International Journal of Obesity (2012) 1–6

www.nature.com/ijo

ORIGINAL ARTICLE

Association between obesity, hypertriglyceridemia and low hepatitis B viral load

C-H Chiang[1,2], H-I Yang [3,4], C-L Jen[5], S-N Lu[6], L-Y Wang[7], S-L You[5], J Su[8,10], UH Iloeje[8] and C-J Chen[5,9] for the REVEAL-HBV Study Group

OBJECTIVE: This study aimed to investigate the metabolic risk factors of high hepatitis B viral load.
DESIGN: Large-scale, community-based cross-sectional study.
SUBJECTS: A total of 3587 hepatitis B virus (HBV)-infected participants without liver cirrhosis at study entry were investigated. High HBV viral load was defined as a serum level $\geqslant 10^4$ copies per ml for hepatitis B e antigen (HBeAg) seronegatives or $\geqslant 10^8$ copies per ml for HBeAg seropositives.
RESULTS: Among HBeAg seropositives ($n = 545$), high HBV viral load was reversely associated with extreme obesity (odds ratio (OR), 0.30; 95% confidence interval (CI), 0.13–0.68; $P = 0.004$) or central obesity (OR, 0.53; 95% CI, 0.34–0.82; $P = 0.004$) after adjustment for gender, hypertriglyceridemia, hyperuricemia and history of hypertension. High HBV viral load remained significantly inversely associated with extreme obesity (OR, 0.17; 95% CI, 0.05–0.63; $P = 0.008$) and central obesity (OR, 0.44; 95% CI, 0.25–0.78; $P = 0.005$) in male HBeAg-seropositive participants in stratification analyses by gender. Among HBeAg seronegatives ($n = 3042$), however, high HBV viral load was inversely associated with hypertriglyceridemia (OR, 0.74; 95% CI, 0.61–0.89, $P = 0.002$) after adjustment for age, gender, high serum alanine aminotransferase level, and extreme obesity or central obesity. High HBV viral load was still inversely associated with hypertriglyceridemia in both female (OR, 0.70; 95% CI, 0.50–0.97; $P = 0.041$) and male (OR, 0.75; 95% CI, 0.60–0.94; $P = 0.011$) HBeAg-seronegative participants.
CONCLUSION: Extreme obesity and central obesity were associated with a low prevalence of high HBV viral load in HBeAg seropositives, especially in men; while hypertriglyceridemia was associated with a low prevalence of high viral load in HBeAg seronegatives in both women and men.

International Journal of Obesity advance online publication, 24 April 2012; doi:10.1038/ijo.2012.63

Keywords: hepatitis B viral load; hepatitis B e antigen; metabolic factor; triglycerides

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a challenging public health issue in Asia Pacific region. In our REVEAL-HBV Study, elevated serum deoxyribonucleic acid of HBV (HBV DNA) levels are associated with an increasing risk of cirrhosis, hepatocellular carcinoma, all-cause and liver-related mortality rates in a dose-response relationship.[1–5] However, anti-viral therapy for chronic HBV carriers with high viral loads but normal liver function is not indicated based on current guidelines.[6]

In some animal models, HBV gene expression is regulated similarly to key metabolic genes in hepatocytes. HBV is considered to behave like a 'metabolovirus'.[7] The prevalence of obesity and metabolic syndrome is increasing in Taiwan in recent years.[8] Metabolic factors have been found to increase the risk of cirrhosis and hepatocellular carcinoma.[9–15] Only few studies examined the relationship between metabolic factors and HBV viral load.[9,16] The novel aim of this study is to investigate the association between selected metabolic factors and the crucial outcome marker, that is, serum HBV DNA levels, in patients with chronic HBV infection.

SUBJECTS AND METHODS

Participants

A total of 3587 participants in REVEAL-HBV Study[1–5,9] who had positive hepatitis B surface antigen (Bag) serostatus, negative serostatus of antibodies against hepatitis C virus, no liver cirrhosis and measurements of serum HBV DNA levels and metabolic factors at enrollment were included in this analysis. All subjects signed written informed consents. Demographic and lifestyle characteristics were collected through personal interview using a structured questionnaire by well-trained public health nurses. Overnight fasting blood samples were collected at baseline, and HBsAg, hepatitis B e antigen (HBeAg), antibodies against hepatitis C virus and serum HBV DNA level were analyzed using commercial kits as described previously.[2–5,9] High HBV viral load was defined as a serum level $\geqslant 10^4$ copies per ml for HBeAg seronegatives or $\geqslant 10^8$ copies per ml for HBeAg seropositives. The study protocol was approved by the Institutional Review Board of the College of Public Health, National Taiwan University.

