

Insulin Resistance in Chronic Hepatitis B Virus Infection

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OBJECTIVES: Chronic hepatitis C virus infection is associated with insulin resistance (IR), and both host and viral factors are important in its development. The association and the predictors of IR in chronic hepatitis B virus (CHBV) infection remain unclear.

METHODS: A total of 69 CHBV-infected subjects were examined to study the relationship between histological findings and anthropometric and biochemical data, including IR determined by the homeostasis model assessment (HOMA-IR). To assess the influence of CHBV infection on IR independent of any effect of hepatic fibrosis, overweight, or sex we also compared fasting serum insulin, C-peptide, HOMA-IR, HOMA- β (measure of β -cell function) and C-peptide-insulin ratio (to distinguish impaired insulin degradation (low ratio) from insulin hypersecretion (normal ratio)) levels between the subset of 14 male normal weight (body mass index, BMI < 23) CHBV patients with stage 0 or 1 hepatic fibrosis and 50 male normal weight healthy controls matched by age and anthropometry (BMI and waist circumference).

RESULTS: A total of 31 (44.9%) CHBV-infected patients were overweight (BMI > 23 kg/m²) and 18 (26.1%) were obese (BMI > 25 kg/m²). IR was seen in 34 (49.3%) patients. BMI (Spearman's coefficient = -0.436; $P < 0.001$) and serum triglyceride levels (Spearman's coefficient = -0.307; $P = 0.010$) were univariate predictors of IR. In multiple linear regression analysis, only BMI ($P < 0.001$) was an independent predictor of HOMA-IR. The subgroup of CHBV-infected patients and the controls had comparable levels of all markers of IR, including fasting glucose, insulin, C-peptide, and HOMA-IR.

CONCLUSIONS: IR in CHBV-infected patients is a reflection of the host metabolic profile and CHBV infection is not in itself correlated with IR.

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INTRODUCTION

The prevalence of diabetes mellitus (DM) associated with virus-related chronic hepatitis is on an average four times higher than in the general population. Virus-related liver cirrhosis further increases the prevalence of both impaired glucose tolerance (IGT) and DM, independently of sex and age, but in relationship with the severity of disease. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections do not appear to have a different impact on glycemic homeostasis (1). As insulin resistance is important in the development of type 2 DM, several clinical studies have investigated insulin resistance in chronic HCV-infected patients, in which it was found that hepatitis C virus may induce insulin resistance (IR) irrespective of the severity of liver disease, and IR may con-

tribute to fibrotic progression in chronic HCV infection (2-4). IR has also been related to nonresponse to peg interferon plus ribavirin in chronic hepatitis C patients (5).

However, only a few studies have evaluated hyperinsulinemia in chronic HBV (CHBV) (6,7). Thus, the association of CHBV infection with the emergence of IR and altered glucose metabolism remains unclear (8).

In this study, we evaluated the degree of IR and its predictors in patients with CHBV infection in Indian patients.

METHODS

Case selection

A total of 69 patients with CHBV, who underwent liver biopsy at Department of Gastroenterology at G.B. Pant Hospital,

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between January 2006 and October 2007 and fulfilled the criteria specified below, were included in this study. The inclusion criteria were: (i) HBV surface antigen (HBsAg) positive for at least the past 6 months, (ii) no regular use of medication(s) known to affect glucose tolerance or insulin secretion, (iii) normal thyroid and kidney functions, (iv) no history of gastrectomy or chronic pancreatitis, (v) no previous antiviral treatment, (vi) normal renal function, and (vi) to avoid the confounding effect of end-stage liver disease on the interpretation of the insulin and IR data, we excluded patients with Child-Pugh grade B or C.

The following conditions were excluded by appropriate tests: (i) concurrent HCV or HIV infection, (ii) autoimmune hepatitis, (iii) primary biliary cirrhosis, (iv) sclerosing cholangitis, (v) hemochromatosis, (vi) α_1 -antitrypsin deficiency, (vii) Wilson's disease or any other cause of liver disease, (viii) patients with an established diagnosis of DM, and (ix) patients with clinical evidence of hepatic decompensation (hepatic encephalopathy, ascites, variceal bleeding, or serum bilirubin level greater than twofold the upper limit of normal). The study protocol was approved by the Human Ethics Committee of the Institute, and written, informed consent was obtained.

