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BRIEF ARTICLE

Association of chronic viral hepatitis B with insulin resistance

Jeong Gyu Lee, Sangyeoup Lee, Yun Jin Kim, Byung Mann Cho, Joo Sung Park, Hyung Hoi Kim, JaeHun Cheong, Dong Wook Jeong, Yu Hyun Lee, Young Hye Cho, Mi Jin Bae, Eun Jung Choi

Jeong Gyu Lee, Yun Jin Kim, Yu Hyun Lee, Mi Jin Bae, Department of Family Medicine, Pusan National University School of Medicine, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
Jeong Gyu Lee, Yun Jin Kim, Yu Hyun Lee, Mi Jin Bae, Department of Family Medicine, Medical Research Institute, Pusan National University Hospital, Busan 602-739, South Korea
Sangyeoup Lee, Medical Education Unit, Pusan National University School of Medicine, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
Sangyeoup Lee, Family Medicine Clinic, Yangsan Pusan National University Hospital, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
Byung Mann Cho, Department of Preventive Medicine and Occupational Medicine, Pusan National University School of Medicine, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
Joo Sung Park, Department of Family Medicine, Dong-A University Medical Center, Busan 602-715, South Korea
Hyung Hoi Kim, Department of Laboratory Medicine, Biomedical Informatics Unit, Pusan National University School of Medicine, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
JaeHun Cheong, Department of Molecular Biology, College of Natural Sciences, Pusan National University, Busan 602-739, South Korea
Dong Wook Jeong, Young Hye Cho, Eun Jung Choi, Family Medicine Clinic, Yangsan Pusan National University Hospital, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea
Author contributions: Lee JG developed study design and concept, collected of data and drafting of the manuscript; Lee S developed study concept, interpretation of data; Kim YJ studied supervision; Cho BM statistical analysis; Park JS interpretation of data; Kim HH acquisition of data; Cheong J technical support; Jeong DW acquisition of data; Lee YH acquisition of data; Cho YH acquisition of data; Bae MJ acquisition of data; and Choi EJ acquisition of data.
Correspondence to: Sangyeoup Lee, MD, Family Medicine Clinic, Yangsan Pusan National University Hospital, Beomeo-ri Mulgeum-eup, Yangsan 626-770, South Korea. saylee@pnu.edu
Telephone: +82-10-91345959 Fax: +82-51-5108125
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Abstract

AIM: To investigate the relationship between chronic viral hepatitis B (CVHB) and insulin resistance (IR) in Korean adults.

METHODS: A total of 7880 adults (3851 men, 4029 women) who underwent a comprehensive medical examination were enrolled in this study. Subjects diagnosed with either diabetes mellitus, or any other disorder that could influence their insulin sensitivity, were rejected. Anthropometry, metabolic risk factors, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, fasting plasma glucose and insulin were measured for all subjects. Homeostasis model assessment (HOMA), quantitative insulin check index (QUICKI), and Mf_{fm} index were used for determining insulin sensitivity. Each participant was categorized into a negative, recovery, or CVHB group. To compare variables between groups, a t-test and/or one-way analysis of variance were used. Partial correlation coefficients were computed to present the association between insulin resistance and other variables. Multiple logistic regression analysis was used to assess the independent association between CVHB and IR.

RESULTS: The mean age of men and women were 48.9 and 48.6 years, respectively. Subjects in the CVHB group had significantly higher waist circumference [(86.0 ± 7.7 cm *vs* 87.3 ± 7.8 cm, $P = 0.004$ in men), (78.3 ± 8.6 cm *vs* 80.5 ± 8.5 cm, $P < 0.001$ in women)], cystatin C [(0.96 ± 0.15 mg/dL *vs* 1.02 ± 0.22 mg/dL, $P < 0.001$ in men), (0.84 ± 0.15 mg/dL *vs* 0.90 ± 0.16 mg/dL, $P < 0.001$ in women)], fasting insulin [(5.47 ± 3.38 μU/mL *vs* 6.12 ± 4.62 μU/mL, P < 0.001 in men), (4.57 ± 2.82 μU/mL *vs* 5.06 ± 3.10 μU/mL, $P < 0.001$ in women)] and HOMA index [(1.24 ± 0.86 *vs* 1.43 ± 1.24, $P < 0.001$ in men), (1.02 ± 0.76 *vs* 1.13 ± 0.87, $P = 0.033$ in women)] compared to control group. The HOMA index revealed a positive correlation with body mass index (BMI) ($r = 0.378$, $P < 0.001$), waist circumference ($r = 0.356$, $P < 0.001$), percent body fat ($r = 0.296$, $P < 0.001$), systolic blood pressure ($r = 0.202$, $P < 0.001$), total cholesterol ($r = 0.134$, $P < 0.001$), triglycerides ($r = 0.292$, $P < 0.001$),