Measurement of selected metabolic factors and clinical factors

Body height and weight was measured according to a standard protocol to derive body mass index (BMI in kg m^{-2}). Extreme obese (BMI $\geqslant 30$) was defined according to the potential public health action points for Asian

[1]Department of Community and Family Medicine, National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin, Taiwan; [2]Department of Family Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan; [4]Molecular and Genomic Epidemiology Research Center, China Medical University Hospital, Taichung, Taiwan; [5]Genomics Research Center, Academia Sinica, Taipei, Taiwan; [6]Department of Gastroenterology, Kaohsiung Chang-Gung Memorial Hospital, Kaohsiung, Taiwan; [7]MacKay Medical College, New Taipei, Taiwan; [8]Research and Development, Bristol-Myers Squibb Company, Wallingford, CT, USA and [9]Graduate Institute of Epidemiology, National Taiwan University, Taipei, Taiwan. Correspondence: Professor C-J Chen, Genomics Research Center, Academia Sinica, No. 128 Academia Road, Section 2 Nankang, Taipei 115, Taiwan.
E-mail: cjchen@ntu.edu.tw
[10]Previous employee.
Received 10 November 2011; revised 17 February 2012; accepted 20 March 2012

populations recommended by World Health Organization.[17] Waist circumference was taken at the midway point between the inferior margin of the last rib and the iliac crest in a horizontal plane at the end of exhalation. Central obesity was defined as a waist circumference $\geqslant 90$ cm for men or $\geqslant 80$ cm for women according to the criteria for metabolic syndrome used in Taiwan (www.bhp.doh.gov.tw). The hypertriglyceridemia was defined as serum triglycerides levels $\geqslant 150\,mg\,dl^{-1}$ and the hypercholesterolemia was defined as serum total cholesterol levels $\geqslant 240\,mg\,dl^{-1}$. The hyperuricemia was defined as serum uric acid levels $\geqslant 8.3\,mg\,dl^{-1}$. A high serum alanine aminotransferase (ALT) level was defined as ALT levels $\geqslant 45\,IU\,l^{-1}$. Information about age, gender, personal history of diabetes mellitus and hypertension was obtained from the personal interview.

Statistical analyses

The categorical and continuous data were presented as number (percent) or mean ± s.d., respectively. In the univariate analyses, the statistical significances of the difference in categorical data among comparison groups were analyzed by χ^2-test. The statistical significances of the difference in continuous variables were based on two-sample Student's *t*-test. Significance levels were determined by two-tailed tests (P value <0.05). Variables with P value <0.20 in univariate analyses were included in multiple logistic regression models to examine their association with high HBV viral load in HBeAg seropositives and HBeAg seronegatives, respectively. Stratification analyses were carried out for associations between high HBV viral load and metabolic factors in different strata of gender. The odds ratio (OR) with its 95% confidence interval (CI) were derived to assess the magnitude of the association among various predictors of high HBV viral load. All the statistical analyses were performed with SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics of HBeAg-seropositive participants

Among 545 HBeAg-seropositive participants included in this analysis, 352 (64.6%) had high HBV viral load defined as serum HBV DNA levels $\geqslant 10^8$ copies per ml. A total of 347 (63.7%) participants were male, 89 (16.4%) had high serum ALT levels, 27 (5.0%) had extreme obesity, 120 (22.1%) had central obesity, 100 (18.4%) had hypertriglyceridemia, 50 (9.2%) had hypercholesterolemia, 15 (2.8%) had hyperuricemia, 12 (2.2%) had history of diabetes mellitus and 20 (3.7%) had history of hypertension. As shown in Table 1, there was a significant inverse association with high HBV viral load for extreme obesity ($P=0.002$), central obesity ($P=0.002$) and hyperuricemia ($P=0.044$). No significant association with high viral load was observed for age, gender, elevated serum ALT level, hypertriglyceridemia, hypercholesterolemia, history of diabetes and hypertension.