Clinical and laboratory assessment

The following data were collected at the time of liver biopsy: age, sex, ethnicity, average current daily alcohol intake (g per day) in the past 6 months, past alcohol intake (g per day) before the past 6 months, weight, and height. Body mass index (BMI) was calculated as weight in kilograms/height in square meters. Patients and controls were categorized as normal weight (BMI <23), overweight (BMI 23.0–24.9), or obese (BMI >25) (9). The following investigations were performed in a fasting venous blood sample: serum levels of albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, triglyceride, insulin and C-peptide, plasma glucose concentration, platelet count, and prothrombin time (PT).

Oral glucose tolerance test. All subjects underwent oral glucose tolerance test (OGTT) with 75g of glucose according to the recommendations of the National Diabetes Data Group of the National Institutes of Health. At 8 am, after a 10- to 12-h overnight fasting period, subjects received 75g OGTT. Blood samples were taken 0, 30, 60, 90, 120, and 180 min after administration to measure the plasma glucose. The definitions (10) were as follows: (i) DM: fasting plasma glucose (FPG) ≥ 126 mg/dl or 2h postprandial plasma glucose (PPG) ≥ 200 mg/dl after a 75-g glucose load; (ii) impaired glucose homeostasis: impaired fasting glucose: FPG from 110 to <126; impaired glucose tolerance: 2h PPG from 140 to <200; (3) normal: FPG <110 mg/dl or 2h PPG <140 mg/dl.

β -Cell function and insulin sensitivity. To evaluate β -cell function and insulin sensitivity, two indices were calculated based on the data in a fasting state.

β -Cell function was assessed by the following equation:

$$\text{HOMA-}\beta(\%) = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times 360}{\text{Fasting glucose (mg/dl)} - 63}$$

Insulin sensitivity was assessed by IR as determined by the homeostasis model assessment (HOMA) method by using the following equation (11):

$$\text{Insulin resistance (HOMA-IR)} = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times \text{Fasting glucose (mg/dl)}}{405}$$

IR calculated by this method has been validated against insulin sensitivity measured directly with the euglycemic/hyperinsulinemic clamp technique in both diabetic and nondiabetic subjects (12,13). To take into account the effect of advanced hepatic fibrosis on increasing serum insulin levels that is partly due to impaired insulin clearance (14), insulin secretion was determined by using the serum C-peptide–insulin ratio.

C-peptide and insulin are secreted in equimolar amounts, and serum C-peptide is not significantly cleared by the liver (15), hence, the C-peptide–insulin ratio allows hyperinsulinemia due to impaired insulin degradation (low ratio) to be distinguished from insulin hypersecretion (normal ratio). Control HOMA–IR values were obtained from a previous study of 20 nonobese, nondiabetic, healthy volunteers (18–80 years) without a family history of diabetes. On the basis of these results, subjects were categorized as insulin resistant if the HOMA–IR was greater than 1.64 (corresponding to the 75th centile) (16).

Histopathology

All liver tissue specimens were evaluated by one pathologist who was unaware of the clinical condition of the patient. Individual biopsy specimens were scored with the use of the Knodell index, which grades the histological activity of hepatitis on a scale from 0 to 18, with higher scores indicating more severe abnormalities (17). The overall Knodell score is the sum of the scores for periportal bridging necrosis (0–10), intra-lobular degeneration and focal necrosis (0–4), and portal inflammation (0–4). Fibrosis was staged as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis, and F4, cirrhosis. Steatosis was assessed as the percentage of hepatocytes containing fat droplets. It was graded as 0 (no steatosis), 1 (<33% of hepatocytes affected), 2 (33–66% of hepatocytes affected), or 3 (>66% of hepatocytes affected) (18).

All subjects gave written informed consent before participation in the study. The protocol was approved by the Institutional Ethical Committee.

Statistical analyses

Continuous variables were summarized as mean \pm s.d. or median (range) and categorical variables as frequency and percentage. The unpaired Student's *t*-test was applied for comparisons of normally distributed variables and χ^2 -test was used for nominal categorical variables. The statistical significance of intergroup differences, for non-normal distributed

