 (10.3%)	6 (7.9)	
Serum HCV RNA (log_{10} *IU/mL*), mean (SD)[c]	5.75 (0.70)	5.86 (0.76)	6.02 (0.56)	.014
Fasting glycemia >6.1 mmol/L, diabetes, n (%)	19 (9.5)	1 (2.6)	3 (3.9)	.14
Serum lipids				
Triglyceride level >1.7 mmol/L, n (%)	18 (9.0)	4 (10.3)	3 (3.9)	.32
Cholesterol level >6.1 mmol/L, n (%)	16 (8.0)	4 (10.3)	2 (2.6)	.20
BMI (kg/m^2)				
Mean (SD)	25.5 (4.2)	23.0 (2.5)	23.9 (3.9)	.002
>27, n (%)	63 (31.5)	3 (7.7)	14 (18.4)	.002
METAVIR activity grade, n (%)[d]				
A0–A1	79 (39.5)	20 (51.3)	31 (40.8)	
A2	106 (53.0)	19 (48.7)	43 (56.6)	.39
A3	15 (7.5)	0 (0)	2 (2.6)	
METAVIR fibrosis stage, n (%)[d]				
F0	8 (4.0)	3 (7.7)	3 (4.0)	
F1	123 (61.5)	27 (69.2)	39 (51.3)	
F2	26 (13.0)	4 (10.3)	13 (17.1)	.52
F3	19 (9.5)	2 (5.1)	7 (9.2)	
F4	24 (12.0)	3 (7.7)	14 (18.4)	
Steatosis, n (%)[d]				
<5%	108 (54.0)	28 (71.8)	35 (46.0)	
5%–10%	32 (16.0)	5 (12.8)	10 (13.2)	.009
11%–29%	28 (14.0)	3 (7.7)	6 (7.9)	
≥30%	32 (16.0)	3 (7.7)	25 (32.9)	

[a]*P* value of the global test. Significant results of 2 × 2 comparisons are reported in the text.
[b]Assessed during the 6 months preceding liver biopsy.
[c]Information missing in 6 patients.
[d]Grouped for statistics.

with daily use of cannabis (OR, 2.1; 95% CI, 1.01–4.5), whereas occasional use did not significantly affect the rate of marked steatosis. Five additional factors independently predicted marked steatosis: activity grade ≥A2 (OR, 2.1; 95% CI, 1.0–4.3), serum HCV RNA load (OR, 1.7; 95% CI, 1.0–2.9), genotype 3 (OR, 5.4; 95% CI, 2.6–11.3), BMI >27 kg/m^2 (OR, 2.1; 95% CI, 1.0–4.3), and hyperglycemia or diabetes (OR, 5.1; 95% CI, 1.8–15.0).

Impact of daily cannabis use according to alcohol intake and viral genotype. Occasional users of cannabis and nonusers were grouped in further analysis, because occasional cannabis use did not arise as a predictor of steatosis severity by multivariate analysis. Considering the strong impact of genotype 3 on steatosis both in the present and previous studies[5,7–10,12,13] and given the higher frequency of genotype 3 in cannabis smokers (Table 2), we investigated the relationship of steatosis to cannabis use following adjustment of viral genotype (Figure 1). The proportion of patients with marked steatosis was significantly higher in daily cannabis users compared with occasional users and nonusers, irrespective of viral genotype ($P = .03$; Mantel–Haenszel test). In light of the higher prevalence of ongoing alcohol abuse in daily cannabis users, we also evaluated the relationship of

steatosis severity to cannabis smoking according to alcohol drinking habits (Figure 2). Following adjustment of alcohol intake, there was a significant relationship between daily cannabis use and marked steatosis ($P = .008$; Mantel–Haenszel test). In addition, subgroup analysis in nonalcohol abusers (<30 g daily) indicated that the prevalence of marked steatosis was higher in daily cannabis users compared with occasional users and nonusers ($P < .002$).

Discussion

Control of comorbidities is currently considered a desirable goal in patients with CHC, particularly in difficult-to-treat patients. A large majority of studies have repeatedly shown that steatosis is an independent predictor of liver fibrosis progression in these patients.[3–15] In addition, steatosis is an established factor of poor response to antiviral therapy, particularly in patients infected with non-3 genotypes.[1,10,30] In the present study, we investigated the impact of cannabis use on severity of steatosis in 315 consecutive patients with untreated CHC. Using multivariate logistic regression analysis, we show that daily cannabis smoking is an independent predictor of steatosis severity, in contrast to occasional or noncannabis smoking.