Clinical characteristics of HBeAg-seronegative participants

Among 3042 HBeAg-seronegative participants of this analysis, 1043 (34.3%) had high HBV viral load defined as serum HBV DNA levels $\geqslant 10^4$ copies per ml. A total of 1850 (60.8%) participants were male, 114 (37.7%) had high serum ALT levels, 137 (4.5%) had extreme obesity, 863 (28.4%) had central obesity, 680 (22.5%) had hypertriglyceridemia, 224 (7.4%) had hypercholesterolemia, 132 (4.4%) had hyperuricemia, 69 (2.3%) had history of diabetes mellitus, 154 (5.1%) had history of hypertension, 1012 (33.3%) were current cigarette smokers and 360 (11.8%) were habitual alcohol drinkers. As shown in Table 2, the prevalence of high HBV viral load was significantly associated with older ages ($P=0.028$), male gender ($P<0.0001$) and elevated serum ALT level ($P<0.0001$). There was a significant inverse association with high HBV viral load for hypertriglyceridemia ($P=0.011$). No significant association with high viral load was observed for extreme obesity, central obesity, hypercholesterolemia, hyperuricemia, history of diabetes and hypertension.

Metabolic factors associated with high HBV viral load in HBeAg seropositives

Table 3 shows the results of multiple logistic regression analyses for HBeAg seropositives including gender, extreme obesity or central obesity, hypertriglyceridemia, hyperuricemia and history of hypertension in two models. Extreme obesity (OR, 0.30, 95% CI, 0.13–0.68, $P=0.004$) and central obesity (OR, 0.53, 95% CI, 0.34–0.82, $P=0.004$) were both significantly inversely associated with high HBV viral load.

Table 4 shows the results of the stratification analysis for HBeAg-seropositive participants by gender. Extreme obesity (OR, 0.17, 95% CI, 0.05–0.63, $P=0.008$) and central obesity (OR, 0.44, 95% CI, 0.25–0.78, $P=0.005$) remained significantly associated with a decreased prevalence of high HBV viral load only in male HBeAg-seropositive participants after multivariate adjustment. No significant association with high viral load was observed for extreme obesity or central obesity in female HBeAg seropositives.

Metabolic factors associated with high HBV viral load in HBeAg seronegatives

Table 5 shows the results of multiple logistic regression analyses for HBeAg seronegatives including age, gender, high serum ALT level, extreme obesity or central obesity and hypertriglyceridemia in two models. Hypertriglyceridemia was significantly inversely associated with high HBV viral load in model 1 (OR, 0.74, 95% CI, 0.61–0.89, $P=0.002$) and model 2 (OR, 0.75, 95% CI, 0.62–0.91, $P=0.003$).

Table 6 shows the results of the stratification analysis for HBeAg-seronegative participants by gender. Hypertriglyceridemia remained significantly associated with a decreased prevalence of high HBV viral load both in female (OR, 0.70, 95% CI, 0.50–0.97, $P=0.041$) and male (OR, 0.75, 95% CI, 0.60–0.94, $P=0.011$)

Table 1. Comparison of clinical profiles of HBeAg-seropositive participants with high and low viral load using 10^8 copies per ml as the cutoff point

Factors	*Low HBV DNA* (N = *193*)	*High HBV DNA* (N = *352*)	P *value*
Age (years), mean ± s.d.	42.11 ± 9.08	41.64 ± 9.05	0.559
Male, *n* (%)	132 (58.29)	215 (65.13)	0.090
High ALT level ($\geqslant 45\,IU\,l^{-1}$), *n* (%)[a]	30 (15.63)	59 (16.81)	0.722
Extreme obesity (body mass index $\geqslant 30\,kg\,m^{-2}$), *n* (%)[a]	17 (8.85)	10 (2.85)	0.002
Central obesity, (waist circumference $\geqslant 90$ cm for men and $\geqslant 80$ cm for women), *n* (%)[b]	56 (29.32)	61 (17.38)	0.002
Hypertriglyceridemia ($\geqslant 150\,mg\,dl^{-1}$), *n* (%)[a]	42 (21.88)	58 (16.52)	0.124
Hypercholesterolemia ($\geqslant 240\,mg\,dl^{-1}$), *n* (%)[a]	17 (8.85)	33 (9.40)	0.833
Hyperuricemia ($\geqslant 8.3\,mg\,dl^{-1}$), *n* (%)[c]	9 (4.69)	6 (1.72)	0.044
History of diabetes, *n* (%)[b]	6 (3.13)	6 (1.71)	0.361
History of hypertension, *n* (%)[b]	10 (5.21)	10 (2.86)	0.165

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OR, odds ratio. [a]Data missing for two participants. [b]Data missing for three participants. [c]Data missing for four participants.

