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The risky body mass index ranges for significant hepatitis B viral load: A campus-based study

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Summary Significant hepatitis B viral load ($\geq 10,000$ copies/mL) was established to increase risk of advanced liver diseases. The aim of this study was to explore the metabolic risk factors for significant hepatitis B viral load. A campus-based cohort consisting of 146 participants of chronic hepatitis B virus (HBV) infection in Northern Taiwan was investigated in 2009. Clinical profiles including serum levels of deoxyribonucleic acid of hepatitis B virus (HBV DNA) were collected. Hepatitis B e antigen (HBeAg) serostatus, high alanine aminotransferase level, body mass index (BMI) ranges, and insulin resistance were related to significant HBV DNA levels in univariate analysis. Compared to individuals with BMI 23–24.9 kg/m² in multivariate analysis, those with BMI ≥ 25 kg/m² (OR = 3.86, 95% CI = 1.38–10.8, $P = 0.010$) and those with BMI < 23 kg/m² (OR = 4.47, 95% CI = 1.32–15.2, $P = 0.016$) were at higher risk for significant HBV DNA levels. This phenomenon was also manifest in HBeAg seronegatives, who contributed to a majority of significant viral load in our study. Furthermore,

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insulin resistance and BMI ≥ 25 kg/m² had positive additive effects on significant HBV DNA levels (adjusted OR=9.34, 95% CI=1.74–50.3, $P=0.009$). In conclusion, having certain BMI ranges (BMI ≥ 25 kg/m² or BMI <23 kg/m²) could be a risk factor of significant HBV DNA levels.

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Introduction

Chronic hepatitis B virus (HBV) infection is a challenging global health issue, especially in the Asia Pacific region. Although the universal vaccination program in Taiwan decreased the carrier rate of hepatitis B surface antigen (HBsAg) from 10% in 1984 to less than 1% in 2004 [1,2], the disease burden there was not yet eradicated. It contributes to more than 122 million USD of Taiwan medical cost for outpatient and inpatient care in 2007 (www.doh.gov.tw) [Statistical Annual Report of Medical Care 2007].

High levels of deoxyribonucleic acid of hepatitis B virus (HBV DNA) lead to an increased risk of cirrhosis and hepatocellular carcinoma [3–5]. However, conventional medical interventions for HBV carriers with a large viral load are not always indicated based on current guidelines [6]. This population should be studied to identify convenient clinical predictors for developing a large viral load, and then to establish further preventive strategies.

Some animal models have shown that HBV gene expression is regulated similarly to key metabolic genes in hepatocytes, and thus HBV is believed to behave like a “metabolovirus” [7]. The prevalence of obesity and metabolic syndrome has been increasing in Taiwan in recent years [8–10]. The naturally acquired HBV infection of university freshmen resulted in a higher risk for developing metabolic syndrome compared to individuals having seroprotective titers from HBV vaccination [11]. Moreover, metabolic factors have been found to increase the risk of progression to late outcomes such as cirrhosis and hepatocellular carcinoma [12–14]. But few epidemiological studies examine the relationship between metabolic factors and the early outcome predictor – hepatitis B viral load [13]. Therefore, we tested the hypothesis that the presence of certain metabolic factors in chronic HBV-infected individuals is associated with significant HBV DNA levels in a campus-based study.

Materials and methods

Participants

Participants with chronic HBV infection (positive HBsAg serostatus for 6 months or longer) were recruited from the student, alumni, faculty and staff population of a university in northern Taiwan from August 1, 2009 to December 15, 2009. Only individuals aged 18 or older were included. Excluded were: (a) those who had been diagnosed with chronic liver diseases including chronic hepatitis C virus infection, autoimmune hepatitis, Wilson disease, alcoholic liver diseases, drug-related hepatitis, decompensated liver diseases, cirrhosis, or malignant hepatic tumors; (b) those who had received liver transplantation or major operations involving the liver, except cholecystectomy; (c) men who consumed more than 30 g, or women who consumed more than 20 g, of alcohol per week; (d) women who were pregnant; (e) those who had medications for any type of chronic diseases except for hyperglycemia, elevated blood pressure, or dyslipidemia within 6 months. Written informed consents were obtained from all participants. Patients with alanine aminotransferase (ALT) levels exceeding twice the upper limit and HBV DNA levels more than 10,000 copies/mL were referred to hepatologists for further evaluation and management. A total of 180 candidates registered in the Hepatitis B databank of National Taiwan University Health Center were invited to participate, and 165 were enrolled with an informed consent. They agreed to participate in questionnaire interview, health examination and blood collection for serological and biochemical assays at study entry. They also gave their consent for confirming their health and viral status through medical record review. Among them, 19 were excluded for negative serum HBsAg or positive serum antibody to hepatitis C virus. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

