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Original Article

Clinical Utility of Fasting Plasma Glucose and Hemoglobin A1C (HbA1C) for the Prediction of Type 2 Diabetes Mellitus Diagnosed by Oral Glucose Tolerance Testing in Cirrhotic Patients with Impaired Fasting Plasma Glucose

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ABSTRACT

Objective: Use of fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels has been ineffective in diagnosing diabetes in cirrhotic patients. The aim of this study was to determine the prevalence and optimal cut-off levels of FPG and HbA1c for effective prediction of type 2 diabetes mellitus (T2DM) as definitely diagnosed by the 75-gram oral glucose tolerance test (75-g OGTT) in cirrhotic patients with impaired fasting plasma glucose (IFG).

Material and Methods: This single-center, cross-sectional study conducted in Nan Hospital included cirrhotic patients with IFG that were diagnosed as T2DM or non-T2DM via 75-g OGTT. The clinical factors associated with the presence of T2DM were investigated using univariate and multivariate regression models.

Results: T2DM was diagnosed according to 75-g OGTT in 55 of the 103 participants (53.40%); impaired glucose tolerance (IGT) was diagnosed in 22.33%, and normal OGTT results were found in 24.27%. An FPG level of ≥104.5 mg/dL and an HbA1c level of ≥5.25% were found to be the optimal cut-off levels for the prediction of T2DM. The FPG level had a sensitivity of 76.4%, 95% confidence interval (CI) [63.0%, 86.8%], and a specificity of 37.5%; 95% CI [24.0%, 52.6%]. HbA1c levels had a sensitivity of 67.3%; 95% CI [53.3%, 79.3%] and a specificity of 37.5%; 95% CI [24.0%, 52.6%]. Hepatitis C virus (HCV) infection, high Child-Pugh score, and high level of FPG before the 75-g OGTT testing were significantly associated with T2DM.

Conclusion: More than half of the cirrhotic patients with IFG had T2DM diagnosed by 75-g OGTT. An FPG level of ≥104.5 mg/dL and an HbA1c level of ≥5.25% were found to be the optimal cut-off levels for the prediction of the presence of T2DM in those with cirrhosis and IFG.

Keywords: cirrhosis; diabetes mellitus; fasting plasma glucose; hemoglobin A1c; oral glucose tolerance test

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INTRODUCTION

Patients with chronic liver disease may have two types of diabetes mellitus (DM): type 2 diabetes mellitus (T2DM) and hepatogenous diabetes (HD). Liver cirrhosis is indicated by decreases in both hepatocyte mass and skeletal muscles during disease progression. Liver cirrhosis, with early-stage hepatogenous diabetes, is characterized by marked postprandial hyperglycemia and increased insulin resistance[1-4]. Insulin resistance in muscular and adipose tissues, in addition to hyperinsulinemia, seems to be the pathophysiologic basis of diabetes in liver disease[4,5]. Retrospective studies have shown that DM is associated with an increased risk of hepatic complications and death in patients with liver cirrhosis[6-10]. DM is associated with hepatic encephalopathy, portal hypertension and, bleeding from esophageal varices in decompensated patients[11-15].

The three standard tests for diagnosis of abnormal glucose metabolism or DM in asymptomatic individuals are the hemoglobin A1c (HbA1c) test, the fasting plasma glucose (FPG) test, and the 2-hour, 75-gram oral glucose tolerance test (75-g OGTT). However, studies on these tests have reported different sensitivities and specificities. The 75-g OGTT is regarded as the gold standard for the diagnosis of T2DM, as it recognizes altered postprandial metabolism. The 75-g OGTT also detects T2DM more accurately than FPG[16-25]. Nevertheless, the 75-g OGTT has not been commonly used in clinical practice due to its complex and time-consuming administration.

Kanda et al.[26] reported that the HbA1c levels in patients with concomitant cirrhosis and diabetes were lower than those in patients with type 2 diabetes alone, because of increased red blood cell turnover caused by hypersplenism. Therefore, HbA1c is not a good marker for diagnosis of diabetes in cirrhotic patients, and the American Diabetes Association (ADA) has recommended that only blood glucose criteria be used to diagnose diabetes in patients with conditions associated with increased red blood cell turnover rate[18,19].

The use of FPG levels has been ineffective in diagnosing diabetes in cirrhotic patients. As described earlier, patients with cirrhosis have been shown to develop insulin resistance in both liver and skeletal muscles, which may cause a more marked elevation in postprandial glucose levels[26-34].

Hence, we conducted this study to determine the prevalence and optimal cut-off levels of FPG and HbA1c for the most accurate prediction of T2DM; as definitely diagnosed by 75-g OGTT in cirrhotic patients with IFG, and to identify risk factors associated with the presence of T2DM.

