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Metabolic syndrome association with fibrosis development in chronic hepatitis B virus inactive carriers

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Abstract

Background and Aim.

There are few data of fibrosis development in chronic hepatitis B (CHB) patients classified as inactive carriers. The aim of this study is to determinate the prevalence of significant fibrosis and probable cirrhosis measured by FibroScan in real inactive CHB carriers and investigate the relationship with virological, epidemiological, and metabolic factors.

Methods

Cross-sectional cohort study including CHB inactive carriers. Liver stiffness measurement was performed with transient elastography (FibroScan). Significant fibrosis (≥ F2) was defined as stiffness > 7.5 kPa, and probable cirrhosis as > 11.8 kPa. Factors associated with significant fibrosis were explored with univariate and multivariate adjusted logistic regression analyses.

Results

Ninety-six CHB inactive carriers were analyzed. Of them, 24 (25%) had significant fibrosis and 7 (7%) probable cirrhosis; mean stiffness was 6.2 ± 2.3 kPa.

Of them, 24% had metabolic syndrome, with higher FibroScan value than those without (8.4 kPa *vs* 5.5 kPa, $P < 0.001$).

Factors associated with significant fibrosis were (odds ratio, 95% confidence interval, *P* value): central obesity (7.1, 1.8–27.9, 0.005), elevated fasting glucose (4.3, 1.3–27.9, 0.036), reduced high-density lipoprotein cholesterol (5.2, 1.2–23.6, 0.032) and elevated triglycerides (6.2, 1.4–28.3, 0.019). Factors as age, sex, transaminases, hepatitis B virus DNA or genotype were not related with liver fibrosis.

The presence of metabolic syndrome has a 69% of positive predictive value and 89% of negative predictive value for significant fibrosis.

Conclusion

Different components of metabolic syndrome are associated with fibrosis development in CHB inactive carriers. In the absence of metabolic syndrome, significant fibrosis is uncommon in this population.

Key words

FibroScan; Fibrosis; HBV; Inactive carriers; Metabolic syndrome

Introduction

Chronic hepatitis B (CHB) is a major cause of liver disease and a global health problem affecting over 350 million people.[1] Hepatitis B virus (HBV) infection is the most common cause of liver cirrhosis and hepatocellular carcinoma.[2] Risk factors for progression to cirrhosis are dependent on the patient (older age, male gender, alcohol intake), coinfection status (hepatitis C and D, human immunodeficiency virus [HIV]) and laboratory parameters (elevated transaminases, high hepatitis B virus DNA [HBV-DNA] levels, positive hepatitis B e antigen [HBeAg] and HBV genotype).[3]

Metabolic syndrome (MS) promotes changes in general population, including alterations in insulin response and hepatic glucose metabolism, lipid storage and transport, and inflammation. Emerging data support a role for lipid and glucose metabolism in fibrosis development and hepatocellular carcinogenesis.[4, 5] The prevalence of non-alcoholic fatty liver disease among patients with MS is 43–64% (depending on the definition of MS used), in Spanish population.[6] In chronic hepatitis C infection, the association with hepatic steatosis is well known;[7] in these patients, hepatic steatosis is present in up to 30–70% of patients and is a risk factor for liver disease progression[8] and it decreases the response to antiviral therapy, independently of hepatitis C genotypes.[9] This association in HBV infection has not been demonstrated, despite several studies have focused in this problem last years.[10, 11] Hepatic steatosis and MS in HBV-infected patients seem to be less frequent than in the general population and in hepatitis C-infected patients.[12, 13] On the other hand, CHB patients with MS were more likely to have advanced fibrosis and cirrhosis than those without.[14] Contrary to hepatitis C, in CHB-infected patients, the degree of hepatic steatosis and insulin resistance are mainly due to metabolic factors but not virological factors.[15]

CHB infection is characterized by a dynamic nature course. Earlier studies assessing fibrosis are based on histological samples, in them, patients with low HBV viral load and persistently normal transaminases were less represented, and virological factors were determinants in the development of hepatic fibrosis. Transient elastography for liver stiffness measurement (LSM) has a good correlation with histological studies assessing advanced fibrosis in hepatitis C-infected patients as well as it has high sensitivity and specificity to detect histological liver cirrhosis also in CHB patients.[16, 17]

Severe fibrosis and cirrhosis are more frequent in HBeAg+ patients than negative and much more than in inactive carriers. Some studies have focused on LSM in inactive carriers, defined as CHB-infected patients with negative HBeAg, persistently normal alanine aminotransferase (ALT) (< 40 IU/L) and HBV-DNA < 10 000 IU/mL,[18, 19] but there are few data with patients complying the inactive carrier definition of the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD) and the Asian-Pacific Association for the Study of the Liver (APASL); in them a inactive HBV carrier must have HBsAg+, HBeAg-, anti-HBe+, normal ALT/AST levels and HBV-DNA < 2000 IU/mL, persistently.