Anthropometric indices and laboratory measurements

Body height and weight were measured using a single stadiometer and body mass index (BMI) was calculated. The participants were classified as normal or underweight (BMI <23 kg/m²), overweight (BMI 23–24.9 kg/m²), or obese (BMI ≥25 kg/m²) according to the potential public health action points for Asian populations as recommended by World Health Organization [15]. Waist circumference (WC) was taken at the end of exhalation in the horizontal plane containing the point midway between the inferior margin of the lowest rib and the iliac crest. Central obesity was defined as WC ≥90 cm for men and WC ≥80 cm for women according to the criteria for metabolic syndrome currently used in Taiwan (www.bhp.doh.gov.tw). Blood pressure (BP) was measured with an electronic sphygmomanometer with the patient seated after resting for at least 10 min. Elevated BP was defined as systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg also based on the criteria for metabolic syndrome used in Taiwan.

Each participant received laboratory tests after fasting for at least 8 h. Serological tests included serum HBsAg, serum antibody to hepatitis C virus, and hepatitis B e antigen (HBeAg) by microparticle enzyme immunoassay (Abbott Laboratories, IL, USA). HBV DNA levels were measured by COBAS TaqMan real-time polymerase chain reaction assay (Roche Diagnostics, Basel, Switzerland), which detects an upper limit of 640,200,000 copies/mL and a lower limit of 35 copies/mL (1 copies/mL = 0.1718 IU/mL). A significant HBV DNA level was defined as 10,000 copies/mL or more. A high ALT level, determined using the COBAS kinetic UV method (Roche Diagnostics, Basel, Switzerland), was defined as 41 IU/L or more for men and 31 IU/L or more for women. A high fasting glucose level, determined using the hexokinase method, was defined as 100 mg/dL or more (1 mg/dL = 0.0555 mmol/L). Serum fasting insulin levels were measured using the COBAS electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland) (1 µIU/mL = 6.945 pmol/L). Insulin resistance scores were determined by the homeostasis model assessment of insulin resistance (HOMA-IR), as calculated by the following formula: HOMA-IR score = fasting insulin (µIU/mL) × fasting glucose (mg/dL) / 405 [16,17]. Participants were categorized as insulin resistant if the HOMA-IR was 2.5 or more [18]. A low high-density lipoprotein cholesterol (HDL-C) level, determined by the homogeneous enzymatic colorimetric assay,

was defined as HDL-C <40 mg/dL for men and <50 mg/dL for women (1 mg/dL = 0.0259 mmol/L). A high low-density lipoprotein cholesterol (LDL-C) level, using the same method, was defined as LDL-C ≥130 mg/dL (1 mg/dL = 0.0259 mmol/L). A high triglycerides level was defined as triglycerides ≥150 mg/dL (1 mg/dL = 0.0113 mmol/L) and a high sensitive C-reactive protein (hs-CRP) level was defined as hs-CRP ≥0.3 mg/dL (1 mg/dL = 10 mg/L).

Statistical analysis

For descriptive analyses values were presented as number (percent) or mean ± standard deviation (SD). For univariate analyses the chi-square test or Fisher exact test was applied to categorical data. Continuous variables were compared using the two-sample Student's *t* test. Absolute HBV DNA levels were compared using the Mann–Whitney–Wilcoxon rank-sum test. Multiple logistic regression analyses were used to examine whether metabolic factors were independently or jointly associated with significant HBV DNA level after adjustment for potential confounding factors. Stepwise subgroup analyses were also performed for HBeAg seronegatives and also for HBeAg seronegatives with normal ALT levels. The odds ratios (ORs) and 95% confidence intervals (CIs) were derived to assess the magnitude of the association between various predictors of high serum HBV DNA levels. Significance levels were determined by two-tailed tests (*P* < 0.05). All the statistical analyses were performed with SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The post hoc statistical power was calculated by the online OpenEpi software version 2.3 (www.OpenEpi.com).

Results

Clinical characteristics of participants

Among the 146 participants in this study were 67 (45.89%) with HBV DNA levels less than 10,000 copies/mL and 11 (7.53%) with levels lower than the detectable limit (<35 copies/mL). As shown in Table 1, there were 79 participants (54.11%) with HBV DNA levels of 10,000 copies/mL or greater (significant HBV DNA levels) and 23 (15.75%) with levels greater than the detectable limit (≥640,200,000 copies/mL). The majority of participants were male (*n* = 114, 78.08%), younger than 40 years (*n* = 120, 82.19%), without high ALT levels (*n* = 101, 69.18%), HBeAg seronegative

Table 1 Clinical profiles of participants by the presence of significant HBV DNA levels.

