Original Article

Insulin Resistance, Steatosis, and Fibrosis in Egyptian Patients with Chronic Hepatitis C Virus Infection

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ABSTRACT

Background/Aim: Both nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus (HCV) infection are common in Egypt, and their coexistence is expected. There is controversy regarding the influence of NAFLD on chronic HCV disease progression. This study evaluates the effect of NAFLD on the severity of chronic hepatitis C (CHC) (necroinflammation and fibrosis) and assesses the relative contribution of insulin resistance syndrome to the occurrence of NAFLD in patients with chronic HCV infection. **Patients and Methods:** Untreated consecutive adults with chronic HCV infection admitted for liver biopsy were included in this study. Before liver biopsy, a questionnaire for risk factors was completed prospectively, and a blood sample was obtained for laboratory analysis. **Results:** Our study included 92 male patients. Their mean ± SD age and aspartate aminotransferase (AST) level were 42 ± 7.7 years (range 20-56) and 68 ± 41.7 U/L (range 16-214), respectively. The mean insulin level and insulin resistance index were 15.6 ± 18.3 mIU/mL (range 5.1-137.4) and 5.9 ± 15.2 (range 0.9-136.2), respectively. Fifty four percent of patients had steatosis and 65% had fibrosis. In multivariate analyses, steatosis was associated with insulin resistance and fibrosis was associated with high AST level, age ≥40 years, and steatosis. **Conclusions:** Steatosis is a histopathologic feature in >50% of patients with chronic HCV infection. Insulin resistance has an important role in the pathogenesis of steatosis, which represents a significant determinant of fibrosis together with high serum AST level and older age.

Key Word: Hepatic fibrosis, hepatic steatosis, insulin resistance, metabolic syndrome, viral hepatitis

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease worldwide.[1] The overall prevalence of chronic HCV infection among world population is 3%.[2] According to an epidemiologic study by a team from Ain-Shams University, Egyptian Ministry of Health (MOH), and World Health Organization (WHO), the prevalence of HCV infection in Upper Egypt was 29.3%.[3] The severity of the disease varies widely from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma. Several factors can be associated with fibrosis progression, including insulin resistance (IR), type 2 diabetes mellitus (DM), dyslipidemia, obesity, and age at infection.[4,5]

The worldwide (including the Middle East) prevalence of non-alcoholic fatty liver disease (NAFLD) ranges from 10-51% depending on the population studied and the methodology used.[6] A study by Strickland and colleagues showed that bright liver by ultrasongraphic examination is present in 35.3% of 271 HCV ribonucleic acid (RNA) negative subjects in Shibin El Kom, Egypt.[7] The most common risk factor for NAFLD was the presence of IR syndrome.[8,9] Hepatic steatosis is also a common histological feature of chronic hepatitis C (CHC). Various factors may be associated with steatosis in patients with chronic HCV infection, including IR, type 2 DM, dyslipidemia, and obesity.[4,5,10,11]

Both NAFLD and HCV infection are common in Egypt, and their coexistence initiates a vicious circle, i.e., they interact with each other.[12] Simple steatosis occurs in 40-70% of patients with chronic HCV infection and nonalcoholic

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steatohepatitis (NASH) occurs in 19%.[13,14] There is some controversy with regard to the influence of NAFLD on fibrosis progression in patients with chronic HCV infection. Several studies in patients with chronic HCV infection suggested an influence of steatosis on the progression of fibrosis.[11,15] However, other studies did not show such an association.[16,17]

Therefore, we decided to conduct a prospective hospital based study of a consecutive group of patients with chronic HCV infection, taking into account confounding factors for both steatosis and fibrosis (multivariate analysis) to investigate the independent factors associated with steatosis and to determine the relationship between steatosis and each of the liver inflammation grade and fibrosis stage.

PATIENTS AND METHODS

Patients
A total of 92 consecutive untreated Egyptian male patients with chronic HCV infection who had undergone liver biopsy in Assiut University Hospital were prospectively included in this study. Patients with clinical or ultrasonographic cirrhosis, hepatocellular carcinoma, any history of alcohol intake, detectable serum HBsAg, and previous administration of interferon-based antiviral therapy were excluded.

