Original Article

Incidence and Factors Associated with Undiagnosed Diabetes by Fasting Plasma Glucose in Cirrhotic Patients

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Background: Abnormal glucose homeostasis, including diabetes mellitus, is common in patients with liver cirrhosis. However, diabetes in these patients is frequently underdiagnosed by fasting plasma glucose (FPG).

Objective: The aim of this study is to determine the incidence and factors associated with undiagnosed diabetes by FPG in cirrhotic patients.

Materials and Methods: Cirrhotic patients without known history diabetes who had normal FPG (<126 mg/dL) were enrolled in this study. A 75-gm oral glucose tolerance test (OGTT) was performed in all patients. Normal glucose tolerance (NGT) was defined as 2-h plasma glucose (PG) <140 mg/dL, impaired glucose tolerance (IGT) as 2-h PG between 140 to 199 mg/dL, and undiagnosed diabetes as 2-h PG ≥200 mg/dL. Demographic parameters were compared between groups, and uni- and multivariate logistic regression analysis was performed to identify factors associated with undiagnosed diabetes.

Results: A total of 84 cirrhotic patients were enrolled, 59.5% were male with a mean age of 60.1 years. The common etiologies of cirrhosis were alcohol, chronic hepatitis B and C virus infection. According to the 75-g OGTT results, 52.4%, 31.1% and 15.5% were classified as NGT, IGT, and diabetes, respectively. Compared between diabetic and non-diabetic, patients with diabetes had significantly higher BMI, more proportion of large varices or ascites, lower platelets, higher INR, and lower serum albumin level. By univariate regression analysis, age, platelet count <100 $x10^3$/uL, presence of large varices or ascites were associated with undiagnosed diabetes. However, by multivariate analysis, only age, and platelet count <100 $x10^3$/uL were independently associated with undiagnosed diabetes with odds ratio of 1.11, and 6.4, respectively.

Conclusion: Undiagnosed diabetes by FPG is prevalent in patients with cirrhosis, and is associated with disease severity. Therefore, OGTT may be considered despite having a normal FPG, especially in patients with advanced liver disease.

Keywords: Cirrhosis, Diabetes, Fasting plasma glucose, Glucose tolerance test

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Liver cirrhosis is the final pathway of various chronic liver diseases, and responsible for significant morbidity and mortality. Pathologically, cirrhosis is characterized by a replacement of normal liver tissue by fibrotic scar formation. Given that liver plays an important function in maintaining normal glucose homeostasis, disorder of glucose metabolism is frequently found in these patients[(1)]. More importantly, recent evidences have shown that impaired glucose tolerance or diabetes has a significant negative impact on the natural history of cirrhosis[(1-3)].

Unfortunately, diabetes in cirrhotic patients is often underdiagnosed by fasting plasma glucose (FPG)[(1)]. This could possibly be explained by the fact that FPG is unable to detect post-prandial hyperglycemia, which is commonly found in patients with impaired hepatic function. Furthermore, glycated haemoglobin (HbA_{1c}), which is routinely used for evaluation of glycemic status in clinical practice, is frequently unreliable in cirrhotic patients[(4)]. Therefore, few studies have evaluated the role of oral glucose tolerance test (OGTT) as a screening test for diabetes in patients with cirrhosis, and shown that OGTT may add incremental diagnostic value in these patients[(5-8)]. However, performing OGTT is more complicated and time-consuming than FPG, hence it is generally not applicable to all patients. Therefore, in this study, we sought to determine the incidence and factors associated with undiagnosed diabetes by FPG in patients with liver cirrhosis.