MATERIAL AND METHODS

A single-center, cross-sectional study was conducted in Nan Hospital. Patients who were at least 18 years of age, with an impaired fasting plasma glucose (IFG) level (FPG 100-125 mg/dL) as recorded on at least two consecutive occasions during the preceding year and who had diagnostic imaging indicating liver cirrhosis were included. Patients with a history of T2DM or were currently undergoing medical therapy affecting their glucose or insulin metabolism were excluded. All participants underwent a 75-g OGTT, according to the standard protocol from the World Health Organization (WHO). Informed consent was obtained from all participants.

Clinical and laboratory assessments

Data collected from medical records included age, gender, body weight, height, body mass index (BMI), comorbidities, and cause of liver cirrhosis. Laboratory data collected included complete blood count (CBC), serum creatinine (Cr), liver function tests (LFT), coagulogram, Child-Pugh score, and Model for End-stage Liver Disease (MELD) score.

The study subjects were advised to follow an unrestricted diet for at least 3 days prior to the 75-g OGTT. The test was performed in the morning after an overnight

fast of 8 hours. During the 75-g OGTT, each subject was asked to drink a 75-g glucose solution and then rest for 2 hours. The test started at time zero, which was when the patients began to consume the solution. The glycemic status outcomes were categorized into three groups in accordance with the ADA criteria:

1. Normal OGTT: 2-hour plasma glucose <140 mg/dL.
2. Impaired glucose tolerance (IGT): 2-hour plasma glucose 140-199 mg/dL.
3. Type 2 diabetes mellitus: 2-hour plasma glucose ≥200 mg/dL.

Statistical analysis

Descriptive statistics; including frequency and percentage, were used for categorical variables. Continuous variables were reported as mean±standard deviation for normally distributed variables and median (25^{th} and 75^{th} percentiles) for non-normally distributed variables. Normality for the distribution of variables was examined by using the Kolmogorov-Smirnov test. The comparison of normally distributed continuous variables between more than two groups was performed using one-way ANOVA, while non-normally distributed variables were analyzed using the Kruskal-Wallis H test. For the two groups, continuous variables were compared using Student's t-test or the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test or Fisher's exact test. Univariate and multivariate predictors of the T2DM group outcomes were evaluated using binary logistic regression analysis (backward stepwise method), and presented as odds ratios (OR), with a 95% confidence interval [CI]. The ROC curve for FPG and HbA1c cut-offs for diagnosis of T2DM via OGTT were presented as AUC, sensitivity, specificity, PPV, and NPV. For all tests performed, a two-tailed p-value<0.05 was considered to be statistically significant. PASW Statistics (SPSS) 18.0 (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

RESULTS

In total, 103 participants met the inclusion criteria. The mean age was 58.23±10.33 years. Of the 103 participants, 80 participants (77.7%) were male, 31 (30.1%) had dyslipidemia, 41 (39.8%) had hypertension and two (1.9%) had cerebrovascular disease (ischemic stroke). In addition, 17 participants (16.5%) were classified as overweight and 36 (35%) had obesity. The etiologies of cirrhosis were alcohol (38.8%), chronic hepatitis B infection (31.1%), and chronic hepatitis C infection (20.4%). Most of the participants had a Child-Pugh class A cirrhosis score, and the mean MELD score of all participants was 10.85±4.02. Baseline characteristics of the participants are listed in Table 1.

According to 75-g OGTT results from the 103 participants, T2DM was diagnosed in 53.40%, IGT was diagnosed in 22.33%, and a normal OGTT result was found in 24.27%. The participants in the T2DM group had significantly higher Child-Pugh scores than those in both the IGT and normal OGTT groups. The T2DM group also had a significantly higher MELD score than the normal OGTT group.

To compare the T2DM group and the non-DM group, we combined the normal OGTT and IGT patients into a non-DM group. Although the BMI was higher in the T2DM group, the difference was not significant. In participants with chronic hepatitis C cirrhosis, significantly more patients were diagnosed as T2DM compared to those diagnosed as non-DM. In the T2DM group, the Child-Pugh score, MELD score, prevalence of ascites, and globulin levels were significantly higher than in the non-DM group. The T2DM group also had significantly lower albumin levels compared to the non-DM group.

Optimal cut-off levels of FPG and HbA1c

The ROC curve was analyzed to determine the optimal FPG and HbA1c cut-off levels for the prediction of T2DM confirmed by 75-g OGTT which demonstrated

in Figure 1 and Figure 2. The FPG level of 104.5 mg/dL had a sensitivity of 76.4%, 95% CI [63.0%, 86.8%] and a specificity of 37.5%; 95% CI [24.0%,52.6%]. Had a positive predictive value (PPV) of 58.3% and a negative predictive value (NPV) of 58.1%. The FPG level of 107.5 mg/dL had a sensitivity of 58.2%, 95% CI [44.1%, 71.8%], and a specificity of 64.6%, 95% CI 49.5%, 77.8%]; with a PPV of 65.3% and an NPV of 57.4%. However, the FPG level of 114.5 mg/dL had a sensitivity of 27.3%, 95% CI [16.1%, 41%] and a specificity of 85.4%, 95% CI [72.2%, 93.9%]; with a PPV of 68.2% and an NPV of 50.6%.