Factor	Non-significant HBV DNA level (<i>n</i> = 67)	Significant HBV DNA level (<i>n</i> = 79)	<i>P</i> -value
Age (years), mean ± SD	32.33 ± 6.96	32.85 ± 9.24	0.699
Male, <i>n</i> (%)	54 (80.60)	60 (75.95)	0.499
HBeAg seronegative, <i>n</i> (%)	65 (97.01)	44 (55.70)	<0.0001
High ALT level, <i>n</i> (%)	13 (19.40)	32 (40.51)	0.006
BMI (kg/m ²), mean ± SD	24.91 ± 3.25	25.38 ± 3.99	0.441
BMI < 23, <i>n</i> (%)	13 (19.40)	23 (29.11)	0.006
BMI 23–24.9 kg/m ²	28 (41.79)	14 (17.72)	
BMI ≥ 25, <i>n</i> (%)	26 (38.81)	42 (53.16)	
WC (cm), mean ± SD	87.16 ± 8.90	87.94 ± 10.62	0.632
Central obesity, <i>n</i> (%)	34 (50.75)	39 (49.37)	0.868
Elevated BP, <i>n</i> (%)	19 (28.36)	26 (32.91)	0.554
Glucose AC (mg/dL), mean ± SD	74.16 ± 9.35	76.65 ± 8.61	0.098
Insulin (μIU/mL), mean ± SD	7.69 ± 4.09	8.89 ± 0.57	0.120
HOMA-IR, mean ± SD	1.42 ± 0.76	1.70 ± 0.99	0.053
Insulin resistance, <i>n</i> (%)	5 (7.46)	16 (20.25)	0.017
Low HDL-C level, <i>n</i> (%)	8 (11.94)	15 (18.99)	0.244
High LDL-C level, <i>n</i> (%)	22 (32.84)	30 (37.97)	0.518
High triglycerides level, <i>n</i> (%)	8 (11.94)	15 (18.99)	0.244
High hs-CRP level, <i>n</i> (%)	7 (10.45)	12 (15.19)	0.396

ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; Glucose AC, overnight fasting glucose; HBeAg, hepatitis B e antigen; HBV DNA, deoxyribonucleic acid of hepatitis B virus (significant $\geq 10^4$ copies/mL; non-significant, $<10^4$ copies/mL); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, high sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference.

Conversion factors to SI units: glucose AC (1 mg/dL = 0.0555 mmol/L), HBV DNA (1 copies/mL = 0.1718 IU/mL), insulin (1 μIU/mL = 6.945 pmol/L).

(*n* = 109, 74.66%), and obese (*n* = 68, 46.58%). Participants with significant HBV DNA levels were more likely to have positive HBeAg serostatus ($P < 0.0001$) and high ALT levels ($P = 0.006$).

Metabolic factors and significant HBV DNA levels

Participants with significant HBV DNA levels were less likely to have BMI 23–24.9 kg/m² ($P = 0.006$) but more likely to have insulin resistance ($P = 0.017$) (Table 1). The post hoc statistical power was 90.11% based on the presence of significant HBV DNA levels across two BMI groups (BMI 23–24.9 kg/m² vs. (BMI < 23 kg/m² or BMI ≥ 25 kg/m²), i.e., overweight vs. non-overweight). The median value of HBV DNA level of individuals with BMI 23–24.9 kg/m² was lower than that of individuals with BMI < 23 kg/m² (3306.0 vs. 38779.0 copies/mL, $P = 0.171$) and that of individuals with BMI ≥ 25 kg/m² (3306.0 vs. 24833.5 copies/mL, $P = 0.027$). Using multivariate logistic regression analyses adjusted for age, gender, HBeAg serostatus, and high ALT level, the ORs of BMI ranges and insulin resistance for significant HBV DNA levels are shown in Table 2. Those with BMI ≥ 25 kg/m² (OR = 3.86, 95% CI = 1.38–10.8,

$P = 0.010$) and those with BMI < 23 kg/m² (OR = 4.47, 95% CI = 1.32–15.2, $P = 0.016$), were at higher risk for significant HBV DNA levels as compared to the those with BMI 23–24.9 kg/m². In addition, participants with positive HBeAg serostatus were at a significantly higher risk for significant HBV DNA levels (OR = 41.8, 95% CI = 8.15–214.0, $P < 0.0001$) than those with negative HBeAg serostatus.

