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The association between insulin resistance and hepatic fibrosis in patients with chronic hepatitis C: An observational, multicenter study in Turkey

LIVER

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Original Article

ABSTRACT

Background/Aims: To evaluate the association between insulin resistance and hepatic fibrosis in patients with chronic hepatitis C.

Materials and Methods: A total of 104 chronic hepatitis C patients were included in this non-interventional, open-label, observational, multicenter, cross-sectional study conducted at 20 gastroenterology clinics in Turkey. The primary end point was the correlation between stage of hepatic fibrosis and insulin resistance evaluated via the homeostasis model of assessment-insulin resistance index. Confounders of hepatic fibrosis and insulin resistance were the secondary end points.

Results: The mean age of patients was 52.8 years; 65.4% were female. Type 2 diabetes was present in 6.8% and insulin resistance noted in 38.0% of patients. Further, 45.7% of the patients had mild (A0/A1) and the remaining had moderate/severe (A2/A3) hepatic necroinflammatory activity. Patient distribution according to Metavir fibrosis stage was as follows: F0/F1 (57.0%); F2 (6.5%); F3 (23.7%); and F4 (12.9%). A univariate analysis revealed significant positive correlations between Metavir fibrosis stage and insulin resistance (r=0.297; p=0.007). Logistic regression analysis showed that significant predictors of insulin resistance were high alanine transaminase levels (odds ratio, 0.97; 95% confidence interval, 0.944-0.997) and liver fibrosis stage (odds ratio, 0.114; 95% confidence interval, 0.021-0.607).

Conclusion: Our findings revealed significant associations between insulin resistance and hepatic fibrosis.

Keywords: Chronic hepatitis C, insulin resistance, hepatic fibrosis

INTRODUCTION

Chronic hepatitis C (CHC) infection is a worldwide problem of growing concern, both medically and socio-economically (1,2) owing to its high prevalence and potential for progression to cirrhosis, liver failure, and hepatocellular carcinoma (3). The hepatitis C virus (HCV)

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perturbs glucose metabolism and leads to insulin resistance (IR) and type 2 diabetes in predisposed individuals (4-6).

It has been suggested that HCV infection be viewed as a metabolic liver disease closely related to metabolic syndrome (MS) (7). In light of recent data indicating that diabetes may be associated with increased hepatic fibrosis progression in patients with chronic HCV infection (8), it has become paramount to determine whether HCV infection can predispose to the development of IR before diabetes occurs (9). It is similarly important to determine if hyperglycemia plays a role in the perpetuation and progression of fibrogenesis, rather than in the initiation of the fibrotic process (10).

IR plays an essential role in the pathogenesis of type 2 diabetes and may be associated with low response rates in chronic hepatitis C patients. (11,12). Thus, clarifying the pathogenic mechanisms involved in diabetes in HCV infection will enable better further identification of those patients at high risk of metabolic complications (13).

The association of glucose tolerance and HCV infection has been reported in only two studies of Turkish patients with CHC (14,15). In this study we aimed to evaluate the association between IR and hepatic fibrosis in chronic hepatitis C patients, independent of any comorbid diabetes.

MATERIALS AND METHODS

One hundred and four consecutive CHC patients composed the final analysis population in this non-interventional, open-label, observational, multicenter, cross-sectional study conducted at 20 gastroenterology clinics in Turkey between July 2009 and September 2010. Patients between 18 and 65 years of age not previously treated for CHC were included. The presence of any co-infection, hepatocellular carcinoma, acquired or congenital liver disease, or severe co-morbid diseases were the primary exclusion criteria.

Patients gave their informed consent following a detailed explanation of the study. The studywas performed in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee of the coordinating center.

End points and data collection

The primary end point was the association between stage of hepatic fibrosis and IR evaluated via the homeostasis model assessment-insulin resistance (HOMA-IR) index. The descriptive evaluation of hepatic fibrosis in CHC patients with respect to IR, diabetes mellitus (DM), and metabolic syndrome and a multivariate analysis of risk factors for IR and liver fibrosis were the secondary end points of the present study.