Table 1. Baseline characteristics of the chronic HBV patients

Parameter	Chronic HBV (n=69)	HOMA-IR <1.64 (n=35)	HOMA-IR ≥1.64 (n=34)	P value*
Age (years) (mean±s.d.)	31.9±11.4	30.8±12.3	33.1±10.6	0.387
Male sex (n (%))	59 (85.5)	30 (85.7)	29 (85.3)	1.0
BMI (kg/m²)				
Mean±s.d.	22.9±4.2	21.8±3.7	24.0±4.4	0.029
Median (range)	16.1–33.3	22.0 (16.1–32.5)	23.9 (16.3–33.3)	
>23	31 (44.9)	12 (34.3)	19 (55.9)	0.09
>25	18 (26.1)	5 (14.3)	13 (38.2)	0.03
Waist circumference (cm)				
Mean±s.d.	82.7±9.7	80.1±8.6	85.1±10.2	0.089
Median (range)	82.0 (63.0–106.0)	78.0 (64.0–96.0)	89.0 (63.0–106.0)	
Alcohol consumption (n (%))	0	0	0	1.0
Platelet (lac/cumm) (median (range))	1.6 (1.0–4.0)	1.57 (1.0–4.0)	1.7 (1.0–4.0)	0.258
Albumin (g/dl) (mean±s.d.)	4.2±0.3	4.2±0.3	4.2±0.2	0.674
ALT (IU/l) (median (range))	58.0 (14.0–358.0)	57.0 (17.0–344.0)	60.0 (14.0–358.0)	0.355
Bilirubin (mg/dl) (median (range))	0.8 (0.4–3.0)	0.8 (0.5–3)	0.85 (0.4–2.0)	0.791
PT prolongation (s) (median (range))	1 (0–2)	1 (0–2)	1 (0–2)	0.708
Cholesterol (mg/dl) (median (range))	151.0 (96.0–367.0)	148.0 (102.0–367.0)	151.0 (96.0–251.0)	0.254
Triglyceride (mg/dl) (median (range))	99.0 (11.0–340.0)	90.0 (11.0–248.0)	110.0 (50.0–340.0)	0.016
Fasting insulin (μU/ml) (median (range))	7.5 (0.7–29.3)	5.0 (0.7–8.3)	11.7 (7.4–29.3)	<0.001
Fasting glucose (mg/dl) (median (range))	87.0 (70.0–130.0)	85.0 (70.0–107.0)	93.0 (73.0–130.0)	<0.001
HOMA-IR (median (range))	1.59 (0.14–7.05)	1.03 (0.14–1.59)	2.52 (1.72–7.05)	<0.001
HOMA-IR ≥1.64 (n (%))	34 (49.3)			
C-peptide (ng/ml) (median (range))	1.98 (0.05–4.79)	1.5 (0.05–3.02)	2.25 (1.4–4.79)	<0.001
C-peptide–insulin ratio (median (range))	0.25 (0.05–3.36)	0.28 (0.05–3.36)	0.19 (0.07–0.40)	<0.001
HOMA-β (%) (median (range))	111.8 (13.17–1053.7)	74.8 (13.2–318.8)	136.9 (51.6–1053.7)	<0.001
OGTT result (n (%))				
Diabetes mellitus	1 (1.4)	0	1 (2.9)	0.088
Impaired glucose tolerance	6 (8.7)	1 (2.9)	5 (14.7)	
Normal glucose tolerance	62 (89.9)	34 (97.1)	28 (82.4)	
Hypertension (n (%))	0	0	0	1.0
Hyperlipidemia (n (%)) (cholesterol >250 and/or triglycerides >150)	15 (21.7)	4 (11.4)	11 (32.4)	0.044
Distribution of stage of fibrosis (n (%))				
0	6 (8.7)	2 (5.7)	4 (11.8)	
1	27 (39.1)	12 (34.3)	15 (44.1)	0.232
2	14 (20.3)	10 (28.6)	4 (11.8)	
3	15 (21.7)	9 (25.7)	6 (17.6)	
4	7 (10.1)	2 (5.7)	5 (14.7)	
HAI (median (range))	4.0 (1–12)	4 (1–10)	4 (2–12)	0.666
HAI <3 (n (%))	15 (21.7)	8 (22.9)	7 (20.6)	

