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Prevalence of hepatic steatosis and associated factors in Iranian patients with chronic hepatitis C

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Abstract

Background: Hepatic steatosis is commonly observed in patients with chronic hepatitis C (CHC). Many studies indicate a relationship between steatosis and fibrosis progression. The aim of this study was to analyze the prevalence of hepatic steatosis and related factors in Iranian CHC patients.

Methods: One hundred and fifteen consecutive patients with CHC were enrolled which were treatment-naïve. The patients were divided into groups with and without steatosis according to the result of liver biopsy (58.3% and 41.7%, respectively). Demographic, histological, biochemical and virological factors were examined and compared in all patients.

Results: In terms of host factors, body mass index (BMI), triglyceride, fasting blood glucose (FBG), necroinflammatory activity and severity in fibrosis of CHC patients with steatosis was significantly higher than the patients without steatosis. Of viral factors, HCV viral load was not significantly altered in patients with steatosis. Moreover, HCV genotypes did not meet such association. Using multivariate regression analysis, parameters of BMI values, FBG level and stage of fibrosis were independently associated with steatosis.

Conclusion: Our data indicate that CHC patients are more susceptible to development of hepatic steatosis. Based on our results, grade of steatosis appears to be associated with hepatic fibrosis progression rate in CHC patients.

Keywords: Chronic hepatitis C, Steatosis, Fibrosis, Necroinflammatory activity.

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Introduction

Hepatitis C virus (HCV) is a major and global public health problem. An estimated 13-170 million people are infected worldwide with one of the six major genotype variants that are specific for different geographical locations. According to the recent studies, 1a is the most common genotype of HCV in Iran (1,2). Approximately 75 to 85% of infected individuals develop a chronic hepatitis C (CHC) infection, which among this 1 to 5% will develop hepatocellular carcinoma (HCC) (1,3).

Fatty liver, or hepatic steatosis (HS), which is an increased fat deposition in the liver, has been recognized as a significant

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cause of cirrhosis (4,5). Hepatic steatosis may be independently associated with obesity, high alcohol consumption, type II diabetes, and hyperlipidemia. Steatosis affects 10-24% of the general population in various countries and in Iranians varies from 2.9% to 7.1% (6-8). Hepatic steatosis is a frequent histological feature in patients with CHC. The overall prevalence of steatosis in patients with CHC infection is between 30 and 70% (9-12). Hepatic steatosis in CHC patients associates with obesity, disorder of fat metabolism, insulin resistance and HCV 3a genotype (13). Furthermore, HS has been shown to be a risk factor for liver disease progression and to interfere with anti-viral treatment (14,15). Viral effects include a decrease of adiponectin levels, and changes to hepatic lipid metabolism that lead to triglyceride accumulation (16).

Many studies have reported a correlation between steatosis and advanced hepatic fibrosis in CHC patients (14,17-19). These Clinical investigations have shown that superimposed steatosis can potentially accelerate hepatic fibrosis in HCV infected patients. The scope of this study was to determine the prevalence of hepatic steatosis and risk factors for its presence in Iranian patients with biopsy-proven chronic hepatitis C.

Methods

One hundred and fifteen consecutive CHC patients were enrolled in the Iran Hepatitis Network and Digestive Disease center, Tehran from May 2012 to March 2014. Liver biopsies were performed on all patients who were proven to have CHC. They had no evidence of co-infection with hepatitis B virus (HBV), hepatitis D virus (HDV), toxic hepatitis, human immunodeficiency virus (HIV) and patients with other liver disease; alcohol consumers (exceeding 20 g per day). The diagnosis of CHC was made based on the following criteria: (1) abnormal serum aminotransferase levels for at least six months; (2) positive test for anti-HCV antibodies; (3) detectable circulating HCV RNA; and (4) liver biopsy consistent with the diagnosis of CHC. None of the patients had undergone previous antiviral treatment. The body mass index (BMI) from all patients was calculated according to the formula of weight (kg) divided by the square of height (m^2) (20). The study was approved by the Local Committee of Ethics and conformed to the ethical guidelines of the Iran Hepatitis Network**.**

Liver histopathology

Liver biopsy was performed on all patients (stained with H&E, Masson's trichrome, and Reticulin) before the consideration of therapy against HCV. The grade of hepatic necroinflammatory changes was classified according to the Knodell histological activity index (HAI, 0-18) score system (21); and the fibrosis stage was set according to the Ishak scoring system (22) on a scale 0–6, corresponding to no fibrosis (0), mild (1-2), moderate (3-4), and severe or cirrhosis (5-6). Fibrosis was considered advanced in cases with staging Ishak ≥3. Hepatic steatosis was graded according to the Brunt classification (23): 0, no steatosis; 1, less than 33% of hepatocytes affected; 2, 33% to 66% of hepatocytes affected; 3, more than 66% of hepatocytes affected. Histopathologic factors were evaluated by an expert pathologist, who was blind in relation to samples.