After enrollment, a complete physical examination was performed and available data on patient demographics, past medical history including detailed history of hepatitis C, vital signs, laboratory tests results (haemogram test, liver enzymes, HCV RNA, etc) and liver biopsy findings were recorded at a single common visit.

All tests and liver biopsies were performed at a single central laboratory. All liver biopsies were evaluated by a single pathologist and all specimens, with the exception of one, were assessed using the Metavir system.

IR and metabolic syndrome criteria

The prevalence of IR was estimated using the HOMA-IR, calculated as fasting insulin (mU/mL) × fasting blood glucose (FBG; mmol/L)/22.5. Patients with a HOMA-IR index ≥2.5 were considered to have IR.

Metabolic syndrome was diagnosed on the basis of waist circumference, FBG, systolic blood pressure, diastolic blood pressure, high-density lipoprotein (HDL) cholesterol, and triglyceride measurements.

Liver biopsy

Liver tissue fragments were processed according to standard histology protocols. The Metavir scoring system was used (16). The grade provides an indication of the activity or amount of inflammation and is rated from 0 to 3 (A0: no activity; A1: mild activity; A2: moderate activity; A3: severe activity), while the stage represents the amount of fibrosis, rated from 0 to 4 (F0: no scarring; F1: minimal scarring; F2: scarring has occurred and extends outside the areas in the liver that contains blood vessels; F3: bridging fibrosis is spreading and connecting to other areas that contain fibrosis; and F4: cirrhosis or advanced scarring of the liver).

Statistical analysis

Power calculations showed that our sample size should have at least 92 patients in order to detect a correlation of ≥0.33 between hepatic fibrosis and IR with 90% power, assuming a type II error of 0.10. To account for the likelihood of missing data, a total of 150 patients were planned for enrollment in the study using a 60% lost-to-follow up ratio. However, within the study enrollment period, 106 patients were registered and, after the exclusion of two patients, 104 patients comprised the analysis population.

Statistical analysis was performed using the SPSS computer software version 13.0 (SPSS Inc., Chicago, IL, USA). Analysis of categorical data was performed using Chi-square and Fisher's tests. Correlation analysis was performed using Spearman's and Pearson's tests. Logistic regression analysis of risk factors for IR, hepatic necroinflammatory activity, and hepatic fibrosis was performed, using the HOMA-IR index (categorical; <2.5 vs. ≥2.5), Metavir inflammation grade (categorical; A0/A1 vs. A2/A3), and Metavir fibrosis stage (categorical; F0-F2 vs. F3/F4) as the dependent variables. Data are expressed as mean (SD),

percent, and median (min-max) where appropriate. Statistical significance was set at $p<0.05$.

RESULTS

Patient characteristics, presence of IR, and metabolic syndrome

The mean age for patients in our sample was 52.8 (±10.1) years; females composed 65.4% of the overall population and the mean body mass index (BMI) was 27.8 (4.7) kg/m^2. There were no significant differences between patients with or without IR in terms of demographics and BMI (Table 1).

The mean levels for FBG and insulin were 99.5 (31.7) mg/dL and 10.8 (8.0) µu/dL, respectively. Type 2 diabetes was present in 6.8% (5/74) of the patients, the mean HOMA-IR index was 2.9 (2.6), and IR was noted in 38.0% (35/92) of the patients. Metabolic syndrome was evident in 11.2% of patients (Table 2).

Serological and virological findings

The mean hepatitis C virus-ribonucleic acid (HCV-RNA) quantitative viral load was 5.74 (±1.11) IU/mL. Genotype 1 was the predominant HCV-RNA genotype in our patients (98.9%), and subtype 1b was the most common subtype (65.9% of patients).