cystatin C (r = 0.069, P < 0.001) and uric acid (r = 0.142, P < 0.001). The QUICKI index revealed a negative correlation with BMI (r = -0.254, P < 0.001), waist circumference (r = 0-0.243, P < 0.001), percent body fat (r = -0.217, P < 0.001), systolic blood pressure (r = -0.132, P < 0.001), total cholesterol (r = -0.106, P < 0.001), triglycerides (r = -0.205, P < 0.001), cystatin C (r = -0.044, P < 0.001) and uric acid (r = -0.096, P < 0.001). For subjects identified with IR, the odds ratio of an accompanying diagnosis of chronic hepatitis B was 1.534 (95% CI: 1.158-2.031, HOMA index criteria) or 1.566 (95% CI: 1.124-2.182, QUICKI criteria) after adjustment for age, gender, BMI, and amount of alcohol consumption.

CONCLUSION: Our study demonstrates that CVHB is associated with IR. CVHB may need to be monitored for occurrence of IR and diabetes mellitus.

Key words: Hepatitis B; Insulin resistance; Diabetes mellitus, type 2; Metabolic syndrome

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INTRODUCTION

Insulin resistance (IR) is the principal indication for development of metabolic syndrome and type 2 diabetes[1,2]. IR appears as a consequence of the inability of insulin to induce the appropriate effect on glucose metabolism. Inordinately large amounts of insulin are required to achieve a normal response in a state of IR. A hyperinsulinemic state causes several clinical abnormalities to appear in the blood vessels, kidneys, and liver, and these represent the major features of metabolic syndrome[3].

Metabolic syndrome generally refers to a combination of metabolic diseases such as abdominal obesity, high blood pressure, dyslipidemia and elevated blood glucose, that appear together in an individual patient[1]. Because metabolic syndrome is recognized as a serious risk factor for cardiovascular disease, prevention and comprehensive management are important in treating this condition[4].

Hepatitis B is one of the most common health problems and it is estimated that, of the world's total population, one third (over 2 billion people) have been infected with hepatitis B virus (HBV)[5]. Approximately two thirds of chronic viral hepatitis B (CVHB) patients live in Asia and the Pacific Islands. HBV infection may cause acute and/or chronic hepatitis and premature death from liver cirrhosis, liver failure or hepatocellular carcinoma[6]. Moreover, CVHB infection is related to other diseases such as polyarteritis nodosa (PAN)[7], glomerulonephritis (GN)[8], serum sickness-like syndrome (prodrome)[9], arthritis[10], and acrodermatitis[11].

Recently, an experimental study suggested that hepatitis B X protein (HBx) impairs the hepatic insulin signaling pathway, and that HBV infection is associated with IR[12]. A previous clinical studies also suggest that hyperinsulinemia occurs in CVHB and hepatitis C[13], and this association has been elucidated in hepatitis C virus (HCV) infection[14,15]. HCV may disturb the insulin signaling pathway by activation of the tumor necrosis factor (TNF) system[16]. IR has been proposed as an important risk factor in patients with chronic hepatitis C, mainly due to its relationship to steatosis development[17] and fibrosis progression[18], and non-response to peginterferon plus ribavirin[19]. However, the effect of HBV infection on human insulin sensitivity remains unclear. In this study, we tested the hypothesis that HBV infection may associate with IR and metabolic syndrome, by comparing incidence of IR and prevalence of metabolic syndrome between HBV-infected study participants and a healthy control group.

