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BRIEF ARTICLES

Clinical expression of insulin resistance in hepatitis C and B virus-related chronic hepatitis: Differences and similarities

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Abstract

AIM: To investigate the prevalence of the clinical parameters of insulin resistance and diabetes in patients affected by chronic hepatitis C (CHC) or chronic hepatitis B (CHB).

METHODS: We retrospectively evaluated 852 consecutive patients (726 CHC and 126 CHB) who had undergone liver biopsy. We recorded age, sex, ALT, type 2 diabetes and/or metabolic syndrome (MS), body mass index (BMI), and apparent disease duration (ADD).

RESULTS: Age, ADD, BMI, prevalence of MS and diabetes in patients with mild/moderate liver fibrosis were significantly higher in CHC. However, the degree of steatosis and liver fibrosis evaluated in liver biopsies did not differ between CHC and CHB patients. At multivariate analysis, age, sex, BMI, ALT and diabetes were independent risk factors for liver fibrosis in CHC, whereas only age was related to liver fibrosis in CHB. We also evaluated the association between significant steatosis (> 30%) and age, sex, BMI, diabetes, MS and liver fibrosis. Diabetes, BMI and liver fibrosis were associated with steatosis > 30% in CHC, whereas only age and BMI were related to steatosis in CHB.

CONCLUSION: These data may indicate that hepatitis C virus infection is a risk factor for insulin resistance.

Key words: Insulin resistance; Diabetes; Metabolic syndrome; Hepatitis C virus; Hepatitis B virus

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INTRODUCTION

Recent years have seen numerous studies devoted to the relationship of such clinical variables as age, gender and body mass index (BMI) with metabolic alterations involving the liver in patients affected by hepatitis C virus (HCV)-related chronic hepatitis. Attention has focused on the metabolic syndrome (MS), diabetes[1-5], steatosis/steatohepatitis[6-10] and associations between these conditions[11-15]. It remains to be established whether the relationship between HCV and deranged cellular metabolic pathways is casual or whether it results from a direct effect exerted by HCV.

In an attempt to shed light on this issue, we examined the prevalence of these phenomena in chronic hepatitis C (CHC) and in chronic hepatitis B (CHB) in order to distinguish between alterations due to presence of an advanced liver disease and those due to HCV[16-18].

We have investigated the prevalence of MS and/or diabetes and their effect on liver fibrosis and/or steatosis/steatohepatitis in a large cohort of patients affected by HCV- or hepatitis B virus (HBV)-related chronic hepatitis. Our aim was to look for differences and simi-

larities between the two types of viral hepatitis and to confirm or refute the hypothesis of metabolic cofactors in HCV-related liver disease(s).

MATERIALS AND METHODS

We retrospectively evaluated 852 consecutive patients (726 CHC and 126 CHB) who underwent clinical evaluation and liver biopsy for HBV- or HCV-related hypertransaminasemia in the Internal Medicine and Hepatology Unit at the Second University of Naples from April 1999 to November 2005. The inclusion criterion was HBsAg-positive or HCV-Ab-positive chronic hepatitis. The exclusion criteria were: patients with a recent (< 6 mo) history of high alcohol consumption (> 30 g/d in females, > 40 g/d in males) or a history of intravenous drug abuse, clinical and/or ultrasound evidence of cirrhosis, an human immunodeficiency virus (HIV)-positive test and HBV/HCV co-infection. In addition to a complete blood count, each patient underwent tests for: serum markers for hepatitis B infection determined by radioimmunoassay (Abbott Laboratories, North Chicago, IL, USA), antibodies to HCV assayed by a second-generation enzyme-linked immunoassay (ELISA; Ortho Diagnostic Systems, Raritan, NJ, USA), the presence of type 2 diabetes according to American Diabetes Association criteria[19] by assessing fasting serum glucose and/or the oral glucose tolerance test (OGTT) on two different occasions, and for the presence of MS based on NCEP-ATP Ⅲ criteria[20]. BMI (kg/m^2) was recorded and the apparent disease duration [(ADD) in years] was determined by considering the exposure to major risk factors as the start of infection. Each patient underwent an echo-assisted liver biopsy performed with a 17G Menghini modified needle (Surecut, TSK Laboratory, Japan) through an intercostal entry. The liver specimens were formalin-fixed, embedded in paraffin and evaluated with the Ishak scoring system for viral liver disease[21] by skilled liver pathologists, who also evaluated the presence of liver steatosis and steato-hepatitis according to Brunt *et al*[22].