Liver biopsy findings

The mean duration between the biopsy and HOMA-IR assessment was 27.9 (99.2) days (median 0 days; n = 99). Metavir findings showed that just under half (45.7%) of the patients had

Table 2. Patient characteristics related to insulin resistance and metabolic syndrome

Blood pressure (BP) (mmHg)[a]		
Systolic	Mean (SD)	126.4 (15.6)
Diastolic	Mean (SD)	79.0 (10.3)
Under BP lowering treatment	n (%)	13 (14.9)
Waist circumference (cm)[b]		
Female	Mean (SD)	97.0 (15.2)
Male	Mean (SD)	97.4 (9.8)
HDL-cholesterol (mg/dL)[c]	Mean (SD)	45.6 (11.9)
Under lipid lowering treatment	n (%)	1 (1.1)
Triglycerides (mg/dL)[d]	Mean (SD)	119.7 (56.8)
Under lipid lowering treatment	n (%)	1 (1.1)
Fasting blood glucose (mg/dL)[a]	Mean (SD)	99.5 (31.7)
Under blood glucose lowering treatment	n (%)	4 (4.1)
Insulin (µu/dL)[e]	Mean (SD)	10.8 (8.0)
HOMA-IR index	Mean (SD)	2.9 (2.6)
Insulin resistance (HOMA-IR ≥2.5) [e]	n (%)	35 (38.0)
Type 2 diabetes mellitus diagnosis[f]	n (%)	5 (6.8)
Under antidiabetic treatment	n (%)	3 (4.1)
Metabolic syndrome-overall diagnosis[g]	n (%)	23 (11.2)

HOMA-IR: homeostasis model assessment-insulin resistance
Missing data for a17, b21, c42, d36, e12, f30, g3 patients

Table 1. Patient demographics and laboratory findings

			Insulin resistance*		
		Total (n=104)	**Absent (n=57)**	**Present (n=35)**	**p**
Age (years)	Mean (SD)	52.8 (10.1)	52.1 (10.7)	54.5 (9.4)	0.248
Female sex	n (%)	68 (65.4)	39 (63.9)	22 (36.1)	0.584
BMI (kg/m^2)	Mean (SD)	27.8 (4.7)	27.6 (5.2)	27.9 (3.9)	0.489
Hematological findings		Mean (SD)		Missing n	
Hemoglobin (g/dL)		13.9 (1.7)		2	
Hematocrit (%)		41.0 (4.8)		3	
Thrombocyte (10^3/uL)		245.2 (136.9)		2	
Prothrombin time (sec)		11.9 (4.2)		11	
Biochemical findings		Mean (SD)		Missing n	
Albumin (g/dL)		4.3 (0.5)		9	
Total protein (g/dL)		7.6 (0.7)		15	
Total bilirubin (mg/dL)		0.9 (0.5)		10	
ALT (U/L)		60.6 (46.6)		7	
AST (U/L)		54.8 (59.4)		6	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; IR: insulin resistance (homeostasis model assessment-insulin resistance index ≥2.5)
*Missing data for 12 patients

Table 3. Patient characteristics according to fibrosis stages

	Metavir fibrosis stages										
	F0		F1		F2		F3		F4		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p value[1]
Age (years)	16	49.1 (11.8)	37	49.6 (11.2)	6	59.2 (1.6)	22	58.3 (5.4)*	12	57.4 (4.2)	0.003
BMI (kg/m^2)	16	26.1 (5.1)	37	28.1 (5.5)	6	29.6 (4.1)	22	28.1 (3.7)	12	27.1 (4.4)	0.480
HCV-RNA (Log)	15	5.6 (1.1)	30	5.6 (1.3)	6	6.2 (0.8)	17	6.0 (0.9)	10	5.9 (1.0)	0.713
HOMA-IR	14	1.3 (0.7)	32	2.8 (2.9)	4	3.3 (2.9)	21	3.8 (3.3)	11	2.7 (1.1)	0.048
ALT (U/L)	15	41.2 (46.4)	36	57.9 (43.4)	6	71.7 (66.1)	19	65.3 (36.9)$^+$	11	91.7 (61.7)$^+$	0.001
AST (U/L)	16	28.5 (7.7)	37	43.5 (22.2)$^+$	6	104.8 (135.1)	19	53.9 (23.8)$^{++}$	10	129.2 (120.6)*,$^{++}$	<0.001
Fasting blood glucose (mg/dL)	14	89.3 (10.6)	32	98.0 (34.6)	4	99.0 (7.7)	21	102.6 (19.6)	11	111.1 (63.5)	0.247
HDL-cholesterol (mg/dL)	8	50.3 (8.2)	22	48.5 (13.4)	5	39.5 (4.6)	12	40.9 (11.7)	6	45.9 (14.9)	0.231
Triglyceride (mg/dL)	10	112.5 (83.4)	23	113.5 (54.1)	5	117.8 (39.3)	14	127.2 (57.6)	7	92.1 (22.2)	0.637