Table 2. Comparison of clinical profiles of HBeAg-seronegative participants with high and low viral load using 10^4 copies per ml as the cutoff point

Factors	*Low HBV DNA (N = 1999)*	*High HBV DNA (N = 1043)*	P *value*
Age (years), mean ± s.d.	46.13 ± 9.87	46.95 ± 9.45	0.028
Male, *n* (%)	1165 (58.43)	685 (65.74)	<0.0001
High ALT level (⩾45), *n* (%)[a]	55 (2.94)	59 (9.23)	<0.0001
Extreme obesity (body mass index ⩾30 kg m^{-2}), *n* (%)[b]	100 (5.02)	37 (3.55)	0.065
Central obesity, (waist circumference ⩾90 cm for men and ⩾80 cm for women), *n* (%)[c]	583 (29.25)	280 (26.87)	0.167
Hypertriglyceridemia (⩾150 mg dl^{-1}), *n* (%)[d]	474 (23.89)	206 (19.81)	0.011
Hypercholesterolemia (⩾240 mg dl^{-1}), *n* (%)[a]	148 (7.45)	76 (7.31)	0.885
Hyperuricemia (⩾8.3 mg dl^{-1}), *n* (%)[e]	88 (4.45)	44 (4.25)	0.797
History of diabetes, *n* (%)[f]	45 (2.25)	24 (2.30)	0.932
History of hypertension, *n* (%)[f]	105 (5.26)	49 (4.70)	0.506

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OR, odds ratio. [a]Data missing for 16 participants. [b]Data missing for 6 participants. [c]Data missing for 7 participants. [d]Data missing for 18 participants. [e]Data missing for 28 participants. [f]Data missing for 4 participants.

Table 3. Multivariate analysis of risk factors associated with high viral load (⩾10^8 copies per ml) in HBeAg-seropositive participants

Risk factors	*Model 1 (N = 536)*		*Model 2 (N = 535)*	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
Gender (male vs female)	0.72 (0.49–1.07)	0.104	0.70 (0.47–1.04)	0.074
Extreme obesity (yes vs no)	0.30 (0.13–0.68)	0.004	—	—
Central obesity (yes vs no)	—	—	0.53 (0.34–0.82)	0.004
Hypertriglyceridemia (yes vs no)	0.85 (0.53–1.35)	0.480	0.92 (0.57–1.47)	0.718
Hyperuricemia (yes vs no)	0.48 (0.16–1.45)	0.194	0.56 (0.18–1.72)	0.310
Hypertension (yes vs no)	0.61 (0.24–1.57)	0.306	0.65 (0.26–1.66)	0.370

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; OR, odds ratio. Central obesity (waist circumference ⩾90 cm for men or ⩾80 cm for women); extreme obesity (body mass index ⩾30 kg m^{-2}); hypertriglyceridemia (serum triglycerides level ⩾150 mg dl^{-1}); hypercholesterolemia (total cholesterol ⩾240 mg dl^{-1}); hyperuricemia (uric acid ⩾8.3 mg dl^{-1}).

HBeAg-seronegative participants after multivariate adjustment. No significant association with high viral load was observed for extreme obesity in female or male HBeAg seronegatives.

DISCUSSION

In this large-scale community-based cross-sectional study, the roles of metabolic factors on high HBV viral load (⩾10^4 copiesper ml for HBeAg seronegatives or ⩾10^8 copies per ml for HBeAg seropositives) in chronic HBV carriers were examined. Our results revealed a special interactive effect on high HBV viral load among hypertriglyceridemia, extreme obesity or central obesity and HBeAg serostatus. Extreme obesity and central obesity were inversely associated with high HBV viral load in HBeAg seropositives, especially in men; while hypertriglyceridemia was inversely associated with high viral load in HBeAg seronegatives in both women and men. We have demonstrated that high HBV viral load increases the risk of HCC and cirrhosis even in HBeAg-seronegative participants with normal liver function,[1–3,5] for whom the anti-viral therapies are not recommended.[6] Here, we further found the association between obesity, hypertriglyceridemia and the crucial outcome marker in chronic HBV infection, that is, HBV viral load.

The seropositivity of HBeAg has a significant impact on high viral load,[2] which is consistent with its leading role on HCC.[18,19] The gender differences are also well studied for HBV viral replication and HCC oncogenesis.[20,21] Thus, we stratified this analysis initially by HBeAg serostatus, and then by gender, to examine the role of metabolic factors on high HBV viral load in various HBeAg and gender groups. We also excluded cirrhotic participants to avoid the interference of ascites with BMI and waist circumference.