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Materials and Methods

Patients

All consecutive patients diagnosed with liver cirrhosis from any cause, aged 18 to 75 years, attending internal medicine clinic, Thammasat University Hospital from October 2016 to October 2017 were considered for inclusion. Inclusion criteria were as follows: (i) evidence of liver cirrhosis based on clinical, laboratory and radiographic data or histology if available; (ii) FPG level of <126 mg/dL. Patients with any of the following criteria were excluded from the study: (i) current or recent (within the previous 3 months) treatment that may influence with the result of OGTT e.g. corticosteroid therapy; (ii) previously diagnosed with diabetes mellitus; (iii) diagnosed with hepatocellular carcinoma; (iv) severe comorbid illness (e.g. advanced heart failure, severe chronic obstructive pulmonary disease, end-stage renal disease, or active non-hepatic malignancies); (v) refusal to participate in this study. Informed consent was obtained from all patients prior to trial entry.

This study was approved by the Institutional Review Board of Thammasat University, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Methods

At the trial entry, demographic data were collected in all patients such as age, sex, body mass index (BMI), cause and duration of cirrhosis, current medications, previous history of liver decompensation (large varices or ascites of any grade). Large varices were defined as large esophageal or gastric varices needed either primary or secondary bleeding prophylaxis. Severity of cirrhosis was graded by Child-Pugh, the Model for End-stage Liver Disease (MELD) and MELD-Na scores. Laboratory investigations included complete blood count (CBC), prothrombin time, serum creatinine and liver function test, serum lipid profile, fasting plasma glucose by hexokinase method, and HbA_{1c} by high-performance liquid chromatography method.

All included patients were scheduled for 75-g OGTT within 1 week after the recruitment. After an overnight fasting, plasma glucose (PG) was measured at 2 h after 75 g oral glucose intake. Normal glucose tolerance (NGT) was defined as 2-h PG <140 mg/dL, impaired glucose tolerance (IGT) was defined as 2-h PG of ≥140 mg/dL, but <200 mg/dL, and undiagnosed diabetes was defined as 2-h PG ≥200 mg/dL[9,10].

Insulin resistance was assessed in 42 (50%) patients who were included after April 2017 by homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated based on the formula: fasting plasma insulin (microU/L) x fasting plasma glucose (nmol/L)/22.5. HOMA-IR >2 indicated an insulin resistance. There was no significant difference in the baseline parameters between patients in whom HOMA-IR were tested and those in whom were not.

Statistical analysis

The results are presented as means, standard deviation (SD) or proportions. Comparisons between groups were performed using Fisher's exact test for categorical variables, and Student's t-test or one-way ANOVA test for continuous variables. Uni- and multivariate logistic regression analysis was carried out to determine factor associated with undiagnosed diabetes. All the statistical calculations were two-sided and were performed using STATA software version 13. A p-value <0.05 was considered to be statistically significant.

Results

Baseline demographic data

In total, 84 patients diagnosed with liver cirrhosis were included in this study. The mean age of study participants was 60.1±9.4 years, with a male preponderance (59.5%) and a mean body mass index (BMI) of 25.3±5.1 kg/m^2. The causes of cirrhosis were as follows: alcohol (29.8%), chronic hepatitis B virus infection (HBV, 25%), chronic hepatitis C virus infection (HCV, 23.8%), alcohol + HCV (6%), nonalcoholic steatohepatitis (4.8%), alcohol + HBV (2.4%), HCV + HCV co-infection (1.2%), and others (7%). Fifteen patients (17.9%) had large varices needed prophylaxis, and 14/84 patients (16.7%) were documented with ascites. The mean MELD and MELD-Na score was 9.1±3.2 and 10.8±3.4, respectively. According to Child-Pugh classification, 68 (81%), 15 (17.9%), and 1 (1.1%) patients were classified into Child-Pugh A, B, and C, respectively.