Our data support available evidence indicating that steatosis is governed by multiple factors in patients with CHC.[1,30] The strong association between steatosis and genotype 3 has been extensively reported previously, and several lines of evidence indicate that HCV genotype 3 exerts a direct steatogenic effect.[1,2] Indeed, in patients with HCV genotype 3, steatosis is more frequent and

Table 3. Univariate Analysis of Factors Associated With Marked Steatosis

	Marked steatosis, n (%)	P
Cannabis use[a]		
Nonsmokers (n = 200)	32 (16.0)	
Occasional smokers (n = 39)	3 (7.7)	.001
Daily smokers (n = 76)	25 (32.9)	
Alcohol intake[a]		
<30 g/day (n = 273)	45 (16.5)	.003
≥30 g/day (n = 42)	15 (35.7)	
Tobacco consumption[a]		
0–10 cigarettes/day (n = 189)	29 (15.3)	.04
>10 cigarettes/day (n =126)	31 (24.6)	
Methadone or buprenorphine treatment		
Absent (n = 292)	51 (17.5)	.02
Present (n = 23)	9 (39.1)	
Genotype		
Non-3 (n = 249)	34 (13.6)	<.001
3 (n = 66)	26 (39.4)	
BMI (kg/m^2)		
≤27 (n = 235)	37 (15.7)	.01
>27 (n = 80)	23 (28.8)	
Hyperglycemia or diabetes		
Absent (n = 292)	49 (16.8)	<.001
Present (n = 22)	11 (47.8)	
Fibrosis stage		
F0–F1 (n = 203)	28 (13.8)	.001
F2–F3–F4 (n = 112)	32 (28.6)	
Activity grade		
A1 (n = 130)	14 (10.8)	.002
A2–A3 (n = 185)	46 (24.9)	
Serum HCV RNA load[b]		
Steatosis ≥30%, mean (SD)	5.98 (0.58)	.058
Steatosis <30%, mean (SD)	5.79 (0.70)	

[a]Assessed during the 6 months preceding liver biopsy.
[b]Information missing in 6 patients.

Table 4. Stepwise Logistic Regression Analysis of Factors Associated With Marked Steatosis

	OR	95% CI	P
Cannabis use[a]			
None	1		
Occasional	0.5	0.1–1.8	.28
Daily	2.1	1.01–4.5	.05
Activity grade			
<A2	1		
≥A2	2.1	1.0–4.3	.04
Serum HCV RNA (log_{10} IU/mL)	1.7	1.0–2.9	.05
HCV genotype			
Non-3	1		
3	5.4	2.6–11.3	<.001
BMI (kg/m^2)			
≤27	1		
>27	2.1	1.0–4.3	.05
Fasting glycemia >6.1 mmol/L or diabetes			
No	1		
Yes	5.1	1.8–15.0	.003

[a]Assessed during the 6 months preceding biopsy.

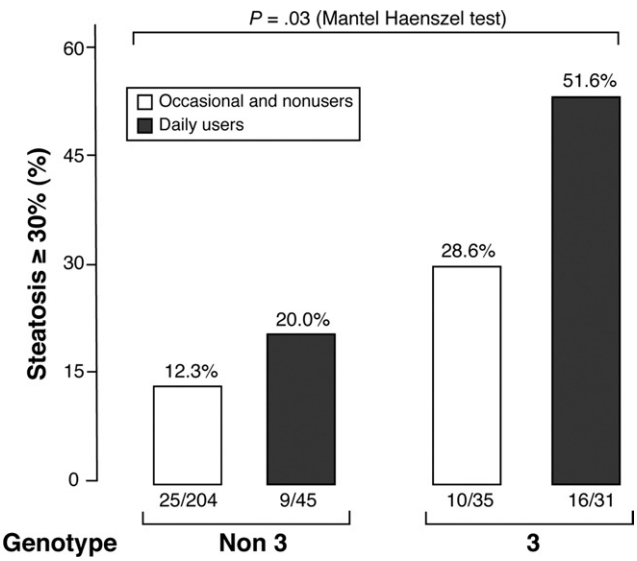

Figure 1. Relationship of marked steatosis to daily cannabis use following adjustment of viral genotype in 315 patients with CHC (*P* value of Mantel–Haenszel test).

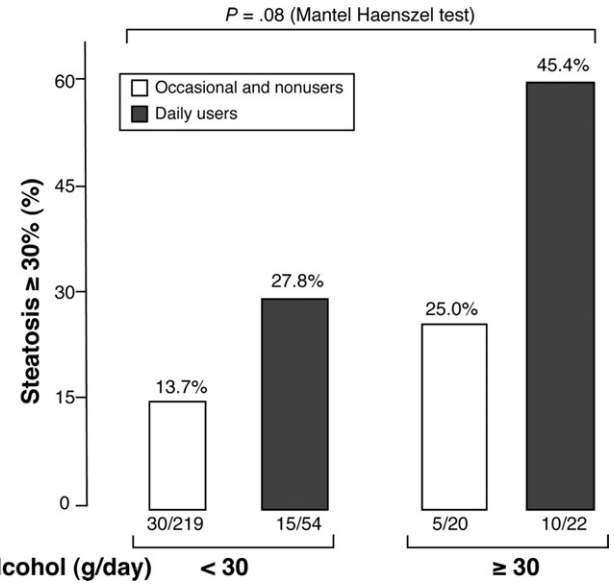

Figure 2. Relationship of marked steatosis to daily cannabis use following adjustment of daily alcohol intake in 315 patients with CHC (*P* value of Mantel–Haenszel test).

