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Obesity and diabetic hyperglycemia were associated with serum alanine aminotransferase activity in patients with hepatitis B infection

Ya-Yu Wang[a,b], Shih-Yi Lin[c,d,*], Wayne Huey-Herng Sheu[c], Pi-Hwa Liu[a], Kwong-Chung Tung[b]

[a]*Division of Family Medicine, Taichung Veterans General Hospital, Taichung 407, Taiwan*
[b]*Department of Veterinary Medicine, College of Veterinary Medicine, National Chung Hsing University, Taichung 402, Taiwan*
[c]*Division of Endocrinology and Metabolism, Department of Medicine, Taichung Veterans General Hospital, Taichung 407, Taiwan*
[d]*Graduate Institute of Clinical Medicine, School of Medicine, National Yang Ming University, Taipei 112, Taiwan*

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Abstract

Several studies have reported that obesity and diabetes are important risk factors for elevated blood aminotransferase activity in individuals with no underlying causes of liver disease. The aim of this study was to determine whether obesity and fasting glucose level were associated with hepatic dysfunction in patients with hepatitis B infection. A total of 934 patients with hepatitis B infection were enrolled, among whom increased alanine aminotransferase (ALT) activity (≥40 IU/L) was observed in 25.1%. By univariate analysis, factors associated with increased ALT activity among patients with hepatitis B infection included body mass index (BMI), fasting blood glucose level, and blood triglyceride and high-density cholesterol levels. By multivariate logistic regression analysis, BMI and fasting blood glucose level were independent predictors of elevated ALT activity, with odds ratios of 1.73 (95% confidence interval, 1.17-2.56) for subjects with a BMI greater than or equal to 25 kg/m^2 and 1.88 (95% confidence interval, 1.06-3.33) for subjects with a fasting blood glucose greater than or equal to 126 mg/dL. Even in subjects with ALT activity within the reference range, ALT activity was found to be associated with BMI. In conclusion, a BMI greater than or equal to 25 kg/m^2 and a fasting blood glucose level greater than or equal to 126 mg/dL were risk factors for increased ALT activity in subjects with hepatitis B infection, suggesting that obesity and diabetic fasting hyperglycemia may aggravate liver injury in this population.

1. Introduction

Numerous epidemiologic studies indicate that obesity and diabetes are associated with an increased risk of nonalcoholic fatty liver disease (NAFLD), which is characterized by hepatitic steatosis with or without necroinflammation [1-7]. Obesity- and diabetes-associated hepatic steatosis may result in histologic progression to steatohepatitis, cirrhosis, or hepatocellular carcinoma [8-11]. Obesity and diabetes are also related to the development of NAFLD in other chronic liver diseases. In chronic hepatitis C (eg, genotypes 1 and 4), obesity and diabetes have been found to be associated with steatosis, which can affect the severity of fibrosis [12]. In Taiwan, viral hepatitis B remains the most important etiology of chronic liver disease in the adult population [13]; and a number of factors, such as viral subtype, sex, hereditary factors, and environmental toxins, have been shown to contribute to the progression of hepatitis B infection [14]. However, the effects of obesity, diabetes, or the other metabolic factors on hepatic function in patients with hepatitis B have not been well studied before. Serum alanine aminotransferase (ALT) activity is a commonly used surrogate marker for the evaluation of hepatocellular damage [15]. Several epidemiologic studies have reported that obesity and diabetes are important risk factors for elevated ALT activity in individuals with no apparent underlying cause of liver disease [16-18]. The aim of the present study

* Corresponding author. Division of Endocrinology and Metabolism, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.
E-mail address: sylin@vghtc.gov.tw (S.-Y. Lin).

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was to evaluate whether obesity and diabetes as well as other metabolic factors (eg, lipid profile) are associated with serum ALT activity in a population with hepatitis B infection in Taiwan. Study of this question is important because results may identify novel clinical determinants that influence hepatitis B disease activity.