We recruited participants aged 30–64 years old. Even if some HBeAg seropositives of high HBV viral load were in the immune-tolerant stage, most HBeAg-seropositive participants (mean age = 41.81 ± 9.06 years) experienced delayed HBeAg seroconversion and an increased incidence of subsequent liver cirrhosis and hepatocellular carcinoma.[22] High HBV viral load in our HBeAg seropositives was considered clinically significant. As most HBeAg seropositives has HBV viral load greater than 10^5 copies per ml (traditional action point for HBeAg-seropositive hepatitis; Supplementary Table 1), we chose 10^8 copies per ml (Table 3) as the cutoff point to define the high HBV viral load in HBeAg seropositives. On the other hand, the use of 10^4 copies per ml as the cutoff point for high HBV viral load in HBeAg seronegatives has been well validated.[1–5,18]

We demonstrated that extreme obesity and central obesity were inversely associated with high HBV viral load in HBeAg seropositives (Table 3). Levels of circulating male sex hormones were also reported to be inversely associated with BMI and waist circumference,[23–25] components of metabolic syndrome,[24,25] and risk of type 2 diabetes.[26,27] Participants with relatively low BMI or waist circumference may thus have high serum androgen levels. In addition, the androgen pathway was positively linked to viral transcription and high HBV viral load in a recent proposed transcriptional model.[20,28] On the basis of the above-mentioned mechanisms, participants with low BMI or waist circumference might have high androgen levels and subsequent high HBV viral load. In other words, participants with extreme obesity or central obesity were considered to have low androgen levels and therefore low HBV viral load. The inverse association between extreme obesity or central obesity and high HBV viral load may also be explained at the transcription level. There are similar activators of both the key gluconeogenic gene

phosphoenolpyruvate carboxykinase and the HBV pre-core/core promoters.[29] Participants with low BMI or waist circumference in this study might be exposed to starvation more frequently than those with extreme obesity, and the gluconeogenic cascade and the accompanied viral replication was thus frequently co-activated.

However, extreme or central obesity was significantly associated with a decreased prevalence of high HBV viral load in male HBeAg-positive participants, not in females (Table 4). There are some explanations: (1) women had much lower levels of male sex hormones than men, and the androgen pathway for the inverse association between obesity and high HBV DNA load would be more predominant in males. (2) The high HBV viral load for HBeAg-positive participants was defined as serum HBV DNA levels $\geqslant 10^8$ copies per ml, and females had a lower prevalence of extreme obesity ($P = 0.007$). Thus, there were only few participants ($n = 7$, 3.5%) having HBV DNA over the cutoff point among female HBeAg seropositives ($n = 198$). The relative risk of high viral load could not be estimated precisely because of the small sample size. Actually, BMI ($P = 0.029$) were reversely associated with logarithmic transformation of HBV viral load in female HBeAg seropositives using multivariate linear regression analysis (Supplementary Table 2).

The significant inverse association between hypertriglyceridemia and high HBV viral load was observed among HBeAg-negative participants in this study (Tables 5 and 6). The underlying mechanism remains unclear. However, this finding is consistent with other population-based study findings that HBV carriers had a lower prevalence of serum triglycerides[30–32] and intrahepatic triglyceride contents.[31] HBV X protein was reported to inhibit the secretion of apolipoprotein B,[33] an essential component for the formation of very-low-density lipoprotein and low-density lipoprotein. The very-low-density lipoprotein is a triglycerides-rich particle. In active replication and transcription of HBV DNA (high HBV viral load), the increase in HBV X protein would contribute to reduced levels of very-low-density lipoprotein, and the serum triglycerides level is thus reduced. But this mechanism cannot explain no association between hypercholesterolemia and

Table 4. Multivariate analysis of risk factors associated with high viral load ($\geqslant 10^8$ copies per ml) in male and female HBeAg-seropositive participants, respectively

Risk factor	*Female HBeAg seropositives*		*Male HBeAg seropositives*	
	*Model 1 (*N = *193)*[a]	*Model 2 (*N = *193)*[b]	*Model 1 (*N = *343)*[a]	*Model 2 (*N = *342)*[b]
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Extreme obesity (yes vs no)	0.52 (0.16–1.68)	—	0.17 (0.05–0.63)[c]	—
Central obesity (yes vs no)	—	0.70 (0.34–1.36)	—	0.44 (0.25–0.78)[c]
Hypertriglyceridemia (yes vs no)	2.27 (0.73–7.01)	2.50 (0.80–7.81)	0.65 (0.38–1.13)	0.69 (0.40–1.20)