Data collection
Every patient completed a questionnaire 1-2 days before liver biopsy. The questionnaire included details on sex, age, occupation, alcohol consumption, smoking, site of residence (rural or urban), education level, any previous surgery or invasive medical procedures, any previous schistosomiasis and/or its parentral therapy, and any other potential source of infection. Measures of height, weight, waist circumference, blood pressure were taken at the same time.

Laboratory evaluation
A fasting venous blood sample was obtained 1-2 days before liver biopsy for analysis of the following parameters: prothrombin time, platelet count, serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and fasting serum levels of glucose, insulin, C-peptide, cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides. The upper limit of normal of ALT and AST levels in our laboratory were 41 U/L.

Definitions and calculations
Chronic HCV infection was defined by detectable serum antibody to HCV (Anti-HCV) and HCV RNA for at least 6 months. Body mass index (BMI) was calculated according to the following equation: BMI = weight (in kilograms)/height^2 (in meters). Overweight was defined as a BMI of 25-29.9 Kg/m^2. Obesity was defined as a BMI $\geq$30 Kg/m^2. Systemic hypertension was defined as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg on at least 2 consecutive measures.

Impaired glucose tolerance was defined as fasting glucose level of 110-125 mg/dL. Diabetes mellitus was defined as fasting glucose level of >126 mg/dL. Dyslipidemia was defined as one or more of the following: cholesterol level of $\geq$200 mg/dL, LDL-cholesterol level of $\geq$130 mg/dL, HDL-cholesterol level of <27 mg/dL, or triglycerides level of $\geq$165 mg/dL. Insulin resistance index (IRI) was calculated according to the following equation: Insulin resistance index (Homeostasis Model [HOMA-IR]) = insulin in μIU/mL − glucose in mmol/L divided by 22.5. An upper limit of normal HOMA-IR is 1.5.[12]

The insulin resistance syndrome (IRS) was defined by the presence of $\geq$3 of the following criteria: entral (abdominal) obesity (waist circumference >102 cm in men or >88 cm in women), hypertriglyceridemia ($\geq$150 mg/dL), low HDL level (<40 mg/dL in men or <50 mg/dL in women), high blood pressure ($\geq$130/85 mm Hg), and high fasting glucose ($\geq$110 mg/dL).[18]

Histopathological evaluation
Liver histopathology was available for all the 92 patients. Histopathologic evaluation was performed without knowledge of the patients' clinical or laboratory data. All liver biopsies were examined by an experienced histopathologist and lesions were graded (necroinflammation) and staged (fibrosis) according to the histological activity index (HAI).[19] Steatosis was defined and graded according to Brunt and colleagues.[20] Liver sections were stained with Hematoxylin and Eosin (H and E) and with special stains, namely reticulin (for reticular fibers) and periodic acid-Schiff (PAS) (for glycogenated nuclei) before being examined.

Statistical analysis
Data were collected in a pre-designed form and entered in a Microsoft *Excel* data sheet before being statistically analyzed using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA) for windows, *version 13*. Data are presented as mean ± SD (maximum-minimum) or number (percentage) as appropriate. Predictive factors for the presence of steatosis and fibrosis were identified using both univariate (Yates corrected chi-square test) and multivariate (stepwise binary logistic regression) analyses to assess the specific effect of each predictor. Factors included in the multivariate analysis were those with a significant level in the univariate analysis. Statistical significance was taken at the 5% level.

246

Volume 17, Number 4
Sha'ban 1432
July 2011

The Saudi Journal of
Gastroenterology

Ethical considerations

The aim of the study was explained to all participants. They were assured that refusing participation in this study will not affect their benefit from all services and treatment. A written consent was obtained from all the participants. Security and confidentiality of all the information obtained was observed. Data was collected by personal interviews with participants by one investigator (AFH). The study was approved by the Assiut Faculty of Medicine Clinical Research Ethical committee, and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

Patients' characteristics

The detailed clinical, laboratory, and pathological characteristics of the 92 patients included in this study are shown in Tables 1a and b. All patients were males, and their mean ± SD age was 42 ± 7.7 years. The mean ± SD serum levels of ALT and AST were 72 ± 39.5 U/L and 68 ± 41.1 U/L, respectively. The mean IRI was 5.9 ± 15.2. Insulin resistance (defined as an IRI >1.5) was detected in 63 (69%) patients.