Among participants with HBeAg seronegative status, subjects with BMI ≥ 25 kg/m² (OR = 3.76, 95% CI = 1.30–10.9, $P = 0.015$) and subjects with BMI < 23 kg/m² (OR = 5.26, 95% CI = 1.59–17.4, $P = 0.007$), were at increased risk for significant HBV DNA levels as compared to subjects with BMI 23–24.9 kg/m² after adjusting for age, gender, high ALT level, and insulin resistance (Table 3). In the subgroup analysis of HBeAg seronegatives with normal ALT levels, the non-overweight participants (OR = 3.97, 95% CI = 1.29–12.2, $P = 0.016$), including the obese (OR = 3.96, 95% CI = 1.18–13.3, $P = 0.026$) and the normal or underweight (OR = 3.70, 95% CI = 1.02–13.4, $P = 0.046$), also were at increased risk for significant HBV DNA levels than their overweight counterparts.

Table 2 Multiple logistic regression analysis of factors for significant HBV DNA levels ($n = 146$).

Factor	OR (95% CI)	P-value
HBeAg serostatus		
Positive vs. negative	41.8 (8.15–214.)	<0.0001
High ALT level (yes vs. no)	1.70 (0.66–4.38)	0.272
BMI (kg/m^2)		
< 23 vs. BMI 23–24.9 Kg/m^2	4.47 (1.32–15.2)	0.016
≥ 25 vs. BMI 23–24.9 Kg/m^2	3.86 (1.38–10.8)	0.010
Insulin resistance (yes vs. no)	1.88 (0.52–6.83)	0.337

Model: age, gender (male vs. female), HBeAg serostatus (positive vs. negative), high ALT level (yes vs. no), BMI ranges, and insulin resistance (yes vs. no).

ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBV DNA, deoxyribonucleic acid of hepatitis B virus (significant, $\geq 10^4$ copies/mL) (1 copies/mL = 0.1718 IU/mL).

Table 3 Multiple logistic regression analysis of BMI ranges for significant HBV DNA levels in HBeAg seronegatives.

BMI (kg/m^2)	HBeAg seronegatives ($n = 109$) ^a		HBeAg seronegatives with normal ALT levels ($n = 82$) ^b	
	OR (95% CI)	P-value	OR (95% CI)	P-value
< 23 vs. BMI 23–24.9 Kg/m^2	5.26 (1.59–17.4)	0.007	3.70 (1.02–13.4)	0.046
≥ 25 vs. BMI 23–24.9 Kg/m^2	3.76 (1.30–10.9)	0.015	3.96 (1.18–13.3)	0.026

ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBV DNA, deoxyribonucleic acid of hepatitis B virus (significant, $\geq 10^4$ copies/mL) (1 copies/mL = 0.1718 IU/mL).

^a Model: age, gender (male vs. female), high ALT level (yes vs. no), BMI ranges, and insulin resistance (yes vs. no).

^b Model: age, gender (male vs. female), BMI ranges, and insulin resistance (yes vs. no).

Interaction between BMI ranges and insulin resistance is shown in Table 4. As compared to overweight individuals without insulin resistance, the OR of obesity without insulin resistance for significant HBV DNA levels was 3.90 (95% CI = 1.30–11.7, $P = 0.015$) after adjustment for age, gender, HBeAg serostatus, and high ALT level. The combination of insulin resistance

and obesity further increased the adjusted risk for significant HBV DNA levels to 9.34 (95% CI = 1.74–50.3, $P = 0.009$). Normal or underweight participants without insulin resistance still had a higher adjusted risk for significant HBV DNA levels (OR = 4.98, 95% CI = 1.42–17.5, $P = 0.012$) than overweight individuals without insulin resistance.

Table 4 Interaction between BMI ranges and insulin resistance on significant HBV DNA levels ($n = 146$).

BMI (kg/m^2)	Insulin resistance	n	Model 1 ^a		Model 2 ^b	
			OR (95% CI)	P-value	OR (95% CI)	P-value
23–24.9	No	40	1.00 (referent)	—	1.00 (referent)	—
23–24.9	Yes	2	— ^c	0.633	— ^c	0.516
≥ 25	No	51	2.53 (1.06–6.01)	0.036	3.90 (1.30–11.7)	0.015
≥ 25	Yes	17	9.62 (2.34–39.6)	0.002	9.34 (1.74–50.3)	0.009
< 23	No	34	3.73 (1.35–10.3)	0.011	4.98 (1.42–17.5)	0.012
< 23	Yes	2	— ^c	0.646	— ^c	0.982

BMI, body mass index; HBV DNA, deoxyribonucleic acid of hepatitis B virus (significant, $\geq 10^4$ copies/mL) (1 copies/mL = 0.1718 IU/mL).