Statistical analysis of data was performed using the SPSS® 13.0 software for Windows®. Non-parametric tests (χ^2 or Fisher's exact), Spearman's rho test, ANOVA, linear and logistic regression tests were performed where appropriate.

RESULTS

As shown in Table 1, HCV-positive patients had a significantly longer ADD ($P < 0.005$), a significantly older age ($P < 0.0001$) and a significantly higher BMI ($P < 0.005$) *vs* HBV-positive subjects. The MS was present in 76 out of 726 HCV patients (10.46%) and in only 2 of the 126 HBV subjects ($P < 0.005$). The prevalence of diabetes did not differ significantly between the two groups, but it was significantly higher in HCV subjects when comparing only patients with mild fibrosis (Ishak S0-S3) at liver biopsy ($P < 0.005$) (Figure 1). The prevalence of diabetes in mild fibrosis patients did not differ between the two groups when patients were stratified by age. No differences were found at liver biopsy as regards grading and staging, neither was there a difference in the prevalence of patients with higher degrees of steatosis.

Table 1 Epidemiological and histological data of the two groups studied

	HCV	HBV	*P*
Epidemiological data			
Number of patients (M/F)	726 (426/300)	126 (83/43)	NS
DD (yr)	25.78 ± 14.22	21.4 ± 11.91	< 0.005
Age (yr)	53.88 ± 13.20	45.68 ± 14.40	< 0.0001
BMI (kg/m^2)	26.74 ± 4.25	25.43 ± 3.43	< 0.005
Metabolic syndrome	76 pt (10.46%)	2 pt (1.72%)	< 0.005
Liver Biopsy (Ishak Score)			
Grading	11.25 ± 3.50	6.61 ± 3.36	NS
Staging	2.66 ± 1.99	2.44 ± 1.57	NS
Steatosis > 30%	98 pt (13.49%)	14 pt (12.06%)	NS

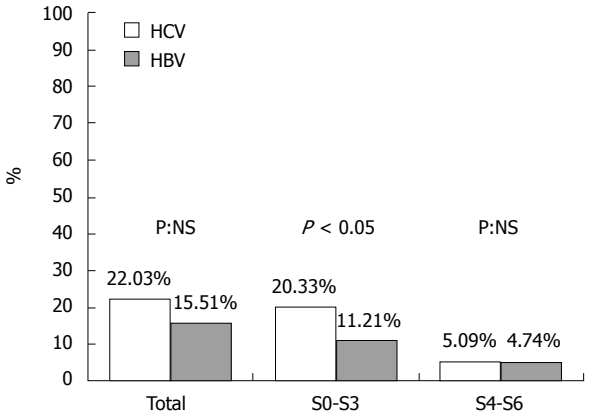

Figure 1 Diabetes prevalence divided by fibrosis score (Ishak).

To evaluate whether age, sex, BMI, ALT, diabetes, MS and steatosis were independent risk factors for liver fibrosis we carried out a univariate and a multivariate analysis in the two groups of patients. At univariate analysis, all the variables tested were significantly related to higher degrees of fibrosis in HCV patients, whereas only age was correlated to liver fibrosis in HBV patients (Table 2). The results of the multivariate analysis confirmed these findings, namely age, sex, BMI, ALT and diabetes were independent risk factors for fibrosis in HCV subjects, whereas only age was related to fibrosis in HBV patients (Table 3).

We next carried out statistical analyses to evaluate whether age, sex, BMI, ALT or diabetes were related to steatosis, which is a well known negative predictor of both disease outcome and response to therapy in HCV patients[23-26]. None of these parameters were significantly associated with degree of steatosis. However, when we did the same analysis considering only patients with steatosis > 30%, a higher BMI, diabetes and fibrosis were correlated with severe steatosis in CHC patients (Tables 4 and 5).