Oral glucose tolerance test

Based on the results of 75-g OGTT, 44 (52.4%), 27 (32.1%), and 13 (15.5%) patients were classified into NGT (group 1), IGT (group 2), and undiagnosed diabetes (group 3), respectively. Table 1 shows the difference in demographic data between the 3 groups. As shown, Child-Pugh score, MELD score, proportions of patients with large varices or ascites, platelet count, prothrombin time, and serum albumin were significantly difference between the 3 groups. Comparing demographic data between patients who had normal OGTT and abnormal OGTT (group 1 vs. group 2 + 3) as shown in the Table 2, patients with abnormal OGTT had significantly higher Child-Pugh score (6.1±1.5 vs. 5.3±0.6, p<0.01), higher MELD score (10.1±3.5 vs. 8.2±2.7, p<0.01), higher MELD-Na score (11.7±3.7 vs. 10.1±3, p = 0.03), higher proportions of patients with large varices or ascites (27.5% and 25%, vs. 9.1% and 4.6%, respectively), higher prothrombin time (14.5±1.9 vs. 13.4±1.6 sec, p<0.01), lower serum albumin (3.4±0.6 vs. 3.7±0.4 g/dl, p<0.01), and higher serum total bilirubin (1.4±1.3 vs. 0.9±0.5 mg/dL, p = 0.02). There was no significant difference in mean FPG, HbA_{1C} and HOMA-IR between the 2 groups.

Table 3 shows the difference in demographic data between patients without and with undiagnosed diabetes (group 1 + 2 vs. group 3). Patients with undiagnosed diabetes were older (65.2±7.8 vs. 59.2±9.1 years, p = 0.04), had higher BMI (27.7±6.6 vs. 24.8±4.7 kg/m^2, p = 0.03), higher proportions of patients with large varices or ascites (38.5% and 46.2% vs. 9.9% and 12.7%, respectively), lower platelet

Table 1. Baseline characteristics of patients according to OGTT results

Parameters	Normal GTT (n = 44)	Impaired GTT (n = 27)	Undiagnosed diabetes (n = 13)	*p*-value
Age (years), mean (SD)	59.5 (9.1)	58.8 (10.1)	65.2 (7.8)	0.11
Male, n (%)	30 (68.2)	14 (28)	6 (46.2)	0.24
BMI (kg/m^2), mean (SD)	25.3 (4.6)	24.1 (4.8)	27.7 (6.6)	0.11
Duration of cirrhosis (years), mean (SD)	3.2 (2)	2.9 (1.8)	2 (2)	0.15
Child-Pugh score, mean (SD)	5.3 (0.6)	6.1 (1.6)	6 (1.2)	<0.01
Class A, n (%)	41 (93.2)	18 (66.7)	9 (69.2)	0.01
Class B to C, n (%)	3 (6.8)	9 (33.3)	4 (30.8)	
MELD score, mean (SD)	8.2 (2.7)	10 (3.9)	10.4 (2.6)	<0.02
MELD Na score, mean (SD)	10.1 (3)	11.4 (4.2)	12.2 (2.4)	0.07
Liver decompensation, n (%)				
Large varices	4 (9.1)	5 (18.5)	6 (46.2)	0.01
Ascites	2 (4.6)	5 (18.5)	5 (38.5)	<0.01
Laboratory parameters, mean (SD)				
Hematocrit (%)	39.1 (7.7)	37.3 (7.6)	39.5 (4)	0.54
WBC (x10^3/uL)	5.7 (1.5)	8.1 (1.9)	5.3 (1.6)	0.19
Platelet (x10^3/uL)	160 (69)	180 (129)	93 (37)	0.02
Prothrombin time (sec)	13.4 (1.6)	14.4 (2.1)	14.8 (1.6)	0.02
AST (U/L)	42 (33)	51 (33)	62 (28)	0.13
ALT (U/L)	45 (39)	65 (75)	52 (24)	0.30
ALP (U/L)	115 (35)	112 (43)	137 (69)	0.57
Albumin (g/dL)	3.7 (0.4)	3.4 (0.6)	3.3 (0.4)	<0.01
Total bilirubin (mg/dL)	0.9 (0.5)	1.4 (1.5)	1.4 (0.9)	0.06
Creatinine (mg/dL)	0.9 (0.3)	1 (0.9)	0.9 (0.4)	0.85
Cholesterol (mg/dL)	190 (38)	158 (52)	164 (27)	<0.01
Triglyceride (mg/dL)	94 (45)	87 (36)	87 (30)	0.70
HDL (mg/dL)	62 (23)	51 (18)	60 (22)	0.13
LDL (mg/dL)	113 (30)	91 (33)	87 (16)	<0.01
FPG (mg/dL)	97 (9)	99 (12)	100 (9)	0.49
HbA_{1c} (%)	5.4 (0.6)	5 (0.9)	5.5 (0.6)	0.12