MATERIALS AND METHODS

Study subjects

This consecutive study conducted at the Center for Health Promotion, Pusan National University Hospital in Busan, South Korea. Data for this study were obtained from 7880 Koreans (3851 men, 4029 women) who underwent a comprehensive medical examination between January 2007 and September 2008. The study participants were eligible if they met all of the following criteria: age ⩾ 18 years, no history of diabetes and hypertension requiring medication, negative for anti-hepatitis C antibody, serum aspartate aminotransferase or alanine aminotransferase (ALT) < 80 IU/L, serum gamma-glutamyl transferase (GGT) < 80 mg/dL, serum creatinine < 1.5 mg/dL, prostate specific antigen < 5.0 ng/mL, α-fetoprotein < 10.0 IU/mL, carcinoembryonic antigen < 5.0 ng/mL (for smokers) or < 2.5 ng/mL (for non-smokers), WBC count < 10 000/μL, and high sensitivity C-reactive protein (hs-CRP) < 1 mg/dL.

Measurements

The health checkup which provided our study data included a physical examination, anthropometric measurements and blood tests. Height and weight were measured to the nearest 0.1 cm and 0.1 kg using standard protocol with subjects wearing a light gown and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest, at the end of a normal expiration of breath and to the nearest 0.1 cm.

Percentage of body fat and total fat mass were measured by bioelectric impedance analysis (Inbody 3.0, Biospace Co, Ltd, Korea). Blood pressure was measured using the right arm of subjects assuming a sitting position, and after they had rested for at least 10 min. By use of an automated blood pressure measurement device (BP-203RV Ⅱ, Colin Corp, Aichi, Japan). Medication history, alcohol intake and smoking habits were obtained by patient interview. The questions relating to alcohol intake included descriptions of the type of alcohol beverage consumed, the weekly frequency of alcohol consumption, and the amount consumed daily. Smoking status was classified as either non-smoker or smoker (former or current). Blood samples were obtained from an antecubital vein after 12 h fasting, typically between 8 and 9 AM. The blood samples were subsequently analyzed at a certified laboratory at Pusan National University Hospital. Lipid profiles, uric acid, and GGT concentrations were measured using an autoanalyzer with the enzymatic colorimetric method (Hitachi7600, Hitachi Ltd, Japan). Cystatin C was measured by turbidimetric immunoassay (HBI Co, Ltd, Korea) using the Modular Analytics E170 (Roche Diagnostics, Switzerland). Hs-CRP was measured using a Behring Nephelometer (DadeBehring, Germany). Fasting plasma glucose was measured by the glucose oxidase method using a Synchron LX 20 (Beckman Coulter, Fullerton, CA, United States). Fasting insulin was measured using a radioimmunoassay (Diagnostic Product Corporation, Los Angeles, CA, United States) with antibody-coated tubes. The mean intra- and interassay coefficient of variation (CV) values were 4.2% and 6.3%, respectively.

Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, and hepatitis B core antibody were measured by enzyme-linked immunosorbent assay (Bio Focus Co, Ltd, Korea). Hepatitis B viral status was classified into three groups (negative/recovery/CVHB), according to serologic patterns. Insulin sensitivity was estimated using homeostasis model assessment (HOMA)-IR [fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405][20], quantitative insulin check index (QUICKI) {1/[log glucose (mg/dL) + log insulin (μU/mL)]}[21,22] and Mf_{fm} index ($\exp^{2.63 - [0.28 \times \ln(\text{insulin})] - [0.31 \times \ln(\text{triglycerides})]}$)[23].

Definition of metabolic syndrome

The prevalence of metabolic syndrome reported in this study was estimated using definitions proposed in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)[24] and the International Diabetes Federation criteria[25] for the diagnosis of metabolic syndrome. We defined central obesity as a waist circumference ⩾ 90 cm in males and ⩾ 85 cm in females, according to geography-specific cut points for waist circumference[26].

Ethical approval

All participants gave informed consent, and this study was approved by the Institutional Review Board at Pusan National University Hospital and is in accordance with the Declaration of Helsinki (E2010-055).