DISCUSSION

In our cohort study, the prevalence of MS and diabetes was significantly higher in patients with HCV-related chronic hepatitis than in patients with HBV-related

Table 2 Univariate analysis (Spearman test) between liver fibrosis (Ishak staging on liver biopsy) and anthropometric, clinical and metabolic characteristics in the two groups of patients

	HCV				HBV			
	Linearity coefficient	Standard error	*P*	*t*	Linearity coefficient	Standard error	*P*	*t*
Age (yr)	0.332	0.046	< 0.0001	7.377	0.532	0.071	< 0.0001	5.689
Sex	0.284	0.046	< 0.05	3.764	0.132	0.108	NS	1.209
BMI	0.243	0.050	< 0.0001	4.633	0.142	0.113	NS	1.162
ALT	0.227	0.045	< 0.0001	4.833	0.157	0.082	NS	1.435
Diabetes	0.211	0.050	< 0.0001	4.532	0.014	0.123	NS	0.103
Metabolic syndrome	0.108	0.039	< 0.05	2.278	0.015	0.011	NS	0.112
Steatosis	0.095	0.045	< 0.05	2.006	0.068	0.187	NS	0.283

Table 3 Multivariate analysis (multiple regression) of the correlation between liver fibrosis (Ishak staging on liver biopsy) and anthropometric, clinical and metabolic characteristics in the two groups of patients

	HCV			HBV		
	Linearity coefficient	Standard error	*P*	Linearity coefficient	Standard error	*P*
Age (yr)	0.0469	0.0068	< 0.0001	0.0561	6.0142	0.0001
Sex	0.0362	0.1794	< 0.05	-	-	-
BMI	0.0417	0.0208	< 0.05	-	-	-
ALT	0.0038	0.0010	< 0.0001	-	-	-
Diabetes	0.4742	0.2172	< 0.05	-	-	-
Metabolic syndrome	0.2830	0.2846	NS	-	-	-
Steatosis	0.0731	0.2326	NS	-	-	-

Table 4 Univariate analysis of the correlation between the presence of higher degrees of steatosis (> 30%) assessed on liver biopsy and anthropometric, clinical and metabolic characteristics in the two groups of patients

	HCV			HBV		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (yr)	1.747	0.888-3.430	NS	4.432	1.056-18.310	< 0.05
Sex	0.845	0.551-1.294	NS	0.549	0.191-1.575	NS
BMI (> 30)	2.510	1.593-3.954	< 0.001	10.435	2.166-38.338	< 0.005
Diabetes	1.894	1.193-3.007	< 0.05	0.913	0.213-4.017	NS
Metabolic syndrome	0.968	0.486-1.931	NS	4.180	0.531-3.367	NS
Fibrosis (staging)	4.700	2.750-8.034	< 0.001	0.459	0.073-2.981	NS

Table 5 Multivariate analysis (logistic regression) of the correlation between the presence of significant steatosis (> 30%) assessed on liver biopsy and anthropometric, clinical and metabolic characteristics in the two groups of patients

	HCV			HBV		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (yr)	-	-	-	1.214	1.085-1.359	< 0.001
BMI (> 30)	2.216	1.186-4.143	< 0.05	1.049	1.007-1.094	< 0.05
Diabetes	2.684	1.444-4.987	< 0.005	-	-	-
Fibrosis (Staging)	4.700	2.750-8.034	< 0.001	-	-	-

chronic liver disease. This suggests that insulin resistance, which is the mechanism underlying MS, might at least in part be related to HCV infection. Insulin resistance is identified with the euglycemic clamp technique[27] or with the homeostasis model assessment insulin resistance (HOMA-IR) test[28]. Neither euglycemic clamp nor the HOMA-IR test was performed in our patients. However, we used the most practical worldwide accepted definition of MS according to the ATP-Ⅲ NCEP clinical criteria[20]. Moreover, unlike other authors[16,29-32], we were able to measure, using these criteria, central obesity which is considered the fundamental condition for a clinical diagnosis of MS[33]. The association of diabetes and severe chronic liver disease is widely recognized[4,16,32,34], therefore the effect of severe liver disease on diabetes onset should be considered when comparing groups of patients affected by chronic liver disease. In our study, we were able to rule out that diabetes was related to the altered hepatic glycaemic homeostasis due to severe liver disease (i.e. cirrhosis). In fact, whereas the total prevalence of diabetes did not differ between HCV and HBV patients, the prevalence of diabetes among patients with mild chronic hepatitis was significantly higher in HCV subjects.