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; OR, odds ratio. Central obesity (waist circumference $\geqslant 90$ cm for men or $\geqslant 80$ cm for women); extreme obesity (body mass index $\geqslant 30\,kg\,m^{-2}$); hypertriglyceridemia (serum triglycerides level $\geqslant 150\,mg\,dl^{-1}$). [a]Extreme obesity (yes vs no), hypertriglyceridemia (yes vs no), hyperuricemia (yes vs no) and hypertension (yes vs no) were included in the model. [b]Central obesity (yes vs no), hypertriglyceridemia (yes vs no), hyperuricemia (yes vs no) and hypertension (yes vs no) were included in the model. [c]*P* value < 0.01

Table 5. Multivariate analysis of risk factors associated with high viral load ($\geqslant 10^4$ copiesper ml) in HBeAg-seronegative participants

Risk factors	*Model 1 (*N = *3016)*		*Model 2 (*N = *3016)*	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
Age at 1-year increment	1.01 (1.00–1.02)	0.018	1.01 (1.00–1.02)	0.013
Gender (male vs female)	1.35 (1.15–1.58)	0.0002	1.34 (1.14–1.57)	0.0004
High ALT level (yes vs no)	2.16 (1.48–3.17)	<0.0001	2.15 (1.47–3.15)	<0.0001
Extreme obesity (yes vs no)	0.72 (0.48–1.07)	0.102	—	—
Central obesity (yes vs no)	—	—	0.92 (0.77–1.10)	0.362
Hypertriglyceridemia (yes vs no)	0.74 (0.61–0.89)	0.002	0.75 (0.62–0.91)	0.003

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; OR, odds ratio. Central obesity (waist circumference $\geqslant 90$ cm for men or $\geqslant 80$ cm for women); extreme obesity (body mass index $\geqslant 30\,kg\,m^{-2}$); hypertriglyceridemia (serum triglycerides level $\geqslant 150\,mg\,dl^{-1}$).

Table 6. Multivariate analysis of risk factors associated with high viral load ($\geqslant 10^4$ copies per ml) in male and female HBeAg-seronegative participants, respectively

Risk factor	*Female HBeAg-seronegative participants (*N = *1177)*[a]		*Male HBeAg-seronegative participants (*N = *1839)*[a]	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
Extreme obesity (yes vs no)	0.56 (0.30–1.03)	0.061	0.86 (0.51–1.46)	0.575
Hypertriglyceridemia (yes vs no)	0.70 (0.50–0.97)	0.041	0.75 (0.60–0.94)	0.011

Abbreviations: CI, confidence interval, HBeAg, hepatitis B e antigen; OR, odds ratio. Extreme obesity (body mass index $\geqslant 30\,kg\,m^{-2}$); hypertriglyceridemia (serum triglycerides level $\geqslant 150\,mg\,dl^{-1}$). [a]Age, high serum ALT level (yes vs no), extreme obesity (yes vs no) and hypertriglyceridemia (yes vs no) were included in the model.

HBV viral load in our HBeAg-negative participants. Further researches are needed to explore the inter-relationship among HBeAg serostatus, dyslipidemia and HBV viral load.

Insulin resistance, oxidative stress and metabolic syndrome are believed to have integral roles in the progression of liver steatosis, nonalcoholic steatohepatitis and subsequent fibrosis, and cirrhosis.[15,34,35] Weight loss and anti-hyperlipidemic agents are utilized for the management of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.[36,37] In this study, we found 'abnormal' metabolic profiles (that is, extreme obesity, central obesity and hypertriglyceridemia) in chronic HBV carriers are associated with low HBV viral load. These findings partially explain why extreme or central obesity was not independently associated with the development of HCC among HBsAg-positive and antibodies against hepatitis C virus-negative participants in our previous report.[9] A cross-sectional hospital-based study in Taiwan showed that HBeAg-negative chronic hepatitis B patients with high BMI and HBV viral load had more advanced stage and grade of liver histology.[38] No association between HBV viral load and extreme or central obesity; and an inverse association between HBV viral load and hypertriglyceridemia were observed in HBeAg seronegatives in our study (Table 5). Liver steatosis was also not significantly associated with HBV viral load (Supplementary Table 3). Therefore, obesity and hypertriglyceridemia contribute to liver damage through oxidative stress, insulin resistance, hepatic inflammation and hepatic steatosis, instead of inducing HBV replication.[39,40] For the implication in clinical and public health practice, we need further clinical trials and animal experiments in the future to delineate how to modify HBV viral loads through careful manipulation of metabolic factors.