Laboratory assessment

The presence of anti-HCV was tested using third generation enzyme linked immunosorbent assay (ELISA, ORTHO HCV 3.0 ELISA, Ortho-Clinical Diagnostics, Raritan, NJ) kits. Liver injury biomarkers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), prothrombin time (PT), total bilirubin (TBIL), direct bilirubin (DBIL), as well as cholesterol (CHOL), triglyceride (TG) fasting blood glucose (FBG), uric acid (UA) and hemoglobin (Hb) levels were performed on an autoanalyzer (Selecta, Germany) using com-

mercial kits. RT-PCR assays were performed using a commercially available kit for the quantification of serum HCV-RNA (CobasAmplicor, Roche Molecular Diagnostic System, Branchburg, NJ, USA); they were expressed in IU/ml (1 IU/ml= 3.4 copies/ml). HCV genotyping was also determined using Versant HCV genotype assay (LiPA, Bayer).

Statistical analysis

All results were expressed as mean (±SD), median (range), or number (percentage). The statistical tests used were Student's t-test, Mann-Whitney U test, chi-squared test and Fisher's exact test. Multiple logistic regression model was used to assess association of independent variables with hepatic steatosis. Data were analyzed with the Statistical Program for Social Sciences (SPSS-16, SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

Our study included 115 adult patients diagnosed with CHC. The general feature (characteristics and laboratory data) and histological finding for each patient are summarized in Table 1 and 2, respectively. We divided all patients into two groups, with and without steatosis, based on the findings of the liver biopsy samples. There were 68 patients (58.3%) with steatosis and 47 patients (41.7%) without steatosis.

The mean (SD) age of all patients was 41.67 (12.37) years (range: 15-73 years). They were predominantly males (80%), and mean BMI (SD) was 25.06 (4.61). In the hepatosteatosis group, age (44.01±11.47 vs. 38.29±12.97, p=0.014) and BMI (26.33±4.82 vs. 23.23±3.63, p<0.001) were significantly higher as compared to the group without hepatosteatosis. However, there was no significant difference in gender between both groups (p>0.05). Univariate analyses between groups according to clinical and histological features are provided in Table 3.

Laboratory and virological data

CHC patients with steatosis showed significantly higher levels of total TG, FBG

Table 1. Demographic and clinical characteristics of the Patients (115 patients with chronic hepatitis C)

Parameter	All patients (n=115)	%
Male	92	80
Female	23	20
Age (years)	41.67±12.37 (15-73)	
BMI (kg/m^2), n (%)	25.06+4.61 (12.89-38.19)	
<25	57	49.6
≥25	58	50.4
CHOL (mg/dL)	160.32±40.53 (68-291)	
TG (mg/dL)	130.44±61.70 (30-441)	
FBG (mg/dL)	97.93±34.27 (50-348)	
UA (mg/dL)	5.84±1.54 (2.50-8.80)	
ALT (IU/L)	76.03±54.81 (10-220)	
AST (IU/L)	58.16±42.25 (10-211)	
ALP (IU/L)	218.50±98.34 (69-559)	
PT (second)	13.05±0.93 (11-16)	
TBIL (mg/dL)	1.17±0.73 (0.20-4.60)	
DBIL (mg/dL)	0.31±0.23 (0.10-2.00)	
Hb (g/dL)	14.38±2.32 (6.60-18.70)	
Viral load (IU/ml), Median	6.7×10^5 (200-6×10^6)	
Genotype		
1	87	75.7
3a	16	13.9
No detectable	12	10.4

Data are presented as the number of patients (%of total patient population) or mean±standard deviation (range of values for all patient data). BMI: body mass index, CHOL, cholesterol, TG: triglyceride, FBG: fasting blood glucose, UA: uric acid, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, PT: prothrombin time, TBIL: total bilirubin, DBIL: direct bilirubin, Hb: hemoglobin.

Table 2. Histological characteristics of the patients

Parameter	Patients with CHC (n = 115)	%
HAI score		
0-3	19	16.5
4-8	65	56.5
9-12	26	22.6
13-18	5	4.4
Stage of fibrosis		
0	19	16.5
1-2	51	44.3
3-4	31	27
5-6	14	12.2
Steatosis		
Absent (0)	48	41.7
Mild (<33%)	45	39.1
Moderate (3-66%)	19	16.5
Severe (>66%)	3	2.6

Data are presented as the number of patients (%). CHC: chronic hepatitis C; HAI: histological activity index.

and ALT than those without steatosis ($p<0.05$). However, the AST, ALP, UA, PT, TBIL, DBIL and Hb were not significantly different between both groups ($p>0.05$). There was no significant association between steatosis and HCV viral load (Mann-Whitney p=0.987). All patients took genotyping tests, which determined that 87 (75.7%) patients were genotype 1, 16 (13.9%) were genotype 3a and it was unclassified in 12 (10.4%) patients. Nevertheless, the presence of steatosis showed no statistical differences among groups with different HCV genotypes and patients with or without steatosis (Table 3).