Table 1. Continued

Parameter	Chronic HBV (n=69)	HOMA-IR < 1.64 (n= 35)	HOMA-IR ≥1.64 (n=34)	P value*
HAI 3–5 (n (%))	33 (47.8)	16 (45.7)	17 (50)	0.717
HAI 6–8 (n (%))	15 (21.7)	9 (25.7)	6 (17.6)	
HAI ≥9 (n (%))	6 (8.7)	2 (5.7)	4 (11.8)	
<i>Distribution of grade of steatosis (n (%))</i>				
0	28 (40.6)	15 (42.9)	3 (38.2)	0.873
1	34 (49.3)	17 (48.6)	17 (50)	
2	79 (10.1)	3 (8.6)	4 (11.82)	
3	0	0	0	
HBV DNA (logcopies/ml) (median (range))	6.45 (3.3–9.98)	5.14 (3.3–9.98)	6.2 (3.3–9.06)	0.324
HBV DNA <4 logcopies/ml (n (%))	7 (10.1)	2 (5.7)	5 (14.7)	
HBV DNA ≥4 to <6 logcopies/ml (n (%))	27 (39.1)	17 (48.6)	10 (29.4)	0.03
HBV DNA ≥6 to <8 logcopies/ml (n (%))	21 (30.4)	13 (37.1)	8 (23.5)	
HBV DNA ≥8 logcopies/ml (n (%))	14 (20.3)	3 (8.6)	11 (32.4)	
HBeAg positive (%)	26 (37.7)	13 (37.1)	13 (38.2)	1.0

ALT, alanine aminotransferase; BMI, body mass index; HAI, histological activity index; HBeAg, hepatitis B early antigen; HBV, hepatitis B virus; HOMA-IR, homeostasis model assessment-insulin resistance; OGTT, oral glucose tolerance test; PT, prothrombin time.
* P values are for comparison between patients with HOMA-IR <1.64 and HOMA-IR ≥1.64.

data, was evaluated by means Wilcoxon’s rank-sum (Mann-Whitney) tests. Spearman’s rank correlation coefficient was used when appropriate. Linear regression analysis was used to identify independent predictors of HOMA-IR among the CHBV subjects. A significance level of 0.05 was used.

RESULTS

Baseline characteristics of the chronic HBV-infected patients

The baseline characteristics of CHBV patients are shown in **Table 1**. The mean age was 31.9±11.4 years; 59 (85.5%) were men, and the mean BMI was 22.9±4.2kg/m² (range, 16.1–33.3kg/m²). A total of 31 (44.9%) patients were overweight (BMI>23kg/m²) and 18 (26.1%) were obese (BMI>25kg/m²). Fibrosis was absent in 6 (8.7%), stage 1 in 27 (39.1%), stage 2 in 14 (20.3%), stage 3 in 15 (21.7%), and stage 4 (cirrhosis) in 7 (10.1%) patients. IR was seen in 34 (49.3%) patients.

To assess the influence of CHBV infection on IR independent of any effect of hepatic fibrosis, overweight, or sex we also compared fasting serum insulin, C-peptide, HOMA-IR, HOMA-β (measure of β-cell function) and C-peptide-insulin ratio (to distinguish impaired insulin degradation (low ratio) from insulin hypersecretion (normal ratio)) levels between the subset of 14 male normal weight (BMI < 23 kg/m²) CHBV patients with stage 0 or 1 hepatic fibrosis and 50 male normal weight healthy controls matched by age and anthropometry (BMI and waist circumference). All volunteers had normal liver and renal function tests, negative viral markers (HBsAg, total anti-HBc, and anti-HCV negative) had normal ultrasound liver and had no known history of DM or any other disease that

may lead to IR. Chronic HBV-infected patients and the controls had comparable levels of all markers of IR, including fasting glucose, insulin, C-peptide, and HOMA-IR (**Table 2**).

Comparison of characteristics between patients with and without insulin resistance

The 69 patients with CHBV infection were then divided into two groups, HOMA-IR <1.64 (n= 35) and HOMA-IR ≥1.64 (n= 34); the latter is considered to be the IR group. The characteristics of each group were compared (**Table 1**). There were significant differences in BMI (P= 0.029), prevalence of hyperlipidemia (P=0.044), fasting insulin (P=0.001), fasting glucose (P<0.001), HOMA-IR (P<0.001), C-peptide (P<0.001), C-peptide-insulin ratio (P<0.001), and HOMA-β (P<0.001).

Factors associated with the degree of insulin resistance

To determine the possible factors involved in the pathogenesis of IR, we assessed whether HOMA-IR was associated with the following factors: age, sex, BMI, albumin, bilirubin, ALT, AST, platelet count, PT prolongation, cholesterol, triglyceride, steatosis grade, histological activity index (HAI) and fibrosis scores, and HBV DNA levels. There was a significant correlation between HOMA-IR and BMI and triglyceride levels (**Table 3**). These two factors were further analyzed by multiple linear regression for prediction of HOMA-IR, and only BMI was found to be significant predictor of HOMA-IR (**Table 4**).

