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ORIGINAL ARTICLE

Diabetes mellitus is associated with gastroesophageal variceal bleeding in cirrhotic patients

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Abstract Diabetes mellitus (DM) has been reported to increase the risk of complications of liver cirrhosis of any etiology and subsequent survival. However, the impact of DM on the development of gastroesophageal variceal bleeding (GEVB) remains unclear. We aimed to elucidate whether DM is an independent risk factor for GEVB among cirrhotic patients. A total of 146 consecutive patients with liver cirrhosis (Child-Pugh Class A, $n = 75$; Class B, $n = 40$; and Class C, $n = 31$) were prospectively enrolled. Data on clinical and biochemical characteristics and history of ascites, GEVB, hepatic encephalopathy, and spontaneous bacterial peritonitis were retrospectively reviewed. Of these 146 patients, 37 (25%) had DM. Patients with DM had significantly higher ratio of Child-Pugh Class B/C ($p = 0.043$), renal insufficiency ($p = 0.002$), and history of GEVB ($p = 0.006$) compared with non-DM patients. GEVB was associated with Child-Pugh Class B/C ($p = 0.001$), ascites ($p = 0.002$), hepatic encephalopathy ($p = 0.023$), and low platelet counts ($p < 0.001$). Based on stepwise multiple logistic regression analysis, Child-Pugh class B/C [odds ratio (OR) = 4.90, $p = 0.003$] and DM (OR = 2.99, $p = 0.022$) were identified as independent predictors of GEVB. In the subgroup analysis, DM significantly correlated with GEVB in patients with Child-Pugh Class A

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($p = 0.042$), but not in patients with Child-Pugh Class B/C ($p = 0.128$). DM is independently associated with GEVB in cirrhotic patients, especially in those with Child-Pugh Class A.

Introduction

Cirrhosis represents the final common pathway of virtually all chronic liver diseases. Patients with liver cirrhosis are at risk of developing many potential life-threatening complications. The 1-year mortality rate in patients with compensated cirrhosis is 1—3.4%, whereas the rate is 20—57% in patients with decompensated cirrhosis [1—3]. Ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, and gastroesophageal variceal bleeding (GEVB) are the most common cirrhotic complications, which are generally thought to be related to portal hypertension. Of these complications, GEVB is undoubtedly the most critical event with the highest risk of mortality [4].

Cirrhosis causes impaired metabolic homeostasis of glucose and leads to "hepatogenous diabetes" [5]. Approximately 30% of cirrhotic patients suffer from this metabolic disorder [6]. There is growing evidence that either hepatogenous diabetes or type 2 diabetes mellitus (DM) is associated with an increased risk of cirrhotic complications. The Verona Diabetes Study, a population-based study on more than 7000 patients with type 2 DM, found an increased risk of death from chronic liver disease and cirrhosis compared with the general population [7]. In addition, several studies have demonstrated an increased incidence of DM, ranging from two- to four-fold, among patients with hepatocellular carcinoma (HCC) [8—10].

Recently, insulin resistance, a prominent feature of type 2 DM, has been proven to be a predictor of portal hypertension [11] and the development of esophageal varices [12]. However, to our knowledge, there are no studies to demonstrate the association between DM and GEVB. The aim of our study was to elucidate whether DM is an independent risk factor for GEVB in cirrhotic patients.

Methods

From February 2013 to May 2013, a total of 146 patients with liver cirrhosis were consecutively enrolled in our outpatient clinic prospectively. The diagnosis of cirrhosis and DM, the severity and complications of cirrhosis, and comorbidity were retrospectively reviewed from January 2008 to January 2013. The complications of cirrhosis were mainly focused on ascites, SBP, hepatic encephalopathy, and GEVB. The diagnosis of DM should be earlier to the onset of GEVB.

Clinical diagnosis of cirrhosis was based on repeated ultrasound findings suggestive of cirrhosis at least twice 3 months apart, supplemented with clinical criteria, such as thrombocytopenia or other signs of portal hypertension [13]. The diagnosis of DM was mainly based on the American Diabetes Association revised criteria, which include the following [14]: fasting plasma glucose level $\geq$ 7.0 mmol/L (126 mg/dL), symptoms of hyperglycemia and casual plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL), and glycated hemoglobin (HbA1C) $\geq$ 6.5% [15]. Those on regular oral antidiabetic agents or under insulin injection were also considered as DM patients. The HbA1c data were recorded within 3 months prior to the GEVB episode in the GEVB group, whereas in the non-GEVB group, an average of three random values was taken.

GEVB should meet the following criteria: clinical signs of bleeding from gastrointestinal tract and endoscopic signs of active or recent bleeding or large varices with a red-colored sign without other bleeding sources. We excluded cases with incomplete chart recordings and HCC. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Chang Gung Memorial Hospital, Kaohsiung, Taiwan. All patients gave written informed consent before enrollment.

Continuous variables were presented as mean $\pm$ standard deviation, and the categorical data were expressed as number (percentage). Chi square test, Fisher's exact test, and the Mann—Whitney *U* test were used wherever appropriate. Independent factors predicting GEVB were identified using stepwise multiple logistic regression analysis. A p value <0.05 was considered statistically significant.

Results

Baseline features of the 146 patients are shown in Table 1. There were 82 men and 64 women, with a mean age of 61 years. Overall, 37 of 146 patients (25%) had DM. The etiology of liver cirrhosis included alcoholism, chronic hepatitis B, chronic hepatitis C, autoimmune hepatitis, primary biliary cirrhosis, and cryptogenic cirrhosis. Seventy-five patients were in Child-Pugh Class A (52%), 40 in Class B (27%), and 31 in Class C (21%), respectively.

Table 2 shows the comparison of the clinical variables and cirrhotic complications between diabetic and nondiabetic patients. Patients with DM were significantly older ($p = 0.022$) and had a higher ratio of chronic kidney disease ($p = 0.002$), Child-Pugh Class B/C ($p = 0.043$), and history of GEVB ($p = 0.006$) compared with non-DM patients.

Table 3 compares the clinical characteristics between patients with and without GEVB. Patients with a history of GEVB had lower platelet counts, a lower albumin level, higher total bilirubin level, a prolonged prothrombin time, and an increasing proportion of ascites and encephalopathy than did non-GEVB patients, and therefore, the ratio of Child-Pugh Class B/C was correspondingly higher. Besides,