This study has some limitations. The age composition (30–65 years) in our study limits the extrapolation of our findings to those who are younger or older. The cross-sectional study design has the difficulty in verifying the causal temporality of the inverse associations between high HBV viral load and abnormal metabolic factors. The anorexic body weight loss caused by immune response in hepatitis flare[6] deserves further discussion. In our present report, extreme obesity and central obesity were associated with a low prevalence of high HBV viral load only in HBeAg seropositives. In our HBeAg-positive participants as shown in Table 1, no significant association with high viral load was observed for serum ALT level. The anorexic body weight loss of abnormal liver function in this group was considered to be non-significant. Long-term follow-up study with serial measurement of HBV viral load, BMI, waist circumference, serum triglycerides level and HBeAg serostatus are essential for the elucidation of the causal temporality. Direct measurement of circulating male sex hormones is also needed to verify our hypotheses linking low BMI or waist circumference with high HBV viral load in male HBeAg seropositives.

In conclusion, this large-scale community-based study analyzed the role of metabolic factors on high HBV viral load stratified by HBeAg serostatus and gender to reduce their confounding effect. In the outpatient care, it is recommended to measure serum HBV DNA level, HBeAg serostatus, serum triglycerides level, waist circumference and BMI for chronic HBV carriers. Although obesity and hypertriglyceridemia may contribute to the liver damage, careful management of significant reduction in body weight or triglycerides in HBV-infected individuals is needed.

CONFLICT OF INTEREST

At no time did the funding sources have access the data, preparation, review or approval of the manuscript. Dr Iloeje is an employee of and holds stock in Bristol-Myers Squibb Company. Dr Su was an employee off and held stock in Bristol-Myers Squibb Company. The remaining authors disclose no conflict.

ACKNOWLEDGEMENTS

This study was supported by research grants from the Department of Health, Executive Yuan, Taipei, Taiwan; Bristol-Myers Squibb Co., USA; National Health Research Institutes, Chunan, Taiwan; and Academia Sinica, Taipei, Taiwan. Other Members of the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) Study Group are as follows: National Taiwan University Hospital: CY Hsieh, HS Lee, PM Yang, CH Chen, JD Chen, SP Huang, CF Jan. National Taiwan University: THH Chen. National Defense Medical Center: CA Sun. Taipei City Psychiatric Center: MH Wu Tzu Chi University: LY Wang, SY Chen. Shin Kong Wu Ho-Su Memorial Hospital: KE Chu Huhsi Health Center, Penghu County: SC Ho, TG Lu Provincial Penghu Hospital: WP Wu, TY Ou Sanchi Health Center, Taipei County: CG Lin Provincial Chutung Hospital: KC Shih Provincial Potzu Hospital: WS Chung, C Li Kaohsu Health Center, Pingtung County: CC Chen. Paihsa Health Center, Penghu County: WC How.

REFERENCES

1 Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol* 2011; **26**: 628–638.
2 Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* 2009; **49**: S72–S84.
3 Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65–73.
4 Iloeje UH, Yang HI, Jen CL, Su J, Wang LY, You SL *et al.* Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007; **5**: 921–931.
5 Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678–686.
6 Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009; **373**: 582–592.
7 Shlomai A, Shaul Y. The "metabolovirus" model of hepatitis B virus suggests nutritional therapy as an effective anti-viral weapon. *Med Hypotheses* 2008; **71**: 53–57.
8 Huang KC. Obesity and its related diseases in Taiwan. *Obes Rev* 2008; **9**(Suppl 1): 32–34.
9 Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL *et al.* Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008; **135**: 111–121.
10 Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005; **54**: 533–539.
11 Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, Noda M *et al.* Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). *Cancer Causes Control* 2009; **20**: 741–750.
12 Lai MS, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. *Hepatology* 2006; **43**: 1295–1302.
13 Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK *et al.* Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. *Gut* 2009; **58**: 111–117.
14 Yu MW, Shih WL, Lin CL, Liu CJ, Jian JW, Tsai KS *et al.* Body-mass index and progression of hepatitis B: a population-based cohort study in men. *J Clin Oncol* 2008; **26**: 5576–5582.
15 Tsochatzis E, Papatheodoridis GV, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008; **27**: 80–89.
16 Chiang CH, Lai JS, Sheu JC, Yen LL, Liu CJ, Huang KC. The risky body mass index ranges for significant hepatitis B viral load: A campus-based study. *Obes Res Clin Pract* 2012; **6**: e31–e38.
17 WHO. Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**: 157–163.
18 Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY *et al.* Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; **347**: 168–174.
19 Huang Y, Lok AS. Viral factors and outcomes of chronic HBV infection. *Am J Gastroenterol* 2011; **106**: 93–95.
20 Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, Chen PJ. Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. *Hepatology* 2009; **50**: 1392–1402.
21 Huang YT, Jen CL, Yang HI, Lee MH, Su J, Lu SN *et al.* Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. *J Clin Oncol* 2011; **29**: 3643–3650.