In this study, we aimed to evaluate the LSM with FibroScan in real inactive CHB carriers, determinate the prevalence of significant fibrosis and probable cirrhosis in our population, and investigate the relationship with virological, epidemiological, and metabolic factors.

Methods

Study population

All patients with CHB in clinical follow-up at Complejo Hospitalario Universitario de A Coruña (Spain) have been examined. The number of patients with CHB in our institution is close to 300 patients. From these, those patients defined as CHB inactive carriers following the criteria established by international associations (EASL, AASLD)[20, 21] with at least 2 years of follow-up were retrospectively included. Persistently, normal ALT were accepted if there were ≥ 3 ALT determinations at unspecified intervals during 6–12 months or predefined intervals during ≥ 12-month periods, respectively, as used previously.[22]

All patients were naïve to antiviral therapy. Patients with an alcohol intake > 30 gr/day, coinfected with other hepatototropic viruses or HIV, known hereditary or immune liver diseases or history of clinical decompensations of cirrhosis were excluded of the study.

Clinical, ultrasonographic and laboratory evaluations

At the clinic visit, smoking, alcohol consumption, drug use, medical and pharmacological histories were always recorded. Anthropometric measurement included body height and weight and waist circumference (measured at a level midway between the lower rib and the iliac crest). Body mass index (BMI) was calculated as weight (Kg) divided by height (m) squared.

Data of the ultrasound examination of the liver carried during the last year before were recorded. It was classified as presence (all grades) or absence.

Blood tests were performed after, at least, 8-h fasting. They included coulter, liver and renal biochemistry, glucose, insulin and lipids. Normal ALT and AST value was considered < 40 IU/L.

MS was defined according to the criteria of the International Diabetes Federation, modified from the National Cholesterol Education Program, Adult Treatment Panel III Guidelines, as three or more of: central obesity (waist circumference ≥ 94 cm in men and ≥ 80 cm in women), BMI > 30 kg/m^2, triglycerides (TG) > 150 mg/dL; reduced high-density lipoprotein cholesterol (HDL-c) (< 40 mg/dL in men and < 50 mg/dL in women); blood pressure ≥ 130/85 mmHg; and fasting plasma glucose ≥ 100 mg/dL; or receiving treatment for the above metabolic abnormalities.[23]

Enzyme-linked immunosorbent assay (ELISA) commercial kits were used to test HBsAg, HBeAg and anti-HBe. HBV genotypes were determined using commercial hybridation assay. HBV-DNA levels were measured using real time commercial PCR methods with lower limit of detection of 10 IU/mL.

LSM

LSM was performed through transient elastography (FibroScan, EchoSense, Paris, France). The liver stiffness was expressed in kilopascals (kPa). All studies were carried out by an experienced operator (more than 400 examinations). The LSM was optimal only if it had at least 10 valid shots, success rate > 60% and IQR/LSM < 30%.

Significant fibrosis (≥ F2) was considered if LSM was > 7.5 kPa, and probable cirrhosis > 11.8 kPa; previously validated cut-off points in a similar population.[18]

Sample size

A total of 105 inactive HBV carriers were identified. Of them, 96 (95%) had an optimal LSM and were included for analysis. This sample size allows us to determine the prevalence of significant and probable fibrosis with a confidence level of 95% and 10% precision.

Moreover, assuming a prevalence of both MS and significant fibrosis around 25% in these patients, this study has 80% power, al alpha = 0.05 for a two-sided test, to detect as statistically significant OR of 4 or higher for the association of MS and significant fibrosis.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Science (spss, version 18.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean (standard deviation) or median (interquartile range) as appropriate, qualitative as number (%). Differences between subgroups were analyzed using Fisher's exact test for categorical parameters and Mann–Whitney test for continuous variables. Factors associated with significant fibrosis were explored using unadjusted and multivariate adjusted logistic regression analyses, including covariates with $P \leq 0.10$ in univariate analyses. Statistical significance was defined as 2-slided, $P < 0.05$.

Results

A total of 105 inactive HBV carriers were identified. Of them, 96 (95%) had an optimal LSM and were included for analysis. The mean age was 46 ± 14 years and 64 (67%) were male. The baseline characteristics are shown in Table 1. Of them, 18 patients (19%) were taking hypolipidemic therapy, 10 (11%) antihypertensives and 6 (6%) oral antidiabetic agents.

