Association Between Metabolic Syndrome and Its Individual Components With Viral Hepatitis B

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Abstract: *Background:* The association between hepatitis B and metabolic syndrome (MetS) has not been well described. Overall epidemiologic evidences for this association have suggested conflicting results. The aim this study was to determine the association between hepatitis B infection and MetS using large U.S. population database, the Third National Health and Nutrition Examination Survey. *Methods:* Individuals aged ≥18 years were included in this study. MetS was defined according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel guideline. The chronic hepatitis B was defined as the presence of hepatitis B surface antigen. The presence of hepatitis B core antibody with/without surface antibody, in the absence of surface antigen, was considered as past exposure to hepatitis B. To represent national estimates, weighted frequencies for chronic hepatitis B and past exposure to hepatitis B are reported. Multivariate logistic regression analysis accounting for age, gender, race, smoking and alcohol status was conducted to identify the independent predictor(s) of MetS. *Results:* This study cohort consisted of total population of 593,594 with chronic hepatitis B and 7,280,620 with past exposure to hepatitis B. Prevalence of MetS among included study cohort was 25.7%. Inverse association was observed between MetS and chronic hepatitis B (adjusted odds ratio, 0.32; 95% confidence interval, 0.12–0.84). Among individual components of MetS, waist circumference was inversely associated with chronic hepatitis B (adjusted odds ratio, 0.31; 95% confidence interval, 0.14–0.71). No significant association was noted between past exposure to hepatitis B and MetS or its individual components. *Conclusions:* In this study, the authors noted significant inverse association between MetS and chronic hepatitis B.

Key Indexing Terms: Metabolic syndrome; NHANES III; Hepatitis B.
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The epidemic of metabolic syndrome (MetS) has been on the rise in conjunction with increasing prevalence of obesity in the United States. The presence of MetS has also been shown to be associated with different types of chronic liver diseases, notably nonalcoholic fatty liver disease (NAFLD) and hepatitis C infection. The association between NAFLD and the MetS is well established. NAFLD is part of the spectrum of the MetS and its presence signifies advanced histology in these patients.[1,2] It is now widely recognized that chronic hepatitis C is associated with insulin resistance and type 2 diabetes.[3] Despite the strong association with MetS among NAFLD and patients with hepatitis C, the correlation between hepatitis B infection and MetS is still elusive.

Some studies have reported the association between individual components of MetS and hepatitis B but others reported the contrary.[4,5] Among individual components, triglyceride levels have consistently been inversely linked with hepatitis B, but association of other metabolic abnormalities (such as increased waist circumference or diabetes) with hepatitis B has not been conclusive.[6–9]

Considering significant public health burden of hepatitis B with estimated prevalence of 800,000 to 1.4 million along with rising epidemic of MetS in United States, we aim to study and systemically determine the association between hepatitis B infection, and MetS and its individual components using a large U.S. population database, the 3rd National Health and Nutrition Survey (NHANES III).

METHODS

The NHANES III is a survey conducted in the United States from 1988 through 1994 by the National Center for Health Statistics. The survey consisted of complex, multistage, stratified clustered samples of civilian aged 2 months and older to collect information about their health and nutrition. The NHANES III was approved by the Center for Disease Control and Prevention's Institutional Review board. The details of study design and sampling methods are described elsewhere.[10]

Study Cohort and Definitions

For this study, subjects aged <18 years old, with missing value for hepatitis B core antibody/hepatitis B surface antigen (HBsAg), with missing values for individual components of MetS, with chronic hepatitis C (defined as positivity to anti-hepatitis C virus), excessive alcohol use with elevated liver enzymes (alanine aminotransferase [ALT] more than 40 U/L in men and more than 31 U/L in women or aspartate aminotransferase more than 37 U/L in men and more than 31 U/L in women) and with elevated transferrin level >50% were excluded. After applying these criteria, our study cohort consisted of total population of 146,158,119 subjects.

Demographic details including age, sex, race and education level were recorded. Social history including smoking and alcohol use were included, and participants were appropriately categorized according to their current and past use. Current smoker was defined as history of ongoing smoking with or without >100 cigarettes in lifetime. Excessive alcohol consumption was defined as more than 2 drinks per day in men and more than 1 drink per day for women.[11] The average alcohol consumption was calculated based on the responses to 2 survey questions that queried about the number of days of drinking over the past 12 months and the number of drinks on a given drinking day.

During the physical examination, subject's body weight, height and waist to hip ratio were measured. The body mass

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index was calculated, and subjects with body mass index ≥30 kg/m^2 were considered to be obese. The presence of MetS was determined based on the guidelines proposed by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III).[12] The ATP III clinical definition of the MetS requires the presence of 3 or more of the following[1]: waist circumference >102 cm in men and >88 cm in women,[2] a triglyceride level ≥150 mg/dL,[3] a high-density lipoprotein (HDL) level <40 mg/dL in men and <50 mg/dL in women,[4] systolic blood pressure ≥130 mm Hg or diastolic pressure ≥85 mm Hg[5] and fasting plasma glucose ≥110 mg/dL. Subjects with MetS were further stratified into 3 categories depending on the presence of MetS components (3, 4 or 5 metabolic abnormalities).