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, FPG = fasting plasma glucose, GTT = glucose tolerance test, HbA_{1C} = glycated haemoglobin, HDL = high-density cholesterol, MELD = model for end-stage liver disease, LDL = low-density cholesterol, WBC = white blood cells

(93±37 vs. 167±96 x10^3/uL, p<0.01), and lower serum albumin (3.3±0.4 vs. 3.6±0.5 g/dL, p = 0.04). The proportion of patients with HOMA-IR >2 was higher in undiagnosed diabetes (77.8 vs. 57.6%), however, this difference did not reach statistical significance (p = 0.44).

Predictors of undiagnosed diabetes

By univariate logistic regression analysis, age, platelet count<100x10^3/uL, presence of large varices needed prophylaxis, and presence of ascites were associated with undiagnosed diabetes (Table 3). However, by multivariate analysis, only age, platelet count <100 x10^3/uL were independently associated with undiagnosed diabetes with odd ratios of 1.11 (1 to 1.23, p = 0.02), and 6.4 (1.2 to 33.6, p = 0.03), respectively.

Discussion

In the present observational study, we have provided several relevant findings. First, IGT and diabetes are frequently found in cirrhotic patients. Second, diabetes in these patients is often under diagnosed by using FPG. In addition, we have shown that there is an association between the severity of liver impairment and the presence IGT or diabetes. These issues are clinically relevant in the care of cirrhotic patients, as several studies have demonstrated that diabetes is a poor prognostic factor in patients with chronic liver diseases[1,2]. Of note, a recent study has found that, in HCV-related cirrhosis, the mortality rate was 2 times higher in diabetic compared with non-diabetic subjects[3].

The incidence of abnormal OGTT in this study was 47.6%, which is considerably higher than general population. The reported incidence of abnormal glucose tolerance test in the healthy individual was around 11 to 20%[11,12]. Physiologically, liver plays a major role in maintaining normal glucose homeostasis. It stores glycogen in the fed state, and release glucose through glycogenolysis and gluconeogenesis during the fasting state. In addition, liver is one of the target organs of insulin. Therefore, in patients with advanced cirrhosis, alterations in glucose metabolism, the so-called hepatogenous diabetes, have been described[1]. The proposed mechanisms of hepatogenous diabetes include: (1) a decrease in hepatic insulin clearance resulting in a down-

Table 2. Difference in baseline characteristics between patients with normal and abnormal GTT (group 1 vs. group 2+3), and patients without and with undiagnosed diabetes (group 1+2 vs. group 3)