2. Patients and methods

2.1. Subjects

A total of 7029 adults who received a voluntary health examination at Taichung Veterans General Hospital during the period December 2000 to July 2002 were enrolled in this study. Upon study entry, participants were interviewed by physicians; and medical history and smoking habits were documented. During the physical examination, body weight (in kilograms) and height (in meters) were measured for calculating body mass index (BMI; in kilograms per square meter). Blood pressure (BP) was measured with the right arm using a standard mercury sphygmomanometers with the subject in the sitting position after 5 minutes of rest; mean systolic and diastolic BP values of 2 measurements were recorded, and the mean BP was calculated ([systolic BP + 2× diastolic BP]/3). A fasting venous blood sample was also obtained.

2.2. Diagnosis of hepatitis B virus infection, obesity, and diabetes mellitus

Hepatitis B serology included examination of antibody to hepatitis B surface antigen (anti-HBs Ab), and hepatitis B surface antigen (HBs Ag) by means of an enzyme immunoassay method (Abbott Laboratories, Wiesbaden, Germany). Positivity for HBs Ag indicated that the subjects had hepatitis B infection. According to World Health Organization guidelines for the adult Asian population, BMI was categorized into normal (BMI <23 kg/m^2), overweight (BMI ≥23 but <25 kg/m^2), or obese (BMI ≥25 kg/m^2) [19]. The fasting plasma glucose level was categorized as normal (<100 mg/dL), impaired fasting glucose (≥100 but <126 mg/dL), and diabetic (≥126 mg/dL) [20]. Subjects with a history of pulmonary, renal, or cardiovascular disease or severe hypertriglyceridemia (serum triglyceride level >400 mg/dL) were excluded. In addition, individuals who were seropositive for anti-hepatitis C antibody and who reported *excessive alcohol drinking* (defined as alcohol consumption >140 g/wk in men and >70 g/wk in women) [21] or had other causes of liver disease were excluded.

2.3. Laboratory measurements

Serum total triglyceride, cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels were measured at the central laboratory of the hospital by an enzymatic method using a chemistry analyzer (Hitachi 7600; Hitachi, Tokyo, Japan). The serum glucose was determined by glucose oxidase procedure (Hitachi 7170, Hitachi). Activities of ALT and aspartate aminotransferase (AST) were measured by means of a kinetic ultraviolet test for clinical chemistry analyzers. The cutoff value for diagnosis of elevated ALT and AST activities was set at 40 IU/L, according to the suggestion of the Blood Center of the Chinese Blood Service Foundation; this standard was also adopted by the National Health Insurance Bureau for eligibility of claims related to liver disorders [22].

2.4. Statistical analysis

Continuous variables measured in this study were expressed as mean values ± SD. Univariate analysis, simple Spearman correlation analysis, and multiple logistic regression analysis were used to determine factors associated with elevated ALT and AST activities (≥40 IU/L) among subjects with hepatitis B infection. Factors included in the analysis were sex, age, BMI, BP, serum fasting blood glucose level, triglyceride level, and HDL-C level. In addition, BMI was stratified into 3 tertiles (<23, ≥23 but <25, and ≥25 kg/m^2); and fasting blood glucose level was stratified into 3 tertiles (<100, ≥100 but <126, and ≥126 mg/dL) to examine their odds ratios (ORs) for elevated aminotransferase activity. Subjects with hepatitis B and aminotransferase activity less than 40 IU/L were divided into 2 groups to determine factors associated with low-normal ALT activity (<20 IU/L) and high-normal ALT activity (≥20 but <40 IU/L). In addition, a linear regression analysis was performed to identify factors associated with ALT activity. All statistical analyses were performed with the SPSS statistical package for Windows, version 10.0 (SPSS, Chicago, IL); and a 2-tailed P value of < .05 was considered statistically significant.