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; HCV-RNA: hepatitis C virus ribonucleic acid; HDL: high density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance

[1]Kruskal-Wallis test

*p<0.01 compared to F1 (Bonferroni correction, significance level set at 0.005)

$^+$p<0.01 and $^{++}$p<0.001 compared to F0 (Bonferroni correction, significance level set at 0.005)

mild hepatic activity and the remaining had moderate/severe hepatic activity. The fibrosis distribution was as follows: F0/F1, 57.0%; F2, 6.5%; F3, 23.7%; and F4, 12.9%.

Characteristics of patients according to Metavir fibrosis stage

Patients with stage F3 hepatic fibrosis were determined to be significantly older than patients with stage F0 fibrosis (58.3 (±5.4) years for F3 vs. 49.1 (±11.8) for F0, p<0.01). There were no significant differences in BMI, HCV-RNA, FBG, HDL-cholesterol, and triglyceride levels with respect to fibrosis stage (Table 3).

HOMA-IR values were significantly higher in patients with F4 than F0 fibrosis (2.7 (±1.1) vs. 1.3 (±0.7), p=0.004) (Table 4, Figure 1).

Relationships between patient characteristics and Metavir scores and HOMA-IR

There were significant correlations between Metavir inflammation grade and patient characteristics (age [n=94 r=0.294 p=0.004], BMI [n=94 r=0.240 p=0.020], ALT level [n=88 r=0.299 p=0.005], aspartate transaminase [AST] level [n=89 r=0.401 p=<0.001], and HCV-RNA [n=79 r=0.226 p=0.045]). Fibrosis stage was significantly correlated with age (n=93 r=0.416 p=<0.001), platelet count (n=91 r=-0.284 p=0.006), prothrombin time (n=82 r=0.346 p=0.001), albumin (n=86 r=-0.218 p=0.044), ALT (n=87 r=0.333 p=0.002), AST (n=88 r=0.431 p=<0.001), and insulin levels (n=82 r=0.238 p=0.031).

Significant positive correlations between hepatic inflammation and fibrosis (n=93; r=0.559; p<0.001) and between IR and Metavir fibrosis (n=82; r=0.297; p=0.007) were observed. However, the correlation between Metavir inflammation and IR was not significant (n=83; r=0.206; p=0.062).

Table 4. Homeostasis model assessment-insulin resistance levels with respect to fibrosis stages

		HOMA-IR	
Fibrosis stage	n	Mean (SD)	p value[1]
F0	14	1.3 (0.7)	vs. F1: 0.026
			vs. F2: 0.089
			vs. F3: 0.021
			vs. F4: 0.0042
F1	32	2.8 (2.9)	vs. F2: 0.687
			vs. F3: 0.393
			vs. F4: 0.242
F2	4	3.3 (2.9)	vs. F3: 0.882
			vs. F4: 0.794
F3	21	3.8 (3.3)	vs. F4: 0.968
F4	11	2.7 (1.1)*	

HOMA-IR: homeostasis model assessment-insulin resistance

[1]p=0.048 (Kruskal Wallis test)

[2]Bonferroni correction, significance level set at p<0.005

HOMA-IR values also showed significant correlation with the presence of metabolic syndrome (n=80 r=0.298 p=0.007).

Logistic regression analysis of risk factors for insulin resistance, hepatic necroinflammatory activity, and fibrosis

Logistic regression analysis with HOMA-IR index, inflammation grade, and fibrosis stage as the dependent variables revealed that high ALT levels (odds ratio [OR]: 0.97; 95% confidence interval [CI]: 0.944-0.997) and hepatic fibrosis stages (OR: 0.114; 95% CI: 0.021-0.607) were significant predictors of IR (Table 5).