This finding confirms reports of a higher prevalence of diabetes in HCV patients[14,29,34], and, *vice versa*, a report of a higher prevalence of HCV in diabetic patients[30]. Moreover, our data are in line with recent reports of a higher prevalence of diabetes in HCV patients compared with other liver diseases (e.g. HBV infection)[1]. In particular, Jan *et al*[17] reported a significantly higher prevalence of MS in HCV patients *vs* HBV patients, and an inverse ratio between HBV infection and clinical expression of MS in a population-based study carried out in Taiwan.

The association between diabetes and HCV-related chronic hepatitis was reported to influence the clinical outcome of liver disease[35-37]. Moreover, diabetes and/or obesity were found to be cofactors of liver disease in that they affect liver fibrosis progress and response to antiviral therapy[23,24,37-39]. Here we report that, besides ALT, sex and age, also diabetes and BMI were independent risk factors for more severe liver fibrosis in HCV-positive patients, whereas they were not associated with the severity of liver fibrosis in HBV subjects. This finding supports the idea that obesity and diabetes might represent clinical epiphenomena of the pathogenesis of HCV infection. In line with this hypothesis, using an animal model, Shintani *et al*[40] found that HCV directly affects serum glycaemic

and insulinaemic levels, probably by acting *via* TNF-α. Similarly, Kawaguchi *et al*[41] reported that HCV directly affects intracellular insulin metabolic pathways *via* genetic up-regulation. However, we cannot exclude the possibility that synergism between the two diseases (diabetes/non-alcoholic steatohepatitis and virus-related chronic hepatitis) affects the outcome of liver fibrosis[7,11].

Steatosis has been associated with more severe liver fibrosis[23-26] as well as with a worse response to antiviral therapy. Moreover, steatosis is defined "metabolic steatosis" in non-3-genotype-infected patients as opposed to the viral steatosis typical of genotype 3 patients[11]. In our cohort of HCV patients, steatosis did not appear to be an independent risk factor for fibrosis stage. The discrepancy between our results and previous findings is apparent. Indeed, univariate and multivariate analyses *vs* fibrosis showed that steatosis was associated with the severity of liver fibrosis in our HCV patients if they were also affected by diabetes and/or obesity. Moreover, at multivariate analysis *vs* steatosis, BMI, diabetes and fibrosis were independent risk factors only for steatosis > 30%. This suggests that histological features of fibrosis, whether related to non-alcoholic steatohepatitis or to virus-associated steatohepatitis, will be found only in cases in which steatosis is > 30%.

This study provides clinical evidence that HCV directly affects insulin resistance in a large Italian retrospective, single-centre, consecutive population of HCV- and HBV-infected subjects. Biological, molecular and genetic studies are required to test this hypothesis.

COMMENTS

Background

Glucose metabolism derangements are common in hepatitis C virus (HCV) patients but there is still a lot of deliberation as to whether the relationship between HCV and deranged cellular metabolic pathways is casual or whether it results from a direct effect exerted by HCV.

Research frontiers

To investigate the prevalence of the clinical parameters of insulin resistance and diabetes in patients affected by chronic hepatitis C (CHC) or chronic hepatitis B (CHB).

Innovations and breakthroughs

A direct comparison of the prevalence of clinical features of insulin resistance in HCV and HBV infection in a large cohort of Italian patients.

Applications

To shed light on the association between insulin resistance and HCV infection and recommend further biological, molecular and genetic studies, and finally to suggest a careful assessment of insulin resistance status in HCV clinical care.

Peer review

The authors retrospectively analyzed a large cohort of consecutively-enrolled HCV (726) and HBV (126) patients undergoing liver biopsy in order to find a correlation between clinical expressions of insulin resistance (diabetes and metabolic syndrome) and HCV liver disease in comparison with HBV-related chronic hepatitis. This is an interesting paper and is of importance.

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