Liver fibrosis progression in patients with chronic hepatitis B: a prospective study with paired transient elastography

VWS Wong *, HLY Chan, GLH Wong

KEY MESSAGES

1. Liver fibrosis progression is uncommon in chronic hepatitis B patients with normal liver function tests.
2. In patients with active disease, antiviral therapy can effectively prevent fibrosis progression and even result in fibrosis regression.
3. Metabolic syndrome approximately doubles the risk of fibrosis progression.
4. Clinicians should monitor and manage metabolic disease in patients with chronic hepatitis B.

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VWS Wong, HLY Chan, GLH Wong

Department of Medicine and Therapeutics, The Chinese University of Hong Kong

* Principal applicant and corresponding author: wongv@cuhk.edu.hk

Introduction

Chronic hepatitis B (CHB) is the leading cause of hepatocellular carcinoma (HCC) and cirrhosis in Asia. More than 400 million people worldwide are estimated to be chronically infected with hepatitis B virus (HBV). The incidence of cirrhosis and advanced liver fibrosis in patients with CHB remains unclear. Ultrasonography and liver biopsy have been used as diagnostic tools. Nevertheless, ultrasonography is operator-dependent and not sensitive to liver fibrosis or early cirrhosis. Although liver biopsy is the gold standard to assess liver fibrosis, it is invasive and may not be acceptable to many patients.

Transient elastography by Fibroscan (Echosens, Paris, France) has been developed as an accurate, reproducible, and non-invasive tool to assess liver fibrosis. By pairing transient elastography and liver biopsies in CHB patients, we developed and validated an algorithm for transient elastography to detect advanced fibrosis and cirrhosis, with area under the receiver operating characteristics curve up to 0.87 and 0.93, respectively.[1] Transient elastography can be used to perform repeated liver fibrosis assessment in a large number of patients. Patients with different disease activity, including those with inactive disease, may be studied. In the current study, we performed serial clinical assessment and transient elastography in CHB patients after an interval of ≥3 years.

Methods

From 2006 to 2008, we conducted a territory-wide screening on the prevalence of advanced liver fibrosis, in relation to the presence of metabolic syndrome, in CHB patients.[2] Over 1400 patients were recruited from primary care clinics and hospitals in Hong Kong. Patients with CHB diagnosed by positive serology tests for serum hepatitis B surface antigen (HBsAg) for at least 6 months were included. Patients with other liver diseases or liver decompensation at baseline were excluded. From 2010 to 2012, patients were invited for follow-up using transient elastography after an interval of ≥3 years. The study protocol was approved by the local ethics committee, and written informed consent was obtained from each patient before enrolment.

All patients completed comprehensive clinical and laboratory (haematological, biochemical and virologic) assessments at baseline and follow-up visits. Anthropometric parameters including body weight, body height, hip circumference, and waist circumference were measured. Serum HBV DNA levels were measured by the TaqMan real-time polymerase chain reaction assay with a range of detection of 20 to $2x10^8$ IU/mL. HBsAg was quantified by Architect HBsAg QT (Abbott Diagnostic), with a final range of detection of 0.05 to 124 950 IU/mL.

According to the modified National Cholesterol Education Program criteria, diagnosis of metabolic syndrome was defined as the presence of any three of the following five factors: (1) central obesity, (2) raised concentration of triglycerides, (3) reduced concentration of high density lipoprotein-cholesterol, (4) raised blood pressure, and (5) raised fasting plasma glucose concentration ≥5.6 mmol/L or previously diagnosed type-2 diabetes mellitus.

Liver stiffness measurement (LSM) was performed using transient elastography according to the manufacturer instructions. The LSM was considered reliable only if 10 successful acquisitions were obtained with an interquartile range ≤30% of

LSM. Liver fibrosis progression was defined as a 30% increase in LSM value from baseline; regression was defined as a >30% decrease in LSM value from baseline.

The annual incidence was estimated by dividing the total number of liver fibrosis progression by the summation of person-time calculated in years. Multivariable analysis by logistic regression model adjusted for the change in serum alanine transaminase (ALT) and HBV DNA level was performed to determine the association between metabolic syndrome and its factors and liver fibrosis progression. Effect sizes were expressed in adjusted odds ratios (OR) and 95% confidence interval (CI).

Results

Of 1407 patients included, 1178 underwent follow-up assessment between 2010 and 2012. Overall, 515 patients had received antiviral therapy after the baseline visit, and 663 patients remained treatment-naïve (Fig). The mean age of the entire cohort was 46 years, and 63% were men. All patients had compensated liver disease. HBeAg was positive in 26%, and the mean HBV DNA level was 4.3 log IU/mL (Table 1).

Fibrosis progression and regression

Of 1178 patients, 972 (83%) had no or mild fibrosis at baseline. During a mean follow-up of 43±7 months, 145 (15%) had liver fibrosis progression, of whom 35 (3.6%) had progressed to advanced fibrosis. At baseline, 206 (18%) patients had advanced fibrosis or cirrhosis. During follow-up, 139 (68%) had fibrosis regression, of whom 66 (32%) no longer had advanced fibrosis. Among patients with advanced fibrosis or cirrhosis at baseline, regression occurred in 112 of 139 (81%) patients who received antiviral therapy, compared with 27 of 57 (47%) who did not (P<0.001). Antiviral therapy was a major disease-modifier.

Metabolic syndrome

Among 663 treatment-naïve patients, 23 of 84 (22%) patients with incident metabolic syndrome developed liver fibrosis progression, compared with 84 of 663 (12%) patients in the entire cohort (P<0.001). Incident metabolic syndrome was a risk factor for liver fibrosis progression, independent of the change in serum ALT and HBV DNA level, compared with patients who did not have metabolic syndrome at both visits (adjusted OR=2.0, 95% CI=1.1-3.5, P=0.015, Table 2). Among the five metabolic factors, incident central obesity (adjusted OR=2.0, 95% CI=1.0-4.1, P=0.05) and low HDL-C level (adjusted OR=1.9, 95% CI=1.0-3.7, P=0.04) were independent risk factors for liver fibrosis progression (Table 2). Patients who had resolved metabolic syndrome or its factors, or those with persistent metabolic syndrome did not have a significantly increased risk of liver fibrosis progression. Nonetheless, there was no association between incident or resolved metabolic syndrome and liver fibrosis regression.

HBeAg-positive patients

Of 247 patients who were HBeAg positive at baseline and had reliable LSM both at baseline and follow-up, none developed hepatic decompensation during

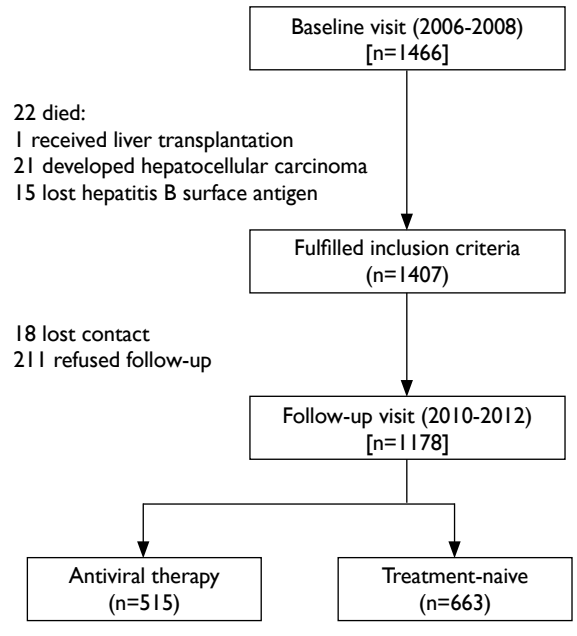

FIG. Study flow chart

TABLE 1. Baseline characteristics of 1178 chronic hepatitis B patients

Characteristic	Value*
Age (years)	46±12
Male	743 (63)
Albumin (g/L)	44±3
Bilirubin (μmol/L)	12 (9-17)
Alkaline phosphatase (IU/L)	70 (58-89)
Alanine aminotransferase (IU/L)	45 (28-77)
Patients with positive hepatitis B e antigen	305 (26)
Hepatitis B virus DNA (log IU/mL)	4.3 (3.0-6.1)
Liver stiffness (kPa)	6.4 (4.8-8.9)
Interquartile range to median ratio of liver stiffness	0.16 (0.11-0.22)
Success rate of liver stiffness measurement (%)	91 (77-100)

* Data are presented as mean±standard deviation, median (interquartile range), or No. (%) of patients

TABLE 2. Multivariable logistic regression analysis of metabolic factors associated with liver fibrosis progression in 663 treatment-naïve patients

Status of metabolic conditions*	Incident		Resolved		Remained positive	
	Adjusted OR (95% CI)†	P value	Adjusted OR (95% CI)†	P value	Adjusted OR (95% CI)†	P value
Liver fibrosis progression						
Metabolic syndrome	2.0 (1.1-3.5)	0.015	0.9 (0.3-3.3)	0.91	0.4 (0.2-1.1)	0.09
Hypertension	0.9 (0.5-1.5)	0.67	0.8 (0.3-2.4)	0.69	1.0 (0.6-1.7)	0.99
Diabetes	1.1 (0.6-1.9)	0.82	0 (0-0)	1.00	1.1 (0.5-2.2)	0.87
Central obesity	2.0 (1.0-4.1)	0.05	1.3 (0.7-2.5)	0.42	1.4 (0.9-2.3)	0.19
Low high density lipoprotein cholesterol	1.9 (1.0-3.7)	0.04	0.8 (0.4-1.5)	0.44	0 (0-0)	1.00
High triglycerides	1.0 (0.5-1.9)	0.85	1.2 (0.5-2.9)	0.66	1.0 (0.4-2.4)	0.94
Liver fibrosis regression						
Metabolic syndrome	0.9 (0.4-1.8)	0.73	1.4 (0.5-4.1)	0.50	1.1 (0.6-2.2)	0.75
Hypertension	1.0 (0.6-1.6)	0.86	1.0 (0.4-2.8)	0.99	1.1 (0.7-1.8)	0.70
Diabetes	0.6 (0.3-1.2)	0.13	1.2 (0.3-6.3)	0.79	1.1 (0.6-2.3)	0.70
Central obesity	1.7 (0.8-3.3)	0.14	0.9 (0.5-1.8)	0.87	0.9 (0.6-1.5)	0.68
Low high density lipoprotein cholesterol	1.6 (0.7-3.1)	0.21	1.0 (0.5-1.8)	0.92	1.4 (0.4-5.3)	0.61
High triglycerides	0.7 (0.4-1.5)	0.41	1.5 (0.7-3.3)	0.33	1.4 (0.6-3.1)	0.43

* Referent to patients remained free from the metabolic conditions at both visits

† Adjusted for the change in serum alanine aminotransferase and hepatitis B virus DNA levels

follow-up and 13 (5.3%) had progressed to advanced fibrosis. The annual incidence was 1.5% (95% CI=0.8-2.6%). Among patients who remained treatment-naïve, advanced age and high HBV DNA at follow-up were associated with fibrosis progression by univariate analysis, whereas only age >40 years remained an independent factor by multivariate analysis (OR=2.1, 95% CI=1.0-5.4, P=0.05).

HBeAg-negative patients

Among 1197 HBeAg-negative patients, 361 (48±11 years of age) had reliable and normal LSM (5.4±1.5 kPa), serum ALT (28±11 IU/mL), and HBV DNA (2.7±1.0 log IU/mL) at baseline and thus were potentially inactive HBV carriers (HBsAg level, 2.5±1.4 log IU/mL). Their LSM at follow-up was 5.3±1.7 kPa. Ten patients (2.8%) had progressed to advanced fibrosis at follow-up. The annual incidence of advanced fibrosis was 0.8% (95% CI=0.4-1.4%).

Discussion

This prospective study confirmed that incident metabolic syndrome increased the risk of liver fibrosis progression in patients with CHB who remained treatment naïve after 3 to 4 years. Fibrosis progression was uncommon in untreated patients, and antiviral therapy could prevent disease progression and even result in fibrosis regression in patients with active disease.

There is an association between metabolic syndrome and cirrhosis. Insulin resistance and other metabolic disturbances can be a result and cause of cirrhosis. In our study, metabolic changes preceded fibrosis progression. This consolidated our previous observation in a cross-sectional study that metabolic syndrome increases the risk of liver cirrhosis in CHB.[2] In a Korean biopsy cohort of 850 CHB patients, metabolic syndrome was strongly associated with advanced fibrosis.[3] The increased risk of advanced liver fibrosis in patients aged >40 years who remained HBeAg-positive was probably a result of the synergistic effect of high viral load and incident metabolic syndrome, itself also increasingly prevalent with age.[4] In fact HBV infection per se may be associated with a lower prevalence of fatty liver and metabolic syndrome, and is distinct from chronic hepatitis C. The inverse association between chronic HBV infection and fatty liver was also observed in a large-scale Taiwanese population study of 33 439 subjects.[5] Nonetheless, hepatic steatosis is observed in up to 18% of CHB patients in the absence of significant alcohol consumption. Therefore concomitant non-alcoholic fatty liver disease in CHB patients remains an issue.

Advanced fibrosis is uncommon in patients in the immune-tolerant phase and inactive carrier state. Using serial transient elastography, we confirmed that fibrosis progression was also rare in these groups. We identified a subset of patients who actually had advanced fibrosis at baseline despite normal ALT and low HBV DNA level. Such patients may have been wrongly considered to be low risk cases.

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