Laboratory Measurements

The laboratory procedures followed in the NHANES III are described in detail elsewhere.[13] All venous blood samples were immediately centrifuged and shipped weekly at −20°C to a central laboratory. Antibodies to hepatitis B core antigen were measured using solid-phase competitive radioimmunoassay, whereas determination of HBsAg was performed using sandwich radioimmunoassay. Cholesterol and triglycerides were measured quantitatively by a peroxidase-catalyzed reaction, and HDL was measured after the precipitation of the other lipoproteins. Low-density lipoprotein (LDL) was calculated using the formula: LDL = total cholesterol − (triglyceride/5) − HDL. LDL was not calculated and reported as a missing value if the triglyceride level was >400 mg/dL.

Definition of Chronic Hepatitis B Infection

Chronic hepatitis B infection was defined as the presence of HBsAg. Individuals with positive hepatitis B core antibody in the absence of surface antigen were considered to have past exposure to hepatitis B.

Statistical Analysis

Basic descriptive statistics, including weighted frequencies and means, weighted percentages and standard error, were used to characterize the study population. Appropriate comparison tests including χ^2 test and Student's t test were used for comparison between groups for categorical variables and continuous variables, respectively.

To represent national estimates, all analyses were conducted using appropriate sample weight, and weighted frequencies are reported to represent cases of chronic hepatitis B, past exposure to hepatitis B and controls. Logistic regression including univariate and multivariate analyses were conducted to identify independent predictors of MetS and its individual components. We further performed subgroup analysis by ALT level to evaluate the effects of chronic liver inflammation. ALT level more than 40 U/L in men and more than 31 U/L in women was considered as elevated ALT. Strength of association is reported as adjusted odds ratio ([aOR] adjusted for age, sex, race, smoking and alcohol use) with 95% confidence interval (CI) and P value. P value of less than 0.05 was considered statistically significant. SAS version 9.2 (SAS institute, Cary, NC) was used for data management and all statistical analyses.

RESULTS

After inclusion criteria, our study cohort consisted of total population of 593,594 chronic hepatitis B, 7,280,620 with past exposure to hepatitis B and 138,283,905 controls. The demographics and characteristics are shown in Table 1. When compared with controls, those with chronic hepatitis B infection were predominantly male (68.1% versus 47.5%, $P < 0.001$) and less obese (9.3% versus 21.7%, $P = 0.012$). They also had a lower non-Hispanic white population compared with controls (43.1% versus 78.3%, $P < 0.001$). There were no differences in the education level, smoking status and alcohol use. Similarly, past exposure to hepatitis B cohort were largely men (54.1% versus 47.5%, $P = 0.011$) and had a lower non-Hispanic white population (44.4% versus 78.3%, $P < 0.001$) when compared with controls. They also had lower education level but higher prevalence of smoking.

Comparison of Individuals With Chronic Hepatitis B With Controls

The prevalence of MetS was significantly lower in those with chronic hepatitis B infection compared with controls (10.4% versus 25.6%, $P = 0.019$). On multivariate analysis, this difference was also observed to be statistically significant (aOR, 0.32; 95% CI, 0.12–0.84). However, when we considered the relationship between chronic hepatitis B infection and each individual component of MetS, we found the inverse association between chronic hepatitis B infection and waist circumference (aOR, 0.31; 95% CI, 0.14–0.71). There were also significant inverse associations noted for chronic hepatitis B with low HDL and impaired fasting glucose (low HDL: aOR,

TABLE 1. Baseline characteristics of study cohort

	Chronic hepatitis B, weighted% (SE)	Past exposure to hepatitis B, weighted% (SE)	Controls, weighted% (SE)
Age, yr	40.9 (2.2)	48.9 (1.1)	42.9 (0.4)
Sex			
Male	68.1 (3.8)	54.1 (2.5)	47.5 (0.5)
Female	31.9 (3.8)	45.9 (2.5)	52.5 (0.5)
Race			
Non-Hispanic white	43.1 (9.9)	44.4 (3.2)	78.3 (1.2)
Others	56.9 (9.9)	55.6 (3.2)	21.7 (1.2)
Education			
Less than high school	18.6 (4.4)	40.0 (3.0)	23.6 (1.1)
High school	35.2 (7.1)	27.2 (2.4)	34.3 (0.9)
More than high school	46.2 (9.9)	32.8 (2.8)	42.1 (1.4)
Current smoker			
Yes	19.8 (4.5)	31.3 (2.2)	26.6 (0.9)
No	80.2 (4.5)	68.7 (2.2)	73.4 (0.9)
Heavy alcohol use			
Yes	4.2 (1.1)	6.6 (1.2)	7.2 (0.5)
No	95.8 (1.1)	93.4 (1.2)	92.8 (0.5)
Body mass index			
≤24.9	68.0 (5.0)	46.6 (3.2)	46.6 (1.0)
25–29.9	22.7 (4.2)	32.4 (3.0)	31.7 (0.5)
≥30	9.3 (2.0)	21.0 (2.0)	21.7 (0.8)
AST level (U/L)	34.0 (5.7)	21.2 (0.4)	20.5 (0.1)
ALT level (U/L)	37.0 (10.1)	16.8 (0.7)	16.8 (0.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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