Table 1. Clinical characteristics and laboratory parameters of the patients

	All cases	Significant fibrosis[a]			Probable cirrhosis[b]		
		Yes	*No*	P	*Yes*	*No*	P
N patients	96	24 (25)	72 (75)		7 (7)	89 (93)	
Age, year	46 ± 14	54 ± 14	43 ± 13	0.001	61 ± 18	45 ± 13	0.004
Male gender	64 (67)	18 (72)	46 (65)	0.34	5 (71)	59 (66)	0.66
Current smoker	15 (16)	4 (17)	11 (15)	0.86	2 (29)	13 (15)	0.30
BMI, kg/m^2	25.4 ± 3.6	27.5 ± 4.5	24.7 ± 3	0.001	28.3 ± 4.9	25.2 ± 3.4	0.027
Waist circumference, cm	85 ± 12	94 ± 12	82 ± 10	< 0.001	96 ± 14	84 ± 11	0.009
Systolic BP, mmHg	132 ± 17	138 ± 16	129 ± 15	0.006	148 ± 9	130 ± 16	0.002
Diastolic BP, mmHg	73 ± 12	78 ± 12	71 ± 11	0.004	78 ± 7	72 ± 12	0.01
Liver stiffness, kPa	6.2 ± 2.3	9.3 ± 2.2	5.1 ± 1.2	< 0.001	12.5 ± 0.8	5.7 ± 1.6	< 0.001
HBV-DNA undetectable	15 (16)	5 (21)	10 (14)	0.51	2 (29)	13 (15)	0.30
HBV-DNA, log copies/mL	2 ± 1	1.8 ± 1.2	2.1 ± 1.0	0.16	1.6 ± 1.0	2.1 ± 1.0	0.15
Genotype Ac	21 (35)	5 (33)	16 (35)	0.89	2 (33)	19 (32)	0.70
Genotype Dc	28 (47)	6 (48)	22 (47)	0.72	3 (50)	26 (46)	0.66
Platelet count, × 10^9/L	226 ± 58	216 ± 42	229 ± 63	0.26	206 ± 52	227 ± 59	0.38
ALT, IU/L	30 ± 9	31 ± 8	29 ± 9	0.61	29 ± 8	30 ± 9	0.87
AST, IU/L	26 ± 8	26 ± 7	26 ± 9	0.99	29 ± 10	26 ± 8	0.16
Albumin, g/dL	4.4 ± 0.6	4.3 ± 0.6	4.4 ± 0.7	0.68	4.3 ± 0.5	4.5 ± 0.7	0.70
Metabolic syndrome	23 (24)	16 (67)	7 (10)	< 0.001	7 (100)	16 (18)	< 0.001
Central obesity	31 (32)	16 (67)	15 (21)	0.002	7 (100)	26 (29)	0.001
Elevated triglycerides	22 (23)	14 (58)	8 (11)	< 0.001	7 (100)	15 (17)	< 0.001
Reduced HDL cholesterol	19 (20)	10 (42)	9 (12)	0.002	4 (57)	15 (17)	0.027
Hypertension	37 (38)	15 (62)	22 (31)	0.006	7 (100)	30 (34)	0.001
Elevated fasting glucose	22 (23)	14 (58)	8 (11)	< 0.001	6 (86)	16 (18)	< 0.001
Steatosisd	23 (25)	11 (48)	12 (17)	0.007	4 (57)	19 (22)	0.01
Hypolipidemic therapy	18 (19)	6 (25)	12 (17)	0.02	2 (29)	16 (18)	0.10
Antihypertensives	10 (11)	3 (12)	7 (10)	0.64	1 (14)	9 (10)	0.46
Antidiabetics agents	6 (6)	2 (8)	4 (6)	0.78	1 (14)	5 (6)	0.62

[a] Stiffness > 7.5 kPa.
[b] Stiffness > 11.8 kPa.
[c] *N* = 60 patients.
[d] Steatosis by ultrasound (*N* = 93 patients).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; HBV, hepatitis B virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

According to the ethnicity, 77 patients (80%) were from Europe (of them, 74 were Spanish), 17 (18%) from Africa (mainly from Senegal) and 2 (2%) from Asia.

Mean LSM was 6.2 ± 2.3 kPa and 24 cases (25%) had significant fibrosis (> 7.5 kPa) and 7 (7%) probable cirrhosis (> 11.8 kPa). Table 1 shows qualitative and quantitative differences between groups.