The potential source of infection was previous surgery or invasive medical procedures in 28 (30%) patients, previous parentral anti-schistosomal therapy in 26 (28%) patients, blood transfusion before 1990 in 13 (14%) patients, and unknown in the remaining 25 (27%) patients probably representing house-hold and/or intra-familial transmission. About half of patients received university education and 75% of them were office workers.

Factors associated with the presence of steatosis

In our study patients, 50 (54%) had steatosis. Steatosis was graded as mild (grade 1) in 23% of patients, moderate (grade 2) in 18%, and marked (grade 3) in 13%. In univariate analysis [Table 2], the presence of steatosis was significantly associated with older age (≥40 years), obesity, central obesity, systemic hypertension, IR, IRS,

Table 1a: Patients' characteristics (n = 92)

Variable	n (%) or Mean ± SD (Range)
Sex (male)	92 (100)
Age	42 ± 7.7 years (20-56)
<40 years: ≥40 years	26 (28): 66 (72)
Residence urban: Rural	52 (57): 40 (43)
Education level	
Illiterate	6 (7)
Primary education	4 (4)
Secondary education	31 (34)
University education	51 (55)
Occupation	
No work	1 (1)
Medical field work	1 (1)
Agricultural field work	7 (8)
Manual work	15 (16)
Office work	68 (74)
Previous surgery or invasive procedures	28 (30)
Previous parenteral antischistosomal therapy	26 (28)
Blood transfusion before 1990	13 (14)
Unknown	25 (27)
Smoking	17 (19)
Body mass index (BMI)	26 ± 3.2 kg/m² (22-37)
Overweight (BMI = 25-30)	44 (48)
Obesity (BMI >30)	12 (13)
Waist circumference	93 ± 11.9 cm (77-132)
Central obesity	19 (21)
Systolic blood pressure	130 ± 13.7 mmHg (100-175)
Diastolic blood pressure	80 ± 10.2 mmHg (50-110)
Systemic hypertension	21 (23)
Insulin resistance syndrome	13 (14)

Results are expressed as number (%) or mean ± SD (minimum-maximum).
BMI = body mass index; n = number; SD = standard deviation

Table 1b: Laboratory and liver biopsy findings in all patients (n = 92)

Variable I	n (%) or Mean ± SD (Range)
Steatosis	50 (54)
Grade 1	21 (23)
Grade 2	17 (18)
Grade 3	12 (13)
Necroinflammation	83 (90)
Grade 1	32 (35)
Grade 2	24 (26)
Grade 3	27 (29)
Fibrosis	60 (65)
Stage 1	20 (22)
Stage 2	16 (17)
Stage 3	13 (14)
Stage 4	11 (12)
ALT level (U/L)	72 ± 39.5 (12-213)
High ALT level >41 U/L	69 (75)
AST level (U/L)	68 ± 41.7 (16-214)
High AST level>41 U/L	63 (69)
Fasting glucose level (mmol/L)	5.9 ± 2.4 (3.6-22.3)
Glucose intolerance	13 (14)
Diabetes mellitus	12 (13)
Fasting insulin level (mIU/ml)	15.6 ± 18.3 (5.1-137.4)
Fasting C-peptide level (ng/ml)	2.7 ± 3.2 (0.8-24.7)
Insulin resistance index	5.9 ± 15.2(0.9-136.2)
High insulin resistance index	63 (69)
Fasting cholesterol level (mg/dL)	154 ± 31.5 (98-242)
Fasting LDL-cholesterol level (mg/dL)	88 ± 27 (34-167)
Fasting HDL-cholesterol level (mg/dL)	40 ± 7.6 (18-61)
Fasting triglycerides level (mg/dL)	135 ± 61.3 (61-392)
Dyslipidemia	21 (23)