Table 1 Baseline characteristics of study subjects

Variables	Men (n = 3851)	Women (n = 4029)
Age (yr)	48.9 ± 10.7	48.6 ± 10.4
BMI (kg/m^2)	24.5 ± 2.8	23.5 ± 2.9
Abdominal circumference (cm)	86.5 ± 7.4	79.2 ± 8.4
Percentage body fat (%)	22.7 ± 5.1	30.1 ± 5.7
Systolic BP (mmHg)	126.3 ± 15.3	122.3 ± 15.4
AST (IU/L)	23.8 ± 8.6	20.9 ± 10.5
ALT (IU/L)	26.8 ± 16.6	19.0 ± 11.5
GGT (IU/L)	38.0 ± 20.1	20.0 ± 12.6
Fasting plasma glucose (mg/dL)	91.6 ± 14.7	88.3 ± 14.1
Fasting insulin (μU/mL)	5.48 ± 3.49	4.64 ± 2.78
Total cholesterol (mg/dL)	196.3 ± 33.3	195.8 ± 35.2
Triglycerides (mg/dL)	138.0 ± 80.9	103.8 ± 63.6
HDL-cholesterol (mg/dL)	50.8 ± 12.5	59.8 ± 14.1
LDL-cholesterol (mg/dL)	124.8 ± 29.5	121.0 ± 31.8
high-sensitivity CRP (mg/dL)	0.15 ± 0.47	0.11 ± 0.37
TSH (μU/mL)	1.79 ± 1.79	2.29 ± 2.15
Uric acid (mg/dL)	5.88 ± 1.25	4.20 ± 0.91

Differences between men and women were statistically significant except for age and total cholesterol (P < 0.05 by t test). BMI: Body mass index; BP: Blood pressure; AST: Aspartate transferase; ALT: Alanine transferase; GGT: Gamma-glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; TSH: Thyroid stimulating hormone.

Statistical analysis

To compare variables between groups, a t test and/or one-way analysis of variance followed by a Scheffé post hoc test or Kruskal-Wallis test were used as appropriate. Pearson partial correlation coefficients were computed to present the association between fasting plasma glucose concentration and other variables after adjustments for age, gender and alcohol consumption. Using multiple logistic regression analysis and adjusting for age, gender and alcohol intake, we estimated the existence of any independent association between IR and HBV status. Statistical analysis was performed using SPSS 12.0 for Windows. A P value of less than 0.05 was considered statistically significant. All statistical tests were two-sided.

RESULTS

Baseline characteristics of study subjects

The subjects were classified as men (n = 3851) and women (n = 4029), and their baseline clinical characteristics were compared (Table 1). The mean age of men and women were 48.9 years and 48.6 years, respectively. Age and total cholesterol level were not statistically different between men and women (P > 0.05). Men had significantly higher results for BMI, abdominal circumference, systolic blood pressure, aspartate aminotransferase, ALT, GGT, fasting plasma glucose, insulin, triglycerides, low-density lipoprotein-cholesterol, hs-CRP, and uric acid (P < 0.001).

Metabolic characteristics according to hepatitis groups

The metabolic data of study participants are shown in Table 2. In both men and women, subjects in the CVHB group were significantly older with larger waist circum-

Table 2 Means and frequencies of metabolic risk factors associated with hepatitis B virus status in men and women (mean ± SD)