Mean HBV-DNA was 2 log copies/mL and 16% ($n = 15$) of patients showed undetectable HBV-DNA viremia. HBV genotype analysis was performed in 81 patients. Finally, information on HBV genotypes could be addressed in 60 patients, with the following distribution: A 21 cases (35%), B 2 (3%), D 28 (47%), E 4 (7%), F 1 (1%), H 4 (7%).

The prevalence of MS was 24% (23 patients) and it increased with age: was 12% for patients of age 20–40, 21% 41–60 and 53% in > 61 years. Those with MS had LSM higher than those without 8.4 ± 3.3 kPa versus 5.5 ± 1.4 kPa ($P < 0.001$).

Mean BMI was 25.4 ± 3.6 kg/m^2, and 42 patients (44%) were overweight or obese (BMI ≥ 25 kg/m^2); mean systolic blood pressure was 132 ± 17 mmHg and diastolic 73 ± 12 mmHg. Mean metabolic factors were as follow: fasting glucose 95 ± 21 mg/dL, total cholesterol 191 ± 36 mg/dL, low-density lipoprotein cholesterol 120 ± 31 mg/dL, HDL-c 56 ± 14 mg/dL, TG 107 ± 58 mg/dL.

Factors associated with hepatic fibrosis

Factors associated with significant fibrosis were explored in multivariate-adjusted logistic regression analysis (Table 2). Central obesity (odds ratio [OR] 7.1), elevated fasting glucose (OR 4.3), low HDL-c (OR 5.2) and elevated TG (OR 6.2) have been associated with significant fibrosis (≥ F2).

Table 2. Multivariate logistic regression analysis on factors associated with significant fibrosis[a]

Parameter	OR	95% CI	*P*
Age	1.035	0.97–1.11	0.308
Male gender	1.037	0.23–4.71	0.962
Central obesity	7.130	1.82–27.87	0.005
Elevated fasting glucose	4.252	1.25–27.95	0.036
Reduced HDL cholesterol	5.219	1.15–23.64	0.032
Elevated triglycerides	6.188	1.36–28.25	0.019
Hypertension	1.850	0.69–6.74	0.206
Steatosis	2.130	0.82–3.26	0.160
Hypolipidemic therapy	1.946	0.78–2.96	0.192

[a] Stiffness > 7.5 kPa.
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

Table 3 shows the prevalence of steatosis and significant fibrosis according to number of MS criteria.

Table 3. Prevalence of steatosis (all grades) and significant fibrosis (> 7.5 kPa) according to number of MS criteria fulfilled

Number of MS criteria	Prevalence of steatosis (%)	Prevalence of significant fibrosis (%)
0	14.2	9.2
1	25.3	17.8
2	38.7	36.8
3	59.4	57.3
4	76.6	70.1
5	91.3	78.4
≥ 3 to 5	65.2	69.6

MS, metabolic syndrome.

Discussion

In our study, 7% of inactive HBV carriers had probable cirrhosis and 25% significant fibrosis, using the cut-offs proposed by Oliveri *et al*.[18] When we used the dual cut-off (F ≥ 2 LSM > 9.4 and ≤ 6.2 kPa) proposed by Vigano *et al*.,[17] the prevalence of significant fibrosis recognized in our population was very similar (20%). To our knowledge, there are few data of LSM in inactive carriers according to the proposed definition, and this is the first study analyzing the influence of MS in liver fibrosis development. A French study with 58 inactive carriers, found that 9% had fibrosis score of > 2 in histological samples.[24] A study in India reported that among inactive HBV carriers, 21% had histologically active liver disease, and 13.8% of patients had significant hepatic fibrosis.[25] Data of Egyptian inactive carriers had been published recently; in them, 20% of patients had fibrosis score ≥ 2 in liver biopsy.[26]

Oliveri *et al*. reported that in chronic HBV carriers, including patients with HBV-DNA > 2000 IU/mL and elevated ALT value, HBV-DNA and ALT were factors associated with fibrosis development; metabolic factors did not achieve statistically significance in multivariate analysis;[18] but 68 patients were inactive HBV carriers and those with dysmetabolic profile had LSM higher than patients without (6.9 kPa *vs* 4.3 kPa, $P < 0.001$). In a recent study published by Wong *et al*. with more than 1000 CHB patients, 32% had possible cirrhosis (defined as FibroScan > 8.4 kPa); male gender (OR 1.8), age > 40 years (OR 1.8), BMI > 25 Kg/m^2 (OR 1.4), albumin < 40 g/L (OR 4.2), elevated ALT (OR 2.8) and alkaline phosphatase (OR 2.4) and MS (OR 1.6) were associated with possible cirrhosis in multivariate logistic regression; OR 1.1 was reported for HBV-DNA > 2 log copies/mL, without statistically significance ($P = 0.65$), despite mean HBV-DNA was 5.0 log copies/mL.[14] Our results are in the same line; in our inactive HBV carriers, different components of MS are associated with significant fibrosis, without influence of viral factors as DNA levels or HBV genotype or hepatic factors as ALT or albumin levels. Of note, only a 16% of the study population showed undetectable HBV-DNA levels, therefore, it is not expected to show any impact of this parameter on the results obtained. Moreover, the univariate analysis did not show any impact of HBV-DNA on the development of fibrosis. Regarding HBV genotype, this parameter can be addressed in more than 62% of patients. Lack of amplification ($n = 21$) or undetectable HBV-DNA viremia ($n = 15$) explain the absence of results for all patients. However, since the majority of our patients population are infected with genotypes A or D, the overall impact of HBV genotypes in the clinical follow-up of inactive CHB cannot be properly evaluated