Histological data

The 115 patients admitted into the study

Table 3. Comparison of groups according to laboratory and histopathological features (univariate analysis).

Parameter	Steatosis (+) N=68	Steatosis (-) N=47	P
Male, n (%)	51 (55.4)	41 (44.6)	0.154
Female, n (%)	17 (73.9)	6 (26.1)	
Age (years)	44.01±11.47	38.29±12.97	0.014
BMI (kg/m^2), n (%)	26.33±4.82	23.23±3.63	<0.001
<25	26 (38.2)	31 (66)	0.004
≥25	42 (61.8)	16 (34)	
CHOL (mg/dL)	164.45±41.28	154.27±39.05	0.195
TG (mg/dL)	143.10±68.38	111.86±44.88	0.008
FBG (mg/dL)	104.67±41.22	87.97±15.80	0.010
UA (mg/dL)	6.01±1.57	5.57±1.46	0.182
ALT (IU/L)	84.05±54.50	64.19±53.68	0.029
AST (IU/L)	65.26±41.85	47.67±41.06	0.176
ALP (IU/L)	228.91±104.03	203.34±88.38	0.232
PT (second)	13.07±0.94	13.03±0.91	0.806
TBIL (mg/dL)	1.14±0.71	1.21±0.76	0.637
DBIL (mg/dL)	0.32±0.28	0.29±0.14	0.506
Hb (g/dL)	14.63±2.18	14.02±2.50	0.175
Viral load log (IU/ml)	707500 (range: 200-4.05×10^6)	604500 (rang: 1600-6×10^6)	0.987
HAI score, n (%)			
score < 7	28 (41.2)	29 (61.7)	0.038
score ≥ 7	40 (58.8)	18 (38.3)	
Fibrosis, n (%)			
Stage < 3	33 (48.5)	33 (70.2)	0.020
Stage ≥ 3	35 (51.5)	14 (29.8)	
Genotype, n (%)			
1	52 (76.5)	35 (74.5)	0.343
3a	11 (16.2)	5 (10.6)	
No detectable	5 (7.3)	7 (14.9)	

Data are presented as the number of patients (%) or the mean±standard deviation. BMI: body mass index, CHOL, cholesterol, TG: triglyceride, FBG: fasting blood glucose, UA: uric acid, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, PT: prothrombin time, TBIL: total bilirubin, DBIL: direct bilirubin, Hb: hemoglobin

Table 4. Association of independent variables with hepatic steatosis inlogistic regression model (n=115).

Independent Variable	Odds Ratio	Lower to Upper 95% CI	P
FBG (mg/dL)	1.031	0.998-1.066	0.065
BMI (kg/m^2)	1.227	1.068-1.409	0.004
Fibrosis	4.145	1.295-13.273	0.017

FBG: fasting blood glucose, BMI: body mass index

were subdivided into four groups (Table 2): without steatosis in 48 (41.7%) patients, mild in 45 (39.1%), moderate in 19 (16.5%), and severe in 3 (2.6%). Considering the HAI score, as it is shown in Table 3, there was a significant association between patients with and without steatosis in terms of liver necroinflammation. Histologically, 70 (60.8%) had CHC with stage 0-2 fibrosis, while 31 (27%) and 14 (12.2%) had stage 3-4 and 5-6 fibrosis, respectively. However, significant associations were found between both groups in terms of Ishak biopsy results for the stages of liver fibrosis.

The final multiple logistic regression model for predictors of Brunt steatosis is shown in Table 4. The independent predictors of hepatic steatosis only included FBG (odds ratio [OR]: 1.031, 95% confidence interval [CI]: 0.998–1.066, p=0.065), BMI (OR: 1.227, 95% CI: 1.068–1.409, p=0.004) and fibrosis (OR: 4.145, 95% CI: 1.295–13.273, p=0.017).

Variables associated with hepatic fibrosis: predictors of fibrosis

Forty-nine out of 115 patients (42.6%) suffered from advanced fibrosis (stage>3), while 66 patients (57.4%) indicated a stage of fibrosis 3 or lower. Using the univariate analysis (results not shown), patients with older age (p=0.024), higher AST (p=0.001), higher HAI score (p< 0.001) and the presence of hepatic steatosis (p=0.023) were significantly associated with clinically advanced fibrosis. There were no significant difference between genotypes' frequencies (0.081) and HCV-RNA titer (p=0.425) and concomitantly those with and without significant fibrosis. There was no correlation with gender (p=0.350), BMI (p=0.540), CHOL (p= 0.943), UA (p=0.983), TG (p=0.506), FBG (p=0.238), ALT (p=0.404), ALP (Pp=0.937), PT (p=0.149), TBIL (p=0.257), DIBL (p=0.277) and Hb (p=0.443).