22 Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. *Hepatology* 2010; **51**: 435–444.
23 Yeap BB, Chubb SA, Hyde Z, Jamrozik K, Hankey GJ, Flicker L *et al.* Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study. *Eur J Endocrinol* 2009; **161**: 591–598.
24 Traish AM, Feeley RJ, Guay A. Mechanisms of obesity and related pathologies: androgen deficiency and endothelial dysfunction may be the link between obesity and erectile dysfunction. *FEBS J* 2009; **276**: 5755–5767.
25 Kupelian V, Hayes FJ, Link CL, Rosen R, McKinlay JB. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. *J Clin Endocrinol Metab* 2008; **93**: 3403–3410.
26 Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; **295**: 1288–1299.
27 Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N *et al.* Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009; **361**: 1152–1163.
28 Yang WJ, Chang CJ, Yeh SH, Lin WH, Wang SH, Tsai TF *et al.* Hepatitis B virus X protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3beta kinase pathways. *Hepatology* 2009; **49**: 1515–1524.
29 Shlomai A, Shaul Y. The metabolic activator FOXO1 binds hepatitis B virus DNA and activates its transcription. *Biochem Biophys Res Commun* 2009; **381**: 544–548.
30 Jan CF, Chen CJ, Chiu YH, Chen LS, Wu HM, Huang CC *et al.* A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study No. 10). *Int J Obes* 2006; **30**: 794–799.
31 Wong VW, Wong GL, Chu WC, Chim AM, Ong A, Yeung DK *et al.* Hepatitis B virus infection and fatty liver in the general population. *J Hepatol* 2012; **56**: 533–540.
32 Luo B, Wang Y, Wang K. Association of metabolic syndrome and hepatitis B infection in a Chinese population. *Clin Chim Acta* 2007; **380**: 238–240.
33 Kang SK, Chung TW, Lee JY, Lee YC, Morton RE, Kim CH. The hepatitis B virus X protein inhibits secretion of apolipoprotein B by enhancing the expression of N-acetylglucosaminyltransferase III. *J Biol Chem* 2004; **279**: 28106–28112.
34 Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. *Clin Liver Dis* 2007; **11**: 75–104ix.
35 Tsochatzis E, Papatheodoridis GV, Manesis EK, Chrysanthos N, Kafiri G, Archimandritis AJ. Hepatic steatosis in chronic hepatitis B develops due to host metabolic factors: a comparative approach with genotype 1 chronic hepatitis C. *Dig Liver Dis* 2007; **39**: 936–942.
36 Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306–317.
37 Lewis JR, Mohanty SR. Nonalcoholic fatty liver disease: a review and update. *Dig Dis Sci* 2010; **55**: 560–578.
38 Lee IC, Huang YH, Chan CC, Huo TI, Chu CJ, Lai CR *et al.* Impact of body mass index and viral load on liver histology in hepatitis B e antigen-negative chronic hepatitis B. *Clin Nutr* 2011; **30**: 647–652.
39 Kumar M, Choudhury A, Manglik N, Hissar S, Rastogi A, Sakhuja P *et al.* Insulin resistance in chronic hepatitis B virus infection. *Am J Gastroenterol* 2009; **104**: 76–82.
40 Zheng RD, Xu CR, Jiang L, Dou AX, Zhou K, Lu LG. Predictors of hepatic steatosis in HBeAg-negative chronic hepatitis B patients and their diagnostic values in hepatic fibrosis. *Int J Med Sci* 2010; **7**: 272–277.

Supplementary Information accompanies the paper on International Journal of Obesity website (http://www.nature.com/ijo)