3. Results

3.1. Prevalence of increased ALT activity in subjects with hepatitis B infection

In the total population screened (N = 7029), 934 subjects fulfilled the inclusion criteria of seropositivity for HBs Ag without other specific systemic disorders. Almost 100% of the female subjects and 90% of the male subjects reported rare alcohol intake, and the remaining 10% of the male subjects reported occasional alcohol intake of less than 140 g/wk. Among the 934 subjects with hepatitis B infection, 25.1% showed ALT activity greater than 40 IU/L; and 13.0% showed AST activity greater than 40 IU/L. Among the subjects with elevated aminotransferase activities, 75% showed ALT activity 1- to 2-fold the upper normal limit (UNL); and 80% showed AST activity 1- to 2-fold the UNL.

3.2. Factors associated with elevated ALT activity in subjects with hepatitis B infection

By univariate analysis, subjects with increased ALT activity were male, had a higher BMI, and showed increased

fasting blood glucose, triglyceride, and total cholesterol levels and increased BP but lower HDL-C levels compared with subjects with normal ALT activity (Table 1). Subjects with elevated AST activity also had a higher BMI, increased fasting blood glucose and triglyceride levels, and increased BP (data not shown). There was a significant correlation between serum ALT activity and BMI ($r = 0.081$, $P < .05$) and serum ALT activity and fasting blood glucose ($r = 0.089$, $P < .01$). By multivariate logistic regression analysis, sex, BMI, and fasting blood glucose were associated with elevated serum ALT activity after adjustment for alcohol consumption. However, relations between AST activity, BMI, fasting glucose, and the other metabolic factors were not observed.

3.3. Effect of BMI and fasting blood glucose on elevated ALT activity in subjects with hepatitis B infection

After categorizing the subjects into groups according to BMI and fasting blood glucose tertiles as described in "Patients and methods," ORs for abnormal ALT activity were 1.73 (95% confidence interval [CI], 1.17-2.56) for subjects with a BMI greater than or equal to 25 kg/m^2 and 1.88 (95% CI, 1.06-3.33) for subjects with a fasting blood glucose greater than or equal to 126 mg/dL (Table 2).

3.4. Factors associated with ALT level in subjects with hepatitis B infection and normal ALT activity

To evaluate whether metabolic parameters were associated with ALT activity in patients with hepatitis B and normal ALT activity, we stratified these subjects into 2 groups: those with ALT activity less than 20 IU/L (low normal) and those with ALT activity between 20 and 40 IU/L (high normal). By univariate analysis, factors associated with high-normal ALT activity included male sex, BMI, fasting blood glucose level, triglyceride level, total cholesterol level, HDL-C level, and BP (Table 3). Serum ALT activity correlated significantly with BMI ($r = 0.23$, $P < .01$), fasting blood glucose level ($r = 0.09$, $P < .05$), triglyceride level ($r = 0.20$, $P < .01$), total cholesterol level ($r = 0.17$, $P < .01$), and HDL-C level ($r = -0.08$, $P < .05$). By linear regression analysis, male sex, BMI, and total cholesterol level significantly predicted ALT activity (adjusted $r^2 = 0.12$, $P < .01$) (Table 4).

Table 1
Characteristics of study subjects with seropositive HBs Ag

	Normal ALT activity (<40 IU/L) (n = 700)	Elevated ALT activity (≥40 IU/L) (n = 234)
ALT activity (IU/L)	24 ± 8	81 ± 75*
Age (y)	47.8 ± 12.1	48.1 ± 11.5
Men (%)	56.4	79.5*
BMI (kg/m^2)	23.7 ± 3.3	25.0 ± 3.6*
Fasting glucose (mg/dL)	97 ± 24	103 ± 37*
Triglyceride (mg/dL)	106 ± 80	130 ± 152*
HDL-C (mg/dL)	59 ± 16	56 ± 16*
Total cholesterol (mg/dL)	187 ± 35	193 ± 34†
Systolic pressure (mm Hg)	118 ± 21	122 ± 21*
Diastolic pressure (mm Hg)	74 ± 14	77 ± 14†

Data were presented as mean ± SD.
* $P < .01$.
† $P < .05$.