more severe,[11,13] shows a positive correlation with serum and liver HCV RNA load,[11,13,31,32] and resolves following successful antiviral therapy.[10,11] In our study, there was a strong relationship between genotype 3 and cannabis use, owing to the predominant intravenous drug use route of transmission in cannabis smokers (Table 2). Nonetheless, the relationship of daily cannabis use to marked steatosis was found irrespective of viral genotype (Figure 1), therefore arguing against a potential confounding effect of viral genotype.

Aside from viral factors, concurrent causes of fatty liver are frequently found in patients with CHC, including overweight or obesity,[7,10,13,14] diabetes mellitus,[7] and insulin resistance,[33] in agreement with the results of our study. "Metabolic" steatosis is predominantly found in patients infected with non–genotype 3 HCV genotypes and shows no or hardly any regression following viral eradication.[10,11] The impact of ongoing alcohol abuse is disputed,[7–9,15] a finding that may be inherent to differences in the referral patterns of patients and to changes in drinking habits following diagnosis of HCV infection. In our cohort, chronic alcoholism was rather infrequent, as shown by a median level of alcohol intake <10 g/day and by a low proportion of individuals with heavy alcohol intake (≥50 g/day: 6.7%). This could explain the lack of significant association between alcohol intake and steatosis in our multivariate analysis. Nonetheless, prevalence of ongoing alcohol abuse was significantly higher in daily cannabis users compared with nonusers, as previously reported.[4,34] To rule out a confounding effect of cannabis, we further explored the impact of daily cannabis use following adjustment of alcohol intake and found a significant relationship between severity of steatosis and daily use of cannabis, irrespective of the level of alcohol intake (Figure 2). Finally, the study design took into consideration other potential confounders of cannabis impact. In this regard, patients with ongoing use of illicit drugs were excluded; in addition, multivariate analysis ruled out an impact of tobacco smoking or maintenance treatment with methadone or buprenorphine.

A growing body of experimental evidence indicates that cannabinoids and their receptors play a crucial role in the pathogenesis of a variety of conditions related to liver diseases, including liver fibrogenesis,[4,35,36] portal hypertension,[37,38] cirrhotic cardiomyopathy,[39] hepatic encephalopathy,[40] ischemia/reperfusion injury,[41] and metabolic steatosis.[25,26] Our present findings strongly support 2 recent studies showing the CB1-dependent steatogenic effects of endocannabinoids in experimental models of nonalcoholic fatty liver disease.[25,26] Interestingly, preliminary results in mice indicate that endogenous activation of CB1 receptors may also contribute to alcohol-induced steatosis.[42] Collectively, these data suggest that a CB1-dependent pathway may be implicated in steatosis of various origins. Whether endocannabinoids are also mediators of genotype 3–dependent virus-induced steatosis remains an open question that deserves further investigation.

We previously reported that daily cannabis use is an independent predictor of fibrosis progression in patients with CHC.[4] Our current findings therefore raise the question as to whether cannabis use may indirectly enhance fibrosis progression via a steatogenic effect. Our former study identified both steatosis and daily cannabis use as independent predictors of fibrosis severity.[4] In agreement with these results, experimental data have shown that distinct pathways are involved in CB1-dependent activation of liver fibrogenesis and steatogenesis. Indeed, we previously showed that liver fibrosis is associated with activation of CB1 binding sites in hepatic myofibroblasts, leading to enhanced proliferation and increased accumulation of liver fibrogenic cells.[36] In contrast, mechanisms underlying metabolic or alcohol-induced steatogenesis may involve enhanced hepatic lipogenesis, following activation of up-regulated CB1 receptors in hepatocytes.[26,42] These data suggest that cannabis may exert independent effects on steatosis and fibrogenesis associated with CHC.

In summary, our results identify daily cannabis smoking as an independent predictor of steatosis severity in patients with CHC. These data further shed light on the potential deleterious effects of daily cannabis use in patients with untreated CHC and support our previous recommendation that patients with CHC should be advised to abstain from daily cannabis use.[4] Finally, our findings support experimental data indicating that CB1 antagonism may open a novel therapeutic strategy for the treatment of nonalcoholic fatty liver disease.[25,26]

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