Parameters	Normal GTT (n = 44)	Abnormal GTT (n = 40)	*p*-value	No diabetes (n = 71)	Diabetes (n = 13)	*p*-value
Age (years), mean (SD)	59.5 (9.1)	60.9 (9.8)	0.51	59.2 (9.4)	65.2 (7.8)	0.04
Male, n (%)	30 (68.2)	20 (50)	0.12	44 (62)	6 (46.2)	0.36
BMI (kg/m^2), mean (SD)	25.3 (4.6)	25.3 (5.6)	1.0	24.8 (4.7)	27.7 (6.6)	0.03
Duration of cirrhosis (years), mean (SD)	3.2 (2)	2.6 (1.9)	0.14	3.1 (1.9)	2 (2)	0.07
Child-Pugh score, mean (SD)	5.3 (0.6)	6.1 (1.5)	<0.01	5.6 (1.2)	6 (1.2)	0.3
Class A, n (%)	41 (93.2)	27 (67.5)	<0.01	59 (83.1)	9 (69.2)	0.36
Class B to C, n (%)	3 (6.8)	13 (32.5)		12 (16.9)	4 (30.8)	
MELD score, mean (SD)	8.2 (2.7)	10.1 (3.5)	<0.01	8.9 (3.3)	10.4 (2.6)	0.12
MELD Na score, mean (SD)	10.1 (3)	11.7 (3.7)	0.03	10.6 (3.5)	12.2 (2.4)	0.12
Liver decompensation, n (%)						
Large varices	4 (9.1)	11 (27.5)	0.04	7 (9.9)	5 (38.5)	0.02
Ascites	2 (4.6)	10 (25)	0.01	9 (12.7)	6 (46.2)	0.01
Laboratory parameters, mean (SD)						
Hematocrit (%)	39.1 (7.7)	38 (6.6)	0.51	38.4 (7.6)	39.5 (4)	0.61
WBC (x10^3/uL)	5.7 (1.5)	7.2 (1.9)	0.24	6.6 (1.3)	5.3 (1.6)	0.49
Platelet (x10^3/uL)	160 (69)	152 (115)	0.7	167 (96)	93 (37)	<0.01
Prothrombin time (sec)	13.4 (1.6)	14.5 (1.9)	<0.01	13.8 (1.9)	14.8 (1.6)	0.06
AST (U/L)	42 (33)	55 (32)	0.09	46 (33)	62 (28)	0.09
ALT (U/L)	45 (40)	60 (63)	0.17	52 (56)	52 (24)	0.99
ALP (U/L)	115 (35)	120 (53)	0.53	123 (40)	137 (69)	0.45
Albumin (g/dL)	3.7 (0.4)	3.4 (0.6)	<0.01	3.6 (0.5)	3.3 (0.4)	0.04
Total bilirubin (mg/dL)	0.9 (0.5)	1.4 (1.3)	0.02	1.1 (1)	1.4 (0.9)	0.33
Creatinine (mg/dL)	0.9 (0.3)	1 (0.7)	0.99	0.9 (0.6)	0.9 (0.4)	0.84
FPG (mg/dL)	97 (9)	99 (11)	0.26	97 (10)	100 (9)	0.38
HbA_{1c} (%)	5.4 (0.6)	5.2 (0.9)	0.4	5.3 (0.7)	5.5 (0.6)	0.21
Fasting insulin (mIU/L)	15.7 (11.9)	19.6 (27.8)	0.56	17.9 (23)	16.2 (8.9)	0.62
HOMA-IR	4.6 (6.1)	3.9 (3.4)	0.69	4.4 (5.3)	3.9 (2.2)	0.82
HOMA-IR >2, n (%)	11/20 (55)	15/22 (68.1)	0.53	19/33 (57.6)	7/9 (77.8)	0.44

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, FPG = fasting plasma glucose, GTT = glucose tolerance test, HbA1C = glycated haemoglobin, HDL = high-density cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, MELD = model for end-stage liver disease, LDL = low-density cholesterol, WBC = white blood cells

Table 3. Uni- and multivariate logistic regression analysis of factors associated with undiagnosed diabetes

Factors	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*p*-value	Odds ratio	95% confidence interval	*p*-value
Age	1.08	1 to 1.16	0.04	1.1	1 to 1.23	0.02
Platelets <100 x10^3/uL	9.2	2.5 to 34.1	<0.01	6.4	1.2 to 33.6	0.03
Large varices	5.9	1.6 to 21.6	<0.01			
Ascites	5.7	1.4 to 22.3	0.01			

regulation of insulin receptors and, consequently, insulin resistance[13], (2) a reduction in advanced-glycation end products clearance due to hepatic impairment[14], (3) an impaired pancreatic beta-cells response to hyperglycemic state associated with liver diseases, which is partly related to changes of a hormone named betatrophin[15], (4) a peripheral insulin resistances associated with some conditions, such as HCV infection, or non-alcoholic fatty liver disease.