in this study. Moreover, with the current data, the HBV genotype, at least genotypes A or D, does not seem to impact in the development of fibrosis.

We hypothesize that CHB infection influences less tan metabolic disturbances in fibrosis development of true inactive carriers. We did not find influence of epidemiological factors as gender or ethnicity in fibrosis development. In the univariate study, the age seemed to be related with significant fibrosis; this association was not demonstrated in the multivariate analysis probably because the influence of the age in inactive carriers could be, partly, due to the worsening of the metabolic profile. In the multivariate analysis, liver steatosis was not associated with significant fibrosis. Since steatosis is very common among patients with MS and all the MS criteria are recognized in our study population, it is noteworthy that the prevalence of steatosis in our population was > 90%.[27] This might explain the lack of association between significant fibrosis and liver steatosis in this study.

Wong *et al*. also estimated that the prevalence of MS was 11% in CHB and 20% in controls;[13] we found a prevalence of 24%. This higher rate is probably due to different reasons, mainly the characteristics of the study population; the prevalence of MS in Spanish population is 15–34%, depending on the criteria used.[6] Therefore, the prevalence in our study for inactive HBV carriers is similar with that reported in general population of Western countries.[28]

Transient elastography has been shown to correlate with fibrosis in CHB.[18, 29] Cut-off values used for advanced fibrosis (> 7.5 kPa) and for probable cirrhosis (> 11.8 kPa) have a positive predictive value of 77% and 86%, respectively, and a negative predictive value of 97% and 96%.[18] In general population, LSM remained higher in subjects with MS than in those without (6.5 ± 1.6 *vs* 5.3 ± 1.5 kPa, $P < 0.001$);[30] in inactive carriers with MS, we found a mean FibroScan value higher (8.4 ± 3.3 kPa) than reported for subjects with MS and without CHB. Most previous studies of LSM with FibroScan reported a failure rate of 5–8% due to obesity (mainly) and other reasons;[31, 32] we excluded 9 cases (5%).

Mechanism connecting steatosis and liver fibrosis are not well known, but are probably related to the oxidative stress generated from fat accumulation in hepatocytes, secretion of inflammatory cytokines and activation of stellate cells.[33] These processes may contribute to further hepatic injury from HBV.[34] However, in the Wong cohort, MS but no steatosis was independently associated with liver fibrosis and cirrhosis,[14] similar to our findings. In chronic hepatitis C-infected patients, steatosis is not associated with severe liver fibrosis, and insulin resistance is the major driving force for liver fibrosis;[35] but HBV does not seem to induce insulin resistance.[36]

Our study has a few limitations. Despite that all patients included in the study were retrospectively followed at least 2 years to ensure they were inactive HBV carriers, the study has a cross-sectional design. Herein, we have analyzed the impact of several parameters (epidemiological, clinical, and metabolic) that might be associated with the development of fibrosis at a given point in time. However, longitudinal studies are required to properly establish those factors influencing the development of fibrosis. This is the case of a recent study published by Wong *et al*.[37] in which they found a low incidence rate of liver fibrosis progression (annual incidence rate 0.8%) among HBV inactive carriers. The sample size is relatively small because only HBV inactive carriers without other hepatic comorbidities have been included. However, this sample size allows us to detect as statistically significant OR of 4 or higher for the association of MS and significant fibrosis. Although some associations with lower OR might not be recognized, we have demonstrated the association between fibrosis and different metabolic parameters, which was mainly the aim of this study.

The assessment of fibrosis was based on transient elastography. Although this methodology has been widely validated, it is possible that FibroScan might slightly overestimate fibrosis in our study population, since the prevalence of significant fibrosis is relatively low. Furthermore, 5% of patients were excluded from analysis due to failed LSM; most of them with central obesity.

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