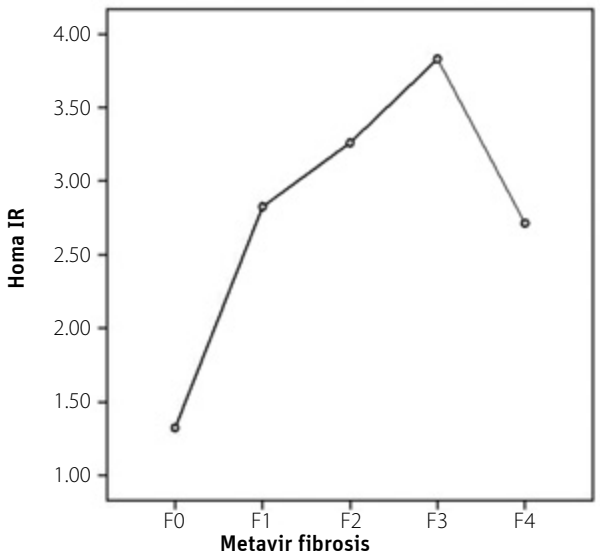

Figure 1. A plot diagram showing homeostasis model assessment-insulin resistance index values at each fibrosis stage.

DISCUSSION

In this study, we sought to clarify the relationship between IR and hepatic fibrosis. IR was evident in 38.0% of patients and type 2 diabetes in 6.8%. A significant relationship between hepatic fibrosis and HOMA-IR was determined from both univariate correlation and logistic regression analyses.

Emphasizing that HCV infection can predispose to the development of IR before diabetes occurs (9), our findings related to IR, type 2 DM, and metabolic syndrome are in agreement with previous studies (6,17). Likewise, in a recent study conducted with Turkish CHC patients, IR was reported in 55% of patients with a mean BMI of 26.8 kg/m^2, and there was a significant association of IR with hepatic fibrosis and steatosis (14).

The identification of type 2 DM in 6.8% of our patients, despite a mean BMI of 27.6 kg/m^2, and the homogeneity of demographics (including BMI values) in our patients, regardless of IR status, support HCV infection as an independent risk factor for diabetes development (18). Our results also support previous findings that IR is associated with both host (visceral obesity) and viral factors in CHC patients (19).

Moreover, the identification of IR in 38% of our patients, while type 2 DM was found only in 6.8%, is worth noting, given that IR has been shown as the best predictor for the development of diabetes, preceding the onset of diabetes by 10 to 20 years. Our findings are also notable due to the association between diabetes and increased fibrosis progression in patients with chronic HCV infection (20) and the likelihood of HCV infection to predispose to the development of IR before diabetes occurs (21).

Our results are compatible with past studies demonstrating a relationship between insulin sensitivity and fibrosis score in non-cirrhotic, non-diabetic patients with chronic HCV (22-25).

Table 5. Logistic regression analysis of risk factors for insulin resistance, hepatic necroinflammatory activity, and fibrosis

HOMA-IR (<2.5/≥2.5)	**Odds ratio**	**p**	**95% CI**
Age	0.980	0.666	0.894-1.074
Sex (male vs. female)	2.087	0.345	0.454-9.594
BMI	1.149	0.116	0.966-1.367
Platelet count	0.995	0.191	0.987-1.003
ALT	0.970	0.031	0.944-0.997
HCV-RNA (<6×105 vs. ≥6×10^5)	0.227	0.110	0.037-1.398
Metavir inflammation grade (A0-A1 vs. A2/A3)	0.432	0.341	0.077-2.430
Metavir fibrosis stage (F0-F2 vs. F3/F4)	0.114	0.011	0.021-0.607
Metavir inflammation grade (A0/A1 vs. A2/A3)			
Age	0.927	0.078	0.851-1.009
Sex (male vs. female)	1.980	0.355	0.466-8.415
BMI	0.938	0.340	0.822-1.070
ALT	0.987	0.079	0.972-1.002
HCV-RNA (<6×105 vs. ≥6×10^5)	2.614	0.182	0.638-10.710
HOMA-IR (<2.5 vs. ≥2.5)	0.573	0.513	0.108-3.030
Metavir fibrosis stage (F0-F2 vs. F3/F4)	10.124	0.009	1.784-57.455
Metavir fibrosis stage (F0-F2 vs. F3/F4)			
Age	0.916	0.100	0.825-1.017
Sex (male vs. female)	1.766	0.489	0.352-8.858
BMI	1.097	0.300	0.921-1.308
Platelet count	1.000	0.962	0.995-1.005
ALT	0.990	0.190	0.974-1.005
HCV-RNA (<6×105 vs. ≥6×10^5)	1.261	0.769	0.267-5.944
HOMA-IR (<2.5 vs. ≥2.5)	0.157	0.021	0.032-0.759
Metavir inflammation grade (A0-A1 vs. A2/A3)	9.241	0.012	1.624-52.583