^a Model 1: each stratum adjusted by age and gender (male vs. female).

^b Model 2: each stratum adjusted by age, gender (male vs. female), HBeAg serostatus (positive vs. negative), and high alanine aminotransferase level (yes vs. no).

^c Sample size too small to have a stable estimate.

Discussion

This research pioneered to investigate the relationship between metabolic factors and significant hepatitis B viral load in a campus-based cohort. Certain BMI ranges ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\text{BMI} < 23 \text{ kg/m}^2$) were positively associated with significant HBV DNA levels. Furthermore, insulin resistance and obesity had additive effects on significant hepatitis B viral load.

Insulin has been known to suppress HBV gene expression in cultured human liver cells [19]. Non-diabetic obese people tend to have subclinical insulin resistance [20,21], and the subsequent attenuated inhibitory effects of insulin on HBV gene replication may partially explain our findings that obesity increased the risk of significant HBV DNA levels. In addition, similar factors activate the key gluconeogenic gene phosphoenolpyruvate carboxykinase and the HBV pre-core/core promoters [22]. Obese individuals might diet intentionally and therefore be exposed to starvation more frequently than their normal-weight counterparts, and thus the gluconeogenic cascade with consequent viral replication would be co-activated more often. Some adipokines are known to influence endogenous hepatic glucose metabolism [23]. For example, resistin increases hepatic glucose production [24], whereas adiponectin suppresses it [25]. In obese patients, high resistin and low adiponectin levels may contribute to increased hepatic glucose production, thereby possibly accelerating HBV gene replication.

Levels of circulating male sex hormones such as androgen are inversely associated with BMI [26,27], components of the metabolic syndrome [28], and risk for type 2 diabetes [29,30]. Besides, a recent animal model demonstrated that higher androgen can increase HBV viral titers through direct binding to the androgen-responsive element sites [31,32]. These findings taken together might explain why individuals with $\text{BMI} < 23 \text{ kg/m}^2$ were at a higher risk of significant HBV DNA levels than those with $\text{BMI} 23\text{--}24.9 \text{ kg/m}^2$. In other words, chronic HBV-infected individuals with low BMI would have high androgen levels and subsequent significant HBV viral load. However, other mechanisms regarding insulin, gluconeogenic cascade and adipokines, as described in the previous paragraph, predominate in those with $\text{BMI} \geq 25 \text{ kg/m}^2$.

Although insulin resistance has been associated with an increased risk for cirrhosis in patients with chronic HBV infection, it has not previously been associated with hepatitis B viral load [33]. Our results revealed that the individuals being

both obese and insulin resistant were at about 9-fold adjusted risk for significant HBV DNA levels compared to those being overweight and not insulin resistant. However, there was no significant additive interaction from insulin resistance in normal or underweight participants. The underlying role of insulin resistance on hepatitis B viral load in different BMI ranges warrants further research.

Unlike the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV study [5,13], no significant association of age and gender with HBV DNA levels was noted in the present study. That could be explained by the fact that this campus-based study population was younger (32.6 ± 8.6 years vs. 45.9 ± 9.8 years) and predominantly male (78.1% vs. 59.3%). Previous studies have reported that HBeAg seroconversion may not be complete in younger populations [6,34,35]. However, about 75% of our participants were HBeAg seronegatives, and 55.7% with significant HBV DNA levels were indeed HBeAg seronegatives. For these participants who are younger and deemed healthy, HBeAg seroconversion is actually followed by the phase of "HBeAg-negative chronic hepatitis B" [36]. Careful assessments and individualized preventive acts should be advocated.

There are several limitations. First, this study is cross-sectional by design and so causal inference cannot be established. This cohort will be followed to look for time-dependent discrepancies between BMI ranges and serum viral load. Second, the participants volunteered rather than being randomly selected and thus the external validity was confined. Third, we did not recruit any diabetic participants. The effect of hyperglycemia on HBV DNA levels was not examined. However, we expect that the effect of BMI ranges on hepatitis B viral load would be less confounded by hyperglycemia. In addition, determining the optimal BMI ranges for chronic HBV-infected individuals to have minimal viral load for all ethnic groups will be another challenge for future investigation.

Conclusion

A campus-based cohort of chronic HBV infection was investigated. We demonstrated that certain BMI ranges ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\text{BMI} < 23 \text{ kg/m}^2$) were positively associated with significant HBV DNA levels, whether in all participants or HBeAg seronegatives. Insulin resistance further had additive effects to obesity on significant hepatitis B viral

load. Future research should be targeted more at the basic mechanism and the preventive strategies.

Conflict of interest statement

The authors declare no conflicts of interest.

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