Variables	Negative (n = 1292)	Recovery from hepatitis B (n = 1956)	Chronic hepatitis B (n = 603)	P value[1]
Hepatitis B virus status in men				
Age (yr)	44.4 ± 11.7	51.4 ± 9.4	50.8 ± 10.7	0.000
Body mass index (kg/m^2)	24.5 ± 2.9	24.5 ± 2.7	24.7 ± 2.9	0.493
Waist circumference (cm)	86.0 ± 7.7	86.5 ± 7.0	87.3 ± 7.8	0.004
Percentage body fat (%)	22.5 ± 5.7	22.8 ± 4.6	23.0 ± 5.0	0.094
Systolic blood pressure (mmHg)	126.4 ± 15.5	126.3 ± 15.0	126.1 ± 15.6	0.922
Total cholesterol (mg/dL)	196.0 ± 33.2	196.8 ± 33.1	195.5 ± 34.5	0.680
Triglyceride (mg/dL)	142.8 ± 84.5	135.6 ± 79.2	135.2 ± 78.2	0.029
HDL-cholesterol (mg/dL)	51.0 ± 12.7	50.9 ± 12.8	50.4 ± 11.4	0.602
Cystatin C (mg/L)	0.96 ± 0.15	0.98 ± 0.16	1.02 ± 0.22	0.000
Fasting glucose (mg/dL)	90.7 ± 15.3	92.1 ± 14.4	91.9 ± 14.4	0.039
Fasting insulin (μU/mL)	5.47 ± 3.38	5.29 ± 3.10	6.12 ± 4.62	0.000
HOMA index	1.24 ± 0.86	1.22 ± 0.80	1.43 ± 1.24	0.000
QUICKI index	0.386 ± 0.065	0.386 ± 0.044	0.385 ± 0.134	0.922
Mf$_{fm}$ index	8.41 ± 2.43	8.58 ± 2.31	8.39 ± 2.63	0.072
Hepatitis B virus status in women				
Age (yr)	45.9 ± 10.7	50.9 ± 9.3	51.6 ± 10.3	0.000
Body mass index (kg/m^2)	23.2 ± 3.0	23.7 ± 2.7	24.0 ± 2.9	0.000
Waist circumference (cm)	78.3 ± 8.6	79.8 ± 8.0	80.5 ± 8.5	0.000
Percentage body fat (%)	29.6 ± 6.8	30.4 ± 4.6	31.0 ± 4.9	0.000
Systolic blood pressure (mmHg)	121.3 ± 15.4	123.0 ± 15.5	124.5 ± 14.3	0.000
Total cholesterol (mg/dL)	193.3 ± 35.4	197.9 ± 35.0	198.1 ± 34.3	0.000
Triglyceride (mg/dL)	102.0 ± 63.5	106.4 ± 66.2	100.3 ± 47.5	0.061
LDL-cholesterol (mg/dL)	118.3 ± 31.6	123.2 ± 31.8	123.7 ± 31.7	0.000
Cystatin C (mg/L)	0.84 ± 0.15	0.87 ± 0.15	0.90 ± 0.16	0.000
Fasting glucose (mg/dL)	88.0 ± 14.6	88.7 ± 13.7	88.3 ± 12.9	0.357
Fasting insulin (μU/mL)	4.57 ± 2.82	4.62 ± 2.67	5.06 ± 3.10	0.010
HOMA index	1.02 ± 0.76	1.03 ± 0.67	1.13 ± 0.87	0.033
QUICKI index	0.401 ± 0.056	0.398 ± 0.051	0.392 ± 0.045	0.013
Mffm index	9.77 ± 2.62	9.58 ± 2.53	9.36 ± 2.25	0.006

[1]Analysis of variance except triglyceride (Kruskal-Wallis test). HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HOMA: Homeostasis model assessment; QUICKI: Quantitative insulin check index.

Table 3 Partial correlation coefficients of insulin sensitivity index to metabolic parameters after adjusting for age, gender, and alcohol consumption

	BMI	WC	BFP	SBP	TC	TG	HDL-C	Cys-C	Uric acid
FPG	0.150	0.151	0.114	0.138	0.087	0.141	-0.102	-0.108	-0.010
Insulin	0.395	0.368	0.313	0.196	0.132	0.293	-0.206	0.105	0.168
HOMA index	0.378	0.356	0.296	0.202	0.134	0.292	-0.202	0.069	0.142
QUICKI index	-0.254	-0.243	-0.217	-0.132	-0.106	-0.205	0.164	-0.044	-0.096
Mf$_{fm}$ index	-0.374	-0.366	-0.318	-0.199	-0.258	-0.628	0.386	-0.116	-0.203

BMI: Body mass index; WC: Waist circumference; BFP: Percent of body fat; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; Cys-C: Cystatin-C; FPG: Fasting plasma glucose; HOMA: Homeostasis model assessment; QUICKI: Quantitative insulin check index. All correlation coefficients are statistically significant (P < 0.001).

ferences, and had higher percentages of body fat, cystatin C, fasting insulin, and HOMA index compared to other groups. There were significant differences between men in the CVHB group and negative group in terms of fasting plasma glucose, but no significant differences were observed for women. QUICKI (P < 0.05) and Mf$_{fm}$ index (P < 0.01) results were significantly lower for women in the CVHB group.