ALT: alanine transaminase; BMI: body mass index; CI: confidence interval; HCV-RNA: hepatitis C virus ribonucleic acid; HOMA-IR: homeostasis model assessment-insulin resistance; OR: odds ratio.

Possibly linked to a mild degree of underlying fibrosis, neither necroinflammatory activity nor fibrosis scores were significantly correlated with the presence of metabolic syndrome in our patients.

The elucidation of the relationship between HCV and IR is of great clinical relevance, because the latter promotes liver fibrosis (26), whereas the relationship between liver fibrosis and IR is difficult to assess (6). Since advanced stages of fibrosis were reported to be independently associated with IR (after excluding cirrhotic patients), and HOMA-IR (but not the C-peptide to insulin ratio) has been reported to increase progressively and sig-

nificantly with fibrosis stage. Thus, it has been suggested that the real connection between IR and HCV infection is initiated in the early stages of liver disease (6). Other studies have shown fibrosis to be associated with liver necroinflammation (21) and steatosis but not IR in a multivariate analysis (27). Consistent with those findings, in our study population, fibrosis was independently related to necroinflammatory activity, and significant associations were determined for IR and fibrosis and for BMI and necroinflammatory activity. These findings emphasize the role of increased insulin levels in the association between increasing BMI and fibrosis (22). In addition, the significant correlation of necroinflammatory activity scores with BMI in our study is consistent with the idea that host metabolic factors associated with an increased BMI may also account for some of the variability in the rate of fibrosis progression in patients with chronic HCV (22).

Our significant correlations between insulin level and liver fibrosis and between BMI and necroinflammatory activity (predicted by hepatic fibrosis) suggest that increased insulin levels may be a factor responsible for the association between BMI and fibrosis in overweight patients with HCV (22). Hence, a reduction in excess body weight and regular physical exercise may have important implications for the management of patients who do not respond to, or are unable to tolerate, antiviral therapy, as strategies to minimize liver injury and decrease fibrosis progression are crucial (22).

The major limitation of the present study is a relatively limited sample size. Because of this, our study may not be generalizable to the general Turkish population regarding IR and hepatic fibrosis. While it is not possible to run the risk of ethical issues concerning liver biopsy, such a comparison would more clearly elucidate the independent effect of hepatitis C infection on the interaction between IR and liver fibrosis. Another limitation is the lack of a complete data set, which causes uncertainty concerning the clinical relevance of our findings. Future studies should focus on the effect of these pathologies, IR and DM on treatment outcomes.

In conclusion, we found that IR was present in more than one-third of Turkish HCV patients and that the HOMA-IR index correlates with liver fibrosis. These findings are important in light of recent reports that diabetes may be associated with increased hepatic fibrosis progression in patients with chronic HCV infection (8). If IR can be identified and treated, this may be helpful to preserve liver function in HCV patients.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.D., S.E.; Design - A.D., S.E.; Supervision - A.D.; Resource - A.D.; Materials - A.D.; Data Collection&/or Processing - A.D., S.K., Y.Ü., S.H., İ.T., M.AKD., H.D., F.G., İ.D., A.D, M.AKA., H.Y., O.C.D., F.Ö., S.A.; Analysis&/or Interpretation - S.K.; Literature Search - X.S.E.; Writing - S.K., S.E.; Critical Reviews - A.D., S.K., S.E.

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