The independent predictors of hepatic fibrosis based on a multivariate analysis, only included AST (OR: 1.016, 95% CI: 1.032–1.047, p=0.048) and HAI score (OR: 6.531, 95% CI: 2.256–18.904, p=0.001).

Discussion

Interactions between chronic hepatitis C virus (HCV) and hepatic steatosis have been strongly noticed (24,25). The purpose of this study was to study the effect of chronic HCV infection on the steatosis among Iranian patients undergoing liver biopsy. Previous studies showed that hepatic steatosis is a common phenomenon in CHC patients (17,26,27). In the patients with biopsy-proven CHC, mainly mild to moderate steatosis was present in 58.3% of the patients. This prevalence is similar to that previously reported in general population (11,28,29). In chronic hepatitis B (CHB) patients, the reported frequency of hepatic steatosis ranges from 27 to 51%, which is lower than that reported for CHC (30,31). In a previous study performed by our group, the prevalence of steatosis in CHB was evaluated. The result showed steatosis was present in 44% of Iranian CHB patients (32).

In the present study, we represent that BMI is significantly associated with steatosis. Furthermore, multivariate analysis confirmed that this association was independent of FBG and hepatic fibrosis. In addition, BMI was also found associated independently with steatosis by other studies (24,33). Initial studies showed that among patients with non-3 genotype, steatosis is associated with BMI. However, this finding did not support by our study (17,19,34).

In this study, there was no link between cholesterol level and the presence of steatosis. Although this figure is similar to that previously reported in the literatures (19,33), but some studies show that steatosis is associated with high cholesterol level (27). However, patients in the steatosis group had significantly higher TG and FBG levels than the non-steatosis group ($p<0.05$).

The results of our study showed that there is a relationship between age and hepatic steatosis and consequently CHC patients with steatosis are older than patients without steatosis. This result is similar to findings by Leandro et al. (14), but contrary to the findings of Hsieh et al. (33) and Hu et al. (35). Concomitantly, in our study, statistical relationship was found between age and the progression of hepatic fibrosis (14,19,33). Our findings showed that older age could be considered as a high risk factor for both hepatic steatosis and fibrosis.

Previous studies have shown that the prevalence of hepatic steatosis in patients with CHC genotype 3a is stronger than patients with other genotypes, and this genotype may be an independent predictor of steatosis (36-38). This suggests that viral factors may lead to altered hepatocyte lipid metabolism. The reason, which is proposed for this finding is that the CHC genotype 3 core protein induces oxidative damages, which in turn leads to progression of steatosis. A study conducted by Kumar et al. showed that treatment of patients with genotype 3 HCV effectively reduces hepatic steatosis (39). In the current study, the genotypes of the virus were determined, but no correlation was observed between HCV genotype and the presence of steatosis. The possible reason for this contradiction is that our sample size was not large enough. A relatively large group of patients is required in order to determine the type of relationship between CHC genotype and steatosis progression. In our study, the severity of steatosis was not correlated with high serum HCV-RNA level. The other studies also support our findings (19,33,40,41). Our findings revealed that virological determinants play a minor role in hepatic steatosis in Iranian CHC patients, and that metabolic factors are important for this condition. Interestingly, studies on hepatitis B virus have shown that the presence of steatosis is associated with lower level of HBV-DNA (42).

In our study, hepatic steatosis was significantly and independently associated with fibrosis. Several studies have demonstrated an association between steatosis and progression of liver fibrosis (17,40). The main reason, which can be expressed for the increased fibrosis in the presence of steatosis, is that ALT levels and necroinflammatory activity are higher in CHC patients with steatosis. It is possible that the liver injury biomarkers lead to progression of fibrosis by increasing the grade of steatosis (17,24,35). The results of this study revealed that the aforementioned factors in patients with steatosis were higher than patients without steatosis. However, some studies do not support the finding (18,33,43).

In the present study, we have observed that the severity of liver fibrosis is independently associated with the presence of hepatic steatosis. However, the assessment of the relationship between steatosis and fibrosis stage, is not a reliable cross sectional-study and to clarify further, analytical studies such as cohort or case-control is needed.

Conclusion

Taken together, the present study revealed that a chronic HCV patient is a major risk factor for hepatic steatosis. Although virological factors play no major role in hepatic steatosis, metabolic factors as well as liver histological findings seem to play important role in determining the severity of steatosis in CHC patients. In our study, steatosis in CHC patients was found to be associated with the severity of fibrosis.

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