Correlation of insulin sensitivity index with metabolic factors

The HOMA index revealed a positive correlation with BMI (r = 0.378, P < 0.001), waist circumference (r = 0.356, P < 0.001), percent body fat (r = 0.296, P < 0.001), systolic blood pressure (r = 0.202, P < 0.001), total cholesterol (r = 0.134, P < 0.001), triglycerides (r = 0.292, P < 0.001), cystatin C (r = 0.069, P < 0.001) and uric acid (r = 0.142, P < 0.001) (Table 3). QUICKI and Mf$_{fm}$ index produced a negative correlation with BMI, waist circumference, percent body fat, systolic blood pressure, total cholesterol, triglycerides, cystatin C, and uric acid (P < 0.001).

Association of insulin resistance and chronic hepatitis B

For the presence of IR, adjusted odds ratios for the CVHB group was 1.534 (95%CI: 1.158-2.031, HOMA index criteria) or 1.566 (95% CI: 1.124-2.182 in QUICKI

Table 4 Logistic regression analysis with insulin resistance as a dependent variable

Variables	Insulin resistance					
	HOMA index criteria			QUICKI criteria		
	β	SE	Odds ratio (95% CI)	β	SE	Odds ratio (95% CI)
Age (yr)	0.009	0.005	1.009 (0.999-1.019)	0.016	0.006	1.016 (1.005-1.028)
Gender						
Men	0.487	0.109	1.627 (1.314-2.015)	0.452	0.131	1.571 (1.215-2.031)
Women			1.000			1.000
Body mass index (kg/m^2)	0.316	0.017	1.372 (1.328-1.417)	0.347	0.020	1.746 (1.663-1.833)
Alcohol consumption (kcal)	0.000	0.000	1.000 (0.999-1.000)	0.000	0.000	1.000 (0.999-1.000)
Hepatitis B virus status						
Negative			1.000			1.000
Recovery from hepatitis B	-0.027	0.112	0.974 (0.782-1.212)	-0.075	0.135	0.928 (0.712-1.210)
Chronic hepatitis B	0.428	0.143	1.534 (1.158-2.031)	0.449	0.169	1.566 (1.124-2.182)

HOMA: Homeostasis model assessment; QUICKI: Quantitative insulin check index.

criteria) (Table 4). Adjusting factors included age, gender, BMI and amount of alcoholic consumption.

DISCUSSION

In this study, CVHB was observed to be associated with IR in subjects free of prior diabetes mellitus. CVHB independently predicted a clinically significant increase in the odds ratio for the development of IR. These results indicate that patients with CVHB may need to be carefully monitored for occurrence of IR and diabetes mellitus. As the present study reports basic data on the association between CVHB and IR in a large community population, these findings support previous proposals that CVHB infection is related to IR.

HBV is the prototype member of a steadily growing family of viruses called hepadnaviruses[27]. It is a partially double stranded virus that uses reverse transcriptase in its replication cycle. CVHB infection is a common health issue in Asia and the Pacific Islands. In Korea, approximately 3.7% of total population are affected in chronic hepatitis B[28]. Most were infected directly from their mother during birth or through contact between children. CVHB infection may increase the occurrence of hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma[29]. In addition, CVHB infection is related to diseases such as PAN, GN, and arthritis[7-9]. Moreover, there is experimental evidence that CVHB infection increases the appearance of both IR and associated diabetes mellitus. A recent animal study suggested that HBx impairs the insulin signaling pathway[12]. These findings provide the basis of a hypothesis for mechanism and are consistent with our study results.

IR is assumed to be caused by an inadequate glucose metabolism capacity which leads to more insulin to be secreted to achieve the same biologic response[30]. Hyperinsulinemia may induce a large variety of abnormalities in blood vessels, kidneys, and muscles, and is the major pathogenesis associated with metabolic syndrome. Diabetes mellitus and metabolic syndrome are also independent risk factors for atherosclerotic disease[31]. Thus, early screening of high risk groups is very important to successful health promotion. The gold standard parameter for determining insulin sensitivity is the hyperinsulinemic euglycemic clamp technique. The HOMA model[20], QUICKI[21], and Mf_{fm} index[23] used in this study show good correlation with the clamp technique and are easily utilized in primary practice.