Results are expressed as number (%) or mean ± SD (minimum-maximum).
ALT = alanine aminotransferase; AST = aspartate aminotransferase;
N = number; LDL = low density lipoprotein; HDL = high density lipoprotein;
SD = standard deviation

Table 2: Factors associated with the presence of steatosis

Variable	Absent (*n* = 42) (%)	Present (*n* = 50) (%)	P value
Age (years)			
<40	17 (40)	9 (18)	0.016
≥40	25 (60)	41 (82)	
Smoking			
No	35 (83)	40 (80)	0.446
Yes	7 (17)	10 (20)	
Overweight			
No	24 (57)	24 (48)	0.253
Yes	18 (43)	26 (52)	
Obesity			
No	41 (98)	39 (75)	0.005
Yes	1 (2)	11 (15)	
Central obesity			
No	38 (90)	35 (70)	0.014
Yes	4 (10)	15 (30)	
Systemic hypertension			
No	42 (100)	29 (58)	0.000
Yes	0 (0)	21 (42)	
Insulin resistance syndrome			
No	40 (95)	39 (78)	0.017
Yes	2 (5)	11 (22)	
High ALT level			
No	13 (31)	10 (20)	0.167
Yes	29 (69)	40 (80)	
High AST level			
No	13 (31)	16 (32)	0.548
Yes	29 (69)	34 (68)	
Glucose intolerance			
No	40 (95)	39 (78)	0.017
Yes	2 (5)	11 (22)	
Diabetes mellitus			
No	41 (98)	39 (78)	0.005
Yes	1 (2)	11 (22)	
High insulin resistance index			
No	24 (57)	5 (10)	0.000
Yes	18 (43)	45 (90)	
Dyslipidemia			
No	37 (88)	34 (68)	0.019
Yes	5 (12)	16 (32)	
Necroinflammation			
No	6 (14)	3 (6)	0.164
Yes	36 (86)	47 (94)	
Fibrosis			
No	22 (52)	10 (20)	0.001
Yes	20 (48)	40 (80)	

Data are expressed as number (percentage). ALT = alanine aminotransferase; AST = aspartate aminotransferase

Table 3: Factors significantly and independently associated with the presence of steatosis

Variable	Odds ratio	95% confidence interval	P value
High insulin resistance index	16.3	3.4-77.7	0.000

was the significant and independent predictor of hepatic steatosis [Table 3].

Factors associated with the presence of fibrosis

A total of 60 (65%) patients had fibrosis. Fibrosis was classified as stage 1 in 20 (22%) patients, stage 2 in 16 (17%), stage 3 in 13 (14%), and stage 4 (cirrhosis) in 11 (12%). In univariate analysis [Table 4], the presence of fibrosis was significantly associated with older age, systemic hypertension, high levels of ALT and AST, IR, steatosis, and necroinflammation. There was no significant association between the presence of fibrosis and smoking, overweight, obesity, central obesity, glucose intolerance, DM, dyslipidemia, and IRS. However, in multivariate analysis [Table 5], fibrosis was significantly, independently associated with high AST level (OR = 6.4, 95% CI = 1.7-24.1), older age (OR = 5.9, 95% CI = 1.7-20.6), and steatosis (OR = 5.1, 95% CI = 1.5-17).

DISCUSSION

There is some controversy with regard to the influence of NAFLD on CHC severity and progression. Either steatosis potentiates the liver cell injury induced by the HCV or it is indicative of a more extensive viral mediated cytodestructive process.[21] In fact, steatosis can be a marker, but not a cause of disease progression. The frequent association between the presence of steatosis and the grade of necroinflammation may suggest that steatosis is a marker of necroinflammation that, in turn, is a marker of fibrosis progression.[22]

In this study that was conducted in 92 patients with treatment-naïve chronic HCV infection, using multivariate analysis, steatosis was significantly and independently associated with IR, but was not associated with necroinflammation. Although an association between steatosis and necroinflammation in patients with chronic HCV infection was reported by few studies,[23,24] Friedenberg and colleagues found that the grade of steatosis was not associated with the grade of necroinflammation.[25] This finding suggest that steatosis is not a necroinflammation byproduct, but may result from a state of IR.