In this study, 15.5% of patients were finally diagnosed with diabetes despite having a normal FPG, indicating that a significant number of patients with cirrhosis have dominant post-prandial hyperglycemia. This number is quite comparable to what has been previous reported from other studies[6,7]. From pathophysiological standpoint, post-prandial hyperglycemia in cirrhotic patients could possibly be caused by insulin resistance, which is common in cirrhosis, leading to a delay in skeletal muscle glucose uptake under the fed state. In addition, skeletal muscle mass is also significantly decreased in these patients as a result of malnutrition[16]. Another possible explanation of post-prandial hyperglycemia is a delayed gastric emptying time, which has been found to be related to cirrhosis[17].

In generally, HbA_{1c} provides good evidence about a blood glucose levels during the previous 2 to 3 months. In this study, there was no difference in the HbA_{1c} level between patients with NGT, IGT, and diabetes. This finding is in line with prior studies showing that HbA_{1c} is unreliable in cirrhotic patients due to several reasons, for instance, high red blood cell turnover rate caused by hypersplenism or bleeding[12].

We have also demonstrated that the severity of cirrhosis was significantly higher in patients with IGT or undiagnosed diabetes, as is demonstrated by higher Child-Pugh score, higher MELD score, higher prothrombin time, lower serum albumin, and higher proportion of patients with large varices needed prophylaxis or ascites. Noteworthy, by multivariate analysis, age and platelet count <100 x10^3/uL were independently associated with undiagnosed diabetes by FPG. This supports the hypothesis that the degree of insulin resistance correlates with the severity of liver dysfunction, as indicated by portal hypertension. Based on this information, diabetes screening by OGTT should be encouraged in a selected group of cirrhotic patients, particularly advanced cirrhosis with portal hypertension, despite having a normal FPG.

The strengths of our study are, so far, many studies have explored a relationship between DM and cirrhosis. However, most studies have focused on a prognostic impact of diabetes on the disease progression, whereas, data on early identification of cirrhotic patients who are at risk of diabetes is limited. In addition, previous studies on the diabetic screening in cirrhosis have been done in a selected population, for example, HCV or HBV-related cirrhosis[5] or hospitalized cirrhotic patients[8]. In this study, we have included a cohort of cirrhotic patients from all causes in an outpatient setting; therefore, we believe these data can be generalized to a broader population.

We also acknowledge limitations of this study. First, this study is a single-center study with a relatively small patient cohort. Second, in asymptomatic patients, diabetes diagnosed based on 2 abnormal OGTT results. However, in this study, OGTT was performed only once, therefore, the incidence of diabetes could be overestimated. Third, the majority of our patients were Child-Pugh A cirrhosis. Hence, if more advanced cirrhotic patients had been included, this might have changed the results. Another limitation of this study is that insulin resistance index was studied in only half of our patients. Although there was a trend toward higher insulin resistance in patients with IGT or undiagnosed diabetes, this difference was not statistically significant. This could be attributed to a relatively small number of patients being tested.

Conclusion

IGT and undiagnosed diabetes by FPG are frequently found in patients with cirrhosis, and are associated with the severity of liver disease. Thus, OGTT may be considered in cirrhotic patients despite having a normal FPG, especially in those with advance liver diseases.

What is already known on this topic?

Liver cirrhosis is often associated with glucose intolerance and diabetes. Impaired glucose metabolism in cirrhotic patients was associated with high prevalence of hepatic complications and negative predictors of survival. Unfortunately, FPG is not sufficient to diagnose diabetes in cirrhotic patients.

What this study adds?

The incidence of abnormal glucose tolerance test in cirrhotic patients from this study was 47.6% that higher

than general population. By multivariate analysis, age and platelet count <100 x10^3/uL were independently associated with undiagnosed diabetes by FPG. Therefore, OGTT may be considered in cirrhotic patients despite having a normal FPG, especially in those with advance liver diseases.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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