Previous studies have proposed association of HBV infection and IR. One previous, retrospective study proposed that maternal HBsAg carrier status was a risk factor for development of gestational diabetes[32]. Sangiorgio *et al*[33] also reported increased frequency of HCV and HBV infection in type 2 diabetic patients. One study reported concordant results using the HOMA model that concluded that hyperinsulinemia occurs in chronic viral hepatitis B and hepatitis C[13]. However, another previous study reported that HBV carriers were not associated with IR[34]. But that study had limitations due to small number of study subjects and high prevalence of fatty liver disease in the subjects.

The mechanism IR plays in CVHB infection remains unknown. There are four proteins that originate from the HBV genome including polymerase, a surface protein, a core protein, and the HBx protein. Among these proteins, HBx may be most closely associated with hepatic steatosis, inflammation, and HBV-related disease[34]. Previous reports proposed that hepatic steatosis and systemic inflammation are associated with IR[35]. HBx protein can induce hepatic steatosis and inflammation, thus CVHB infection is possibly associated with an impaired insulin signaling pathway[36]. A recent report concluded that chronic inflammation had effect on IR[37]. HBV may induce activation of proinflammatory cytokines TNF-α, interleukin (IL)-6, and IL-1β associated with fat accumulation[29]. Hepatic steatosis has already been demonstrated to be related to IR, and this association has been clearly identified in HCV infection. HCV proteins present due to infection may also disturb the insulin signaling pathway. IR with chronic hepatitis C has also been related to steatosis development and fibrosis progression[13-15].

The strength of this study was inclusion of healthy volunteers, which provided greater validity compared to hospital-based or institutional based populations. Other strengths included the large sample size, characterization of multiple confounders that influence IR, and the availability of 3 IR index or insulin sensitivity markers which are validated and widely used, and were also used for determining the degree of IR in previous studies.

This study had several limitations. Because of the cross-sectional nature of this study, it was difficult to prove a causal relationship between HBV infection and IR. Also, our results may not be able to be generalized to other ethnic groups because the present study was conducted exclusively using ethnic Koreans. A weakness in terms of clinical data is that daily variability of insulin within individuals is high, and a single, daily sample may not accurately characterize the actual level. Moreover, there are numerous other factors that influence IR such as condition of skeletal muscles, engagement in physical activity, and severity of liver injuries. Future studies that overcome these limitations are needed to confirm our findings.

In conclusion, CVHB may be associated with IR as identified by HOMA-index, QUICKI, and Mf_{fm} index results. These findings should be explored further.

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COMMENTS

Background

Insulin resistance (IR) is the principal indication for development of metabolic syndrome and type 2 diabetes. Chronic viral hepatitis B (CVHB) is one of the most common health problems and previous clinical studies also suggest that hyperinsulinemia occurs in CVHB. However, the effect of hepatitis B virus (HBV) infection on human insulin sensitivity remains controversial. The authors therefore investigated the hypothesis that HBV infection may associate with IR and metabolic syndrome, by comparing incidence of IR between HBV-infected subjects and healthy group.

Research frontiers

There are four proteins that originate from the HBV genome including polymerase, a surface protein, a core protein, and the hepatitis B X protein (HBx) protein. Among these proteins, HBx may be most closely associated with hepatic steatosis, inflammation, and HBV related disease. Moreover, recent experimental study suggested that HBx impairs the hepatic insulin signaling pathway.

Innovations and breakthroughs

CVHB was observed to be associated with IR in subjects free of prior diabetes mellitus. CVHB independently predicted a clinically significant increase in the odds ratio for the development of IR. These results indicate that patients with CVHB may need to be carefully monitored for occurrence of IR and diabetes mellitus.

Applications

CVHB infection is a common health issue in Asia and the Pacific Islands. CVHB may need to be monitored for occurrence of insulin resistance and diabetes mellitus.

Terminology

Homeostasis model assessment index is calculated by equation of [fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405], quantitative insulin check index is calculated by equation of {1/[log glucose (mg/dL) + log insulin (μU/mL)]}, Mf_{fm} index is obtained by equation of $(\exp^{2.63 - [0.28 \times \ln(\text{insulin})] - [0.31 \times \ln(\text{triglycerides})]})$.

Peer review

This study investigated the association of insulin resistance and chronic viral hepatitis B. The authors evaluated a numerous population of HBV infected patients and compared their metabolic features with control group. This manuscript reinforce further evaluations on a real clinical impact of this association.

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