Table 1 Comparison of baseline characteristics between the three OGTT groups

Characteristic	Total (n=103)	Normal (n=25)	IGT (n=23)	DM (n=55)	p-value
Male	80 (77.7)	22 (88.0)	16 (69.6)	42 (76.4)	0.292
Age (years)	58.23±10.33	56.32±8.84	62.26±12.91	57.42±9.47	0.095
BMI	23.37±4.25	23.30±3.61	22.18±2.76	23.90±4.94	0.267
Dyslipidemia	31 (30.1)	7 (28.0)	8 (34.8)	16 (29.1)	0.853
Hypertension	41 (39.8)	7 (28.0)	13 (56.5)	21 (38.2)	0.123
Chronic kidney disease	10 (9.7)	1 (4.0)	4 (17.4)	5 (9.1)	0.323
Active alcohol drinking	19 (18.4)	6 (24.0)	3 (13.0)	10 (18.2)	0.628
HBV infection	32 (31.1)	7 (28.0)	10 (43.5)	15 (27.3)	0.344
HCV infection	21 (20.4)	3 (12.0)	2 (8.7)	16 (29.1)	0.061
Alcohol drinking	40 (38.8)	14 (56.0)	6 (26.1)	20 (36.4)	0.049
CTP score	5.81±1.57	5.20±0.50	5.35±0.65	6.27±1.98	0.002
CTP Class A	85 (82.5)	24 (96.0)	21 (91.3)	40 (72.7)	0.020
CTP Class B	12 (11.7)	1 (4.0)	2 (8.7)	9 (16.4)	0.302
CTP Class C	6 (5.8)	0 (0.0)	0 (0.0)	6 (10.9)	0.074
MELD score	10.85±4.02	9.48±3.32	10.22±3.38	11.75±4.37	0.040
History of EV bleeding	33 (32.0)	7 (28.0)	5 (21.7)	21 (38.2)	0.323
History of HE	2 (1.9)	1 (4.0)	0 (0.0)	1 (1.8)	0.717
History of ascites	14 (13.6)	1 (4.0)	1 (4.3)	12 (21.8)	0.042
History of SBP	2 (1.9)	0 (0.0)	0 (0.0)	2 (3.6)	1.00
History of HCC	7 (6.8)	2 (8.0)	2 (8.7)	3 (5.5)	0.671
Diabetes mellitus evaluation					
Fasting blood sugar (mg/dL)	108.68±6.37	105.64±5.24	109.57±6.32	109.69±6.52	0.022
Fasting blood sugar (Before OGTT) (mg/dL)	108.50±7.14	107.28±5.47	105.87±5.69	110.15±7.97	0.029
HbA1C (%)	5.46±0.62	5.52±0.50	5.29±0.58	5.50±0.68	0.336
75-g OGTT(mg/dL)	198.07±61.67	122.00±10.48	165.70±17.60	246.18±39.06	<0.001
Laboratory profile					
Hemoglobin (g/dL)	13.01±1.94	13.47±1.83	12.77±2.12	12.91±1.92	0.386
Platelets (10^3 cell/cu.mm)	142.39±65.82	150.28±57.49	157.30±62.48	132.56±70.02	0.253
BUN (mg/dL)	13.49±7.22	12.16±4.12	14.63±7.00	13.62±8.35	0.491
Creatinine (mg/dL)	0.98±0.42	0.94±0.40	1.01±0.28	0.99±0.48	0.842
Total bilirubin (mg/dL)	1.13 (0.73-1.64)	1.19 (0.67-1.40)	0.88 (0.71-1.16)	1.18 (0.86-1.88)	0.096
Albumin (g/dL)	3.77±0.62	3.99±0.57	3.92±0.46	3.60±0.67	0.014
Globulin (g/dL)	3.88±0.78	3.69±0.58	3.56±0.61	4.09±0.87	0.008
PT (seconds)	14.27±2.43	13.60±1.99	14.07±2.51	14.65±2.53	0.179
INR	1.24±0.22	1.19±0.18	1.22±0.23	1.28±0.24	0.198

BMI=body mass index; HBV=hepatitis B virus; HCV=hepatitis C virus; CTP=Child-Turcotte-Pugh; MELD=model for end stage liver disease; EV=esophageal varix; HE=hepatic encephalopathy; SBP=spontaneous bacterial peritonitis; HCC=hepatocellular carcinoma; BUN=blood urea nitrogen