Table 2
Logistic regression analysis of elevated ALT activity in the patients with seropositive HBs Ag

Variable	OR	95% CI
Men (vs women)	2.92	2.00-4.27
BMI (kg/m^2)		
<23	1	–
23-25	1.02	0.67-1.56
≥25	1.73	1.17-2.56
Fasting glucose (mg/dL)		
<100	1	–
100-126	1.13	0.75-1.69
≥126	1.88	1.06-3.33
Total cholesterol	1.00	0.99-1.01
Triglyceride	1.00	0.99-1.01
HDL-C	1.00	0.99-1.01
Mean BP	1.00	0.99-1.02

4. Discussion

Results of this study showed that obesity and diabetic hyperglycemia increased the risk of elevated ALT activity in patients with chronic hepatitis B. The lack of association between AST activity and BMI or fasting glucose indicated that AST activity was less organ specific; AST is released not only by damaged liver but also by the heart, skeletal muscle, kidney, etc [15,23]. Among our study participants, only a minority of the men reported occasional alcohol intake, at an amount less than 140 g/wk, which is much less

Table 3
Characteristics of study subjects with seropositive HBs Ag and normal ALT activity

	Low-normal ALT (<20 IU/L) (n = 230)	High-normal ALT (≥20 but <40 IU/L) (n = 470)
ALT activity (IU/L)	15 ± 3	28 ± 6*
Age (y)	46.9 ± 13.3	48.3 ± 11.4
Men (%)	41.3	63.5*
BMI (kg/m^2)	22.5 ± 3.1	24.3 ± 3.3*
Fasting glucose (mg/dL)	93 ± 19	98 ± 26*
Triglyceride (mg/dL)	87 ± 46	116 ± 91*
HDL-C (mg/dL)	62 ± 17	58 ± 16*
Total cholesterol (mg/dL)	181 ± 32	190 ± 35†
Systolic pressure (mm Hg)	114 ± 24	120 ± 20*
Diastolic pressure (mm Hg)	71 ± 15	75 ± 13*

Data were presented as mean ± SD.
* $P < .01$.
† $P < .05$.

Table 4
Multivariate linear regression analysis of normal ATL activity in the patients with seropositive HBs Ag

	Regression coefficient	SE	*P* value
Age	-0.05	0.03	.21
Sex (men vs women)	0.23	0.59	<.01
BMI	0.17	0.09	<.01
Fasting glucose	0.05	0.01	.21
Total cholesterol	0.11	0.01	<.01
Triglyceride	0.07	0.01	.13
HDL-C	0.06	0.02	.19
Mean BP	0.03	0.02	.42

than the minimum amount required for a hepatotoxic effect in men [21]. Thus, we believe that our findings of associations between increased ALT activity, obesity, and diabetic hyperglycemia are not confounded by alcohol intake. Several previous studies reported that a considerable proportion of cases of hepatic steatosis, ranging from 20% to 70%, occurred in patients with chronic hepatic B and that obesity was an important contributing factor [24-29]. It has been proposed that obesity predisposes hepatocytes to lipid peroxidation and oxidative stress, thus increasing the possibility of hepatic injury, fibrosis, and even cirrhosis as a result of hepatic inflammation. Indeed, 3 recent, large, population-based studies found that obesity predicted the development of cirrhosis, hepatocellular carcinoma, and liver-related death in patients with chronic hepatitis B [30-32]. Results of the present study add to the growing body of evidence indicating that metabolic factors, such as obesity, are involved in the progression of chronic hepatitis B. However, the present study was limited by the fact that we did not measure other biomarkers of hepatic steatosis or inflammation, such as γ-glutamyltransferase [33]; and we were therefore unable to evaluate the severity of liver injury. As such, we could not confirm that increased ALT activity in obese subjects was related to hepatic lipotoxicity. Notwithstanding the fact that elevated ALT activity alone in patients with chronic hepatitis B may not be sufficient to reflect disease severity, it has been reported that even mildly elevated ALT activity (eg, between 0.5× and 2× UNL) considerably increases the risk of hepatic complications [34,35]. In addition, liver biopsies may not be feasible in such an asymptomatic population undergoing physical checkups. In the present study, we did not determine the exact viral status of hepatitis B infection, such as circulating hepatitis B virus DNA level, which is a well-known determinant of disease progression [36]. A recent study in patients with hepatitis B reported that obesity-associated hepatic steatosis could affect hepatitis B particle clearance and thus alter the natural course of hepatitis B infection [37]. Results of an animal study showed that the hepatitis B virus may have a direct steatogenic effect [38]. These findings suggest that there may be a synergistic effect between hepatitis B virus activity and obesity with respect to hepatic steatosis, resulting in inflammation and injury. Further investigation on the relations between hepatitis B DNA level and obesity with respect to disease progression may be warranted.