In addition, using multivariate analysis, we found that fibrosis was associated with older age (≥40 years), high AST level, and steatosis. Several studies reported an association between fibrosis and steatosis in patients with chronic HCV infection,[11,15] while some studies failed to find such

glucose intolerance, DM, dyslipidemia, and fibrosis. There was no significant association between the presence of steatosis and smoking, overweight, high levels of ALT and AST, and necroinflammation. However, in multivariate analysis [Table 3], only insulin resistance (odds ratio (OR) = 16.3 (95% confidence interval (CI) = 3.4-77.7)

Table 4: Factors associated with the presence of fibrosis			
Variable	Absent (n = 32) (%)	Present (n = 60) (%)	P value
Age (year)			0.000
<40	17 (53)	9 (15)	
≥40	15 (47)	51 (85)	
Smoking			0.083
No	29 (91)	46 (77)	
Yes	3 (9)	14 (23)	
Overweight			0.215
No	19 (59)	29 (48)	
Yes	13 (41)	31 (52)	
Obesity			0.137
No	30 (94)	50 (83)	
Yes	2 (6)	10 (17)	
Central obesity			0.483
No	26 (81)	47 (78)	
Yes	6 (19)	13 (22)	
Systemic hypertension			0.004
No	30 (94)	41 (68)	
Yes	2 (6)	19 (32)	
Insulin resistance syndrome			0.266
No	29 (91)	50 (83)	
Yes	3 (9)	10 (17)	
High ALT level			0.001
No	15 (47)	8 (13)	
Yes	17 (53)	52 (87)	
High AST level			0.000
No	18 (56)	11 (18)	
Yes	14 (44)	49 (82)	
Glucose intolerance			0.098
No	30 (94)	49 (82)	
Yes	2 (6)	11 (16)	
Diabetes mellitus			0.137
No	30 (94)	50 (83)	
Yes	2 (6)	10 (17)	
High insulin resistance index			0.020
No	15 (47)	14 (23)	
Yes	17 (53)	46 (77)	
Dyslipidemia			0.174
No	27 (84)	44 (73)	
Yes	5 (16)	16 (27)	
Steatosis			0.001
No	22 (69)	20 (33)	
Yes	10 (31)	40 (67)	
Necro inflammation			0.000
No	9 (28)	0 (0)	
Yes	23 (72)	60 (100)	

Data are expressed as number (percentage). ALT = alanine aminotransferase; AST = aspartate aminotransferase

Table 5: Factors significantly and independently associated with the presence of fibrosis			
	Odds ratio	95% confidence interval	P value
High AST level	6.4	1.7-24.1	0.006
Age ≥40 years	5.9	1.7-20.6	0.005
Steatosis	5.1	1.5-17	0.009

AST = aspartate aminotransferase

an association.[16,17] Steatosis was significantly associated with stellate cell activation in patients with chronic HCV infection.[26] Several studies reported an association between fibrosis and age in patients with chronic HCV infection.[5,27] The role of ageing in fibrosis progression can be related to a higher vulnerability to environmental factors (especially oxidative stress) or reduction in blood flow, mitochondria capacity, or immune capacities.[28]

In the present study, there was an association between fibrosis and necroinflammation. However, using multivariate analysis, there was no such association. Several studies on patients with chronic HCV infection showed an association between fibrosis and necroinflammation and suggested that necroinflammation is implicated in the fibrogenesis process,[29,30] Stellate cells are activated around necroinflammation lesions.[31] Some studies found no significant relationship between necroinflammation grades and fibrosis progression.[32,33] However, necroinflammation is a dynamic process in chronic HCV infection and may fluctuate over time. Indeed, the necroinflammation grade reflects the severity of necrosis and inflammation at a given point.[34]

In univariate analysis, there was an association between fibrosis and smoking. However, using multivariate analysis, there was no association between fibrosis and smoking. Tsochatzis and colleagues reported significantly higher necroinflammatory grade in Egyptian smokers with chronic HCV infection,[35] but the total lifetime smoking history was not associated with necroinflammation, suggesting that smoking may have a rapid and reversible hepatotoxic effect.[36]

A link between steatosis and IR has already been reported in previous studies,[11,37] and was attributed to host metabolic disorders or due to HCV infection. Infection with HCV can induce a state of IR independent of the known major risk factors.[38] In addition, Kawagutchi et al., 2004 reported that HCV infection changes a subset of hepatic molecules regulating glucose metabolism. A possible mechanism is that HCV core-induced suppressor of cytokine signaling (SOCS) 3 promotes proteosomal degradation of IR substrates 1 and 2.[39] Furthermore, Akuta et al., 2009 have shown that amino acid substitutions in the HCV core region are the important predictor of severe insulin resistance in patients without cirrhosis and DM.[40]

HCV infection may directly impair the mechanism of insulin signal transduction.[41] Also, it has been shown that the HCV core protein induces gene expression and activity of sterol regulatory element binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor gamma (PPARgamma), increasing the transcription of genes

involved in hepatic fatty acid synthesis.[42,43] Whether IR is due to host metabolic factors or a direct effect of HCV cannot be determined by this study and warrants further investigation. Treatment of IR may lead to improvement of steatosis and consequently, fibrosis in patients with chronic HCV infection. This suggests that all patients with chronic HCV infection should be screened for IR and its associated metabolic disorders such as type 2 DM, dyslipidemia, systemic hypertension, obesity, and central obesity.[44]

In agreement with this study, a study by Zechini *et al.*, showed a statistically significant positive correlation between baseline aminotransferase values with the hepatitis activity index and fibrosis score.[45] Also, a study by Assy *et al.*, reported a significant positive correlation between AST values and the extent of hepatic fibrosis ($r = 0.64$).[46] Moreover, AST was an independent predictor of significant fibrosis ($F \geq 2$) in chronic HCV patients from Central Saudi Arabia who are infected with Genotype 4, the same genotype that is prevalent in Egypt.[47]

The inclusion of only male patients is one of the strengths of this study to avoid the previously confirmed negative role of menopause on steatosis and the potential benefit of hormone replacement therapy on hepatic fibrosis in HCV infected patients.[48] In addition, all patients were treatment-naïve. This excludes any confounding effect(s) previous treatment on both the laboratory and the histopathological findings. Also, none of our patients had any history of alcohol intake. This represents another strength of this study due to the well-known impact of ethanol consumption on hepatic steatosis,[49,50] a factor that confounds other studies on HCV patients preformed in areas where alcohol consumption is prevalent. A potential limitation of the present study is the lack of data related to serum HCV load, which may not significantly impact the results. Indeed, continuous fluctuation of viral load makes the reliance on a single HCV RNA quantity unsatisfactory. Also, in contrary to the case of HBV infection where viral load predicts outcome, HCV quantity is not an independent predictor of pathology.[48] Another limitation of this study is the deficiency of data related to intake calorie and physical activity as IR can be caused by over-eating or physical inactivity. Unfortunately, this was not included in this study protocol and needs to be considered in any future study addressing this issue.

In conclusion, in this prospective study of patients with naïve chronic HCV infection, hepatic steatosis was associated with and was a significant determinant of hepatic fibrosis, together with older age and high serum AST levels, but is not a marker of disease severity. The main independent predictor of steatosis, in this study was IR. Centers established to providing interferon-based anti-HCV therapy should be joined with a parallel campaign for the prevention, detection, and management of IR-associated metabolic disorders. There should also be programs for increasing public awareness, early detection, and treatment of these problems. This program will have a positive impact not only on decreasing the rate of progression of CHC and increasing HCV response to antiviral therapy, but will also contribute to decreasing the rate of cardiovascular diseases associated with IR syndrome.

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250
Volume 17, Number 4
Sha'ban 1432
July 2011

The Saudi Journal of
Gastroenterology

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