β-Cell function and insulin sensitivity and liver fibrosis

We examined the differences of the indices related to β-cell function and insulin sensitivity between the minimal or no

Table 2. Comparison of male normal BMI (<23) HBV cases (fibrosis stage 0 or 1) with male normal BMI (<23) matched healthy controls

Parameter	Chronic HBV (n= 14)	Controls (50)	P value
Age (year) (mean±s.d.)	26.14±7.38	26.4±3.98	0.123
BMI (kg/m²)			
Mean±s.d.	19.8±2.3	20.5±1.04	0.304
Median (range)	19.9 (16.1–22.6)	20.4 (19.3–22.5)	
Waist circumference (cm)			
Mean±s.d.	76.9±7.7	74.8±6.2	0.305
Median (range)	74.5 (64.0–91.0)	76.0 (63.0–89.0)	
Alcohol consumption (%)	0	0	
Platelet (lac/cumm) (median (range))	1.7 (1.0–3.0)	1.6 (1.0–2.5)	0.730
Albumin (g/dl) (mean±s.d.)	4.1±0.3	4.3±0.3	0.161
ALT (IU/l) (median (range))	35.5 (14.0–80.0)	27.0 (17.0–32.0)	0.024
Bilirubin (mg/dl) (median (range))	0.7 (0.5–2.0)	0.6 (0.4–1.4)	0.741
PT prolongation (s) (median (range))	0.5 (0.0–2.0)	0.6 (0.0–2.0)	0.602
Cholesterol (mg/dl) (median (range))	131.5 (110.0–251.0)	154.0 (94.0–200.0)	0.513
Triglyceride (mg/dl) (median (range))	110.0 (50.0–340.0)	99.0 (62.0–177.0)	0.731
Fasting insulin (μU/ml) (median (range))	7.35 (0.9–11.9)	4.51 (1.0–9.32)	0.172
Fasting glucose (mg/dl) (median (range))	92.5 (77.0–116.0)	92.0 (76.0–98.0)	0.104
HOMA-IR (median (range))	1.53 (0.19–2.91)	1.04 (0.18–2.3)	0.117
C-peptide (ng/ml) (median (range))	1.9 (0.05–3.19)	1.2 (0.5–3.78)	0.190
C-peptide–insulin ratio (median (range))	0.26 (0.05–1.11)	0.23 (0.05–1.55)	0.896
HOMA-β (%) (median (range))	85.22 (13.17–184.00)	54.72 (27.69–186.46)	0.567
OGTT result (%)			
Diabetes mellitus	0	0	
Impaired glucose tolerance	1 (7.1)	2 (4)	0.53
Normal glucose tolerance	13 (92.9)	48 (96)	
Hypertension (%)	0	0	1.0
Hyperlipidemia (%) (cholesterol >250 and/or triglycerides >150)	3 (21.4)	9 (18)	1.0

ALT, alanine aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HOMA-IR, homeostasis model assessment-insulin resistance; OGTT, oral glucose tolerance test; PT, prothrombin time.

fibrosis (F0 and F1; $n=36$) and significant fibrosis (F2, F3, and F4; $n=33$) groups in HBV patients. Median (range) of insulin (7.1 (0.9–16.5) vs. 7.8 (0.7–29.27); $P=0.096$), HOMA-IR (1.50 (0.19–4.73) vs. 1.84 (0.14–7.05); $P=0.091$), HOMA-β (109.12 (13.5–432.0) vs. 119.0 (13.17–1053.72); $P=0.650$), C-peptide (1.75 (0.5–4.53) vs. 2.0 (0.05–4.79); $P=0.125$), and C-peptide–insulin ratio (0.25 (0.13–3.36) vs. 0.25 (0.05–2.83); $P=0.442$) were comparable between patients with the minimal or no fibrosis (F0 and F1) and significant fibrosis (F2, F3, and F4), respectively.

DISCUSSION

This study, in subjects without a history of DM, shows that IR was found in 49.3% of CHBV-infected patients. The HOMA model has been validated for determining the degree of IR. HOMA-IR accounts for approximately 65% of the variability in insulin sensitivity assessed by the glucose clamp technique (12,19). It is as good a predictor of clamp-determined insulin sensitivity as the short insulin tolerance test (20) or the intravenous glucose tolerance test analyzed with the minimal model (21). HOMA-IR strongly predicts the development of type 2

Table 3. Correlates of HOMA-IR

Variable	Spearman's rank sum correlation	P value
Age	0.173	0.154
Sex	0.017	0.893
BMI	0.384	0.001
Albumin	-0.026	0.835
Bilirubin	-0.056	0.650
ALT	-0.007	0.952
AST	-0.112	0.361
Platelet count	0.142	0.245
PT prolongation	0.071	0.563
Cholesterol	0.109	0.371
Triglycerides	0.298	0.013
Steatosis grade	0.110	0.367
HAI score	0.064	0.603
Fibrosis score	-0.102	0.405
HBV DNA levels	-0.012	0.929

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; PT, prothrombin time.

Table 4. Multiple logistic regression analysis for factors associated with HOMA-IR

Variable	B	B (s.e.)	95% CI of B	P value
BMI	0.149	0.038	0.074-0.226	<0.001
Triglyceride	0.003	0.002	0.002-0.008	<0.224

BMI, body mass index.

diabetes, independent of obesity, body fat distribution, and glucose tolerance status (22). In this study, our results showed that there was a significant correlation between HOMA-IR and BMI and triglyceride levels and on multiple linear regression, BMI was found to be the only predictor of HOMA-IR. This is in line with known observations that IR is associated with obesity and dyslipidemia (7). Although correlation between BMI and HOMA-IR holds true irrespective of ethnic origin, it should be noted that Indian population is not comparable to Caucasian population and the cutoffs for overweight (>23.0 kg/m²) and obesity (>25.0 kg/m²) are lower than the criteria for Caucasian population (9).

The typical obesity phenotype observed in Asian Indians consists of higher percentage of body fat at a lower value of BMI and less lean body mass as compared to Caucasians (23).

In this study CHBV infection was not correlated with IR. Castro *et al.* (1) reported that the incidence of glycemic abnor-

malities was similar in CHBV and chronic HCV. In a study from Iran, it was found that hyperinsulinemia occurs in chronic viral hepatitis B and hepatitis C although this study lacked a control group (6). In recent case-control study from Taiwan CHBV infection was not correlated with IR (7). Thus, unlike chronic HCV infection, CHBV infection is not a disorder with heightened IR. To the contrary, CHBV infection may even be protective. Thus, two recent studies from China and Taiwan, respectively, have shown inverse relationships between the prevalence of metabolic syndrome and positive HBsAg status (8,24).

Thus IR in CHBV-infected patients is related to host factors. In patients with chronic HCV infection IR has been related to the host factors (various components of metabolic syndrome) or related to the virus itself (HCV genotype 3). Preliminary data from HBV patients also suggest that IR/hepatic steatosis in these patients may be related to host factors rather than viral factors (7,25-27). Also the degree of IR was not found to correlate either hepatic necroinflammatory activity or fibrosis stage or HBV DNA levels in CHB. Longitudinal studies examining the impact of IR on the natural history of CHB are required. Also this study did not have genotypes for the CHBV-infected patients and the influence of genotypes if any on IR remains to be seen.

Surprisingly, no relation could be demonstrated between IR and steatosis, despite the association of IR with BMI. This raises the possibility that HBV may have a direct steatogenic effect, independent of IR. Recently, it has been shown that HBV X protein induces hepatic steatosis by transcriptional activation of sterol regulatory element-binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor gamma (PPAR γ) (28).

In our study, there was no significant difference in serum insulin level between patients with minimal or no fibrosis and those with significant fibrosis. Accordingly, it is unlikely that impairment of insulin clearance induced by worsening liver fibrosis accounted for IR in our patients.

In summary, IR in CHBV-infected patients is a reflection of the host metabolic profile and CHBV infection is not in itself correlated with IR. IR is not correlated with histological severity in CHBV-infected patients.

CONFLICT OF INTEREST

Guarantor of the article: Shiv K. Sarin, MD, DM, FNA, FNASc.

Specific author contributions: Manoj Kumar, Ajay Choudhury, Nitin Manglik, and Shiv K. Sarin were responsible for the study design, patient recruitment and care, and data analysis. Syed Hissar was responsible for laboratory tests and database management. Archana Rastogi and Puja Sakhuja were responsible for histological assessment and scoring. All investigators participated in drafting the paper, and approved the final version of the paper.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Chronic hepatitis C virus (HCV) infection is associated with insulin resistance, and both host and viral factors have a role in its development.
- ✓ The association and the predictors of insulin resistance in chronic HBV (CHBV) infection remain unclear.

WHAT IS NEW HERE

- ✓ This study, in subjects without a history of diabetes mellitus, shows that IR was found in 49.3% of chronic HBV infected patients.
- ✓ On multiple linear regression, BMI was found to be the only predictor of HOMA-IR.
- ✓ Insulin resistance in CHBV-infected patients is related to host factors.
- ✓ Insulin resistance is not correlated with histological severity in CHBV infected patients.

REFERENCES

1. Castro N, Carroccio A, Ganci A *et al.* Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. *Diabetes Metab* 2001;27:476–81.
2. Hui JM, Sud A, Farrell GC *et al.* Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology* 2003;125:1695–704.
3. Muzzi A, Leandro G, Rubbia-Brandt L *et al.* Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients. *J Hepatol* 2005;42:41–6.
4. Fartoux L, Poujol-Robert A, Guechot J *et al.* Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005;54:1003–8.
5. Romero-Gómez M, Del Mar Vilorio M, Andrade RJ *et al.* Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;128:636–41.
6. Mohammad Alizadeh AH, Fallahian F, Alavian SM *et al.* Insulin resistance in chronic hepatitis B and C. *Indian J Gastroenterol* 2006;25:286–9.
7. Wang CC, Hsu CS, Liu CJ *et al.* Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. *J Gastroenterol Hepatol* 2008;23:779–82.
8. Jan CF, Chen CJ, Chiu YH *et al.* A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-Based Integrated Screening Study, 10). *Int J Obes (Lond)* 2006;30:794–9.
9. Misra A, Misra R, Wijesuriya M *et al.* The metabolic syndrome in south asians: continuing escalation & possible solutions. *Indian J Med Res* 2007;125:345–54.
10. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539–53.
11. Matthews DR, Hosker JP, Rudenski AS *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
12. Bonora E, Targher G, Alberiche M *et al.* Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000;23:57–63.
13. Petrides AS, Vogt C, Schulze-Berge D *et al.* Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. *Hepatology* 1994;19:616–27.
14. Bonora E, Coscelli C, Orioli S *et al.* Hyperinsulinemia of chronic active hepatitis: impaired insulin removal rather than pancreatic hypersecretion. *Horm Metab Res* 1984;16:111–4.
15. Merli M, Leonetti F, Riggio O *et al.* Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. *Hepatology* 1999;30:649–54.
16. Madan K, Batra Y, Gupta SD *et al.* Non-alcoholic fatty liver disease may not be a severe disease at presentation among Asian Indians. *World J Gastroenterol* 2006;12:3400–5.
17. Knodell RG, Ishak KG, Black WC *et al.* Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431–5.
18. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis* 2001;21:3–16.
19. Emoto M, Nishizawa Y, Maekawa K *et al.* Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. *Diabetes Care* 1999;22:818–22.
20. Bonora E, Moghetti P, Zaccanaro C *et al.* Estimates of *in vivo* insulin action in man: comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab* 1989;68:374–8.
21. Saad MF, Anderson RL, Laws A *et al.* A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Insulin Resistance Atherosclerosis Study*. *Diabetes* 1994;43:1114–21.
22. Haffner SM, Kennedy E, Gonzalez C *et al.* A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996;19:1138–41.
23. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome and Asian Indians). *Curr Sci* 2002;83:1483–96.
24. Luo B, Wang Y, Wang K. Association of metabolic syndrome and hepatitis B infection in a chinese population. *Clin Chim Acta* 2007;380:238–40.
25. Altıparmak E, Koklu S, Yalınkılıç M *et al.* Viral and host causes of fatty liver in chronic hepatitis B. *World J Gastroenterol* 2005;11:3056–59.
26. Gordon A, McLean CA, Pedersen JS *et al.* Hepatic steatosis in chronic hepatitis B and C: predictors, distribution and effect on fibrosis. *J Hepatol* 2005;43:38–44.
27. Thomopoulos KC, Arvaniti V, Tsamantas AC *et al.* Prevalence of liver steatosis in patients with chronic hepatitis B: a study of associated factors and of relationship with fibrosis. *Eur J Gastroenterol Hepatol* 2006;18:233–7.
28. Kim KH, Shin HJ, Kim K *et al.* Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. *Gastroenterology* 2007;132:1955–67.