In the present study, we found that the diabetic range of fasting blood glucose was an independent risk factor for abnormal ALT activity in hepatitis B infection. Type 2 diabetes mellitus has been shown to be a predictor of cirrhosis in chronic hepatitis B infection [39]. In in vitro studies, hyperglycemia alone has been shown to stimulate the production of connective tissue growth factors from hepatic stellate cells and has been implicated in the progression of liver disease [40]. Our observation that fasting hyperglycemia was associated with abnormal ALT activity appears to support these experimental and clinical findings. It should be noted that viral hepatitis in the presence of cirrhosis can be associated with impaired glucose tolerance [41]. However, the present study excluded subjects with decompensated liver function; and the probability of an indirect association between ALT activity and fasting blood glucose due to underlying disease severity appeared unlikely. Pathology studies have demonstrated that insulin resistance is associated with more severe grades of hepatic steatosis and fibrotic change in patients with hepatitis B infection [42,43]. It has been proposed that insulin resistance and its associated metabolic derangements, including elevated circulating fatty acid and insulin levels, may be another plausible mechanism for the development of NAFLD [6,7]. Although blood insulin and free fatty acid concentrations were not measured in the present study, the association of a high fasting glucose level with other features of metabolic syndrome, such as hypertriglyceridemia, low HDL-C, and overweight, which was reported in our previous study [44], indicates that elevated ALT activity may not be solely associated with diabetic fasting hyperglycemia but rather with a state of insulin resistance in patients with chronic hepatitis B.

Of note, results of the present study provided evidence for an association between ALT activity within the reference range and BMI in patients with hepatitis B. A comparable relation between ALT activity and BMI has also been observed in a healthy blood donor population [45,46]. It has been reported that high-normal ALT activity (0.5× to 1× UNL) predicts insidious, continued liver damage in patients with chronic hepatitis B [34,35]; and it has been speculated that obesity may carry with it a continuum of risk of subtle hepatic injury even in individuals with mild ALT elevation. Our present finding also raises the question of whether the UNL for ALT should be reassessed, particularly in obese patients with chronic hepatitis B infection.

In patients with NAFLD and/or hepatitis C infection, modest weight reduction by lifestyle change and pharmacologic intervention with insulin sensitizers have been shown to result in improved blood liver enzyme levels and the other metabolic variables, such as fasting insulin level, insulin sensitivity, and lipid parameters [47,48]. Determination of whether there is a comparable effect of weight reduction in

patients with hepatitis B and obesity and elevated ALT activity will require further studies.

In conclusion, obesity and diabetic fasting hyperglycemia were independently associated with elevated ALT activity in patients with hepatitis B infection. Body mass index also predicted ALT activity within the normal ALT range. Although the exact pathogenetic mechanisms of obesity and diabetic hyperglycemia with respect to histologic progression and hepatitis B virus activity in subjects with hepatitis B infection require further investigation, the maintenance of proper body weight and fasting blood glucose level should be advised among patients positive for HBs Ag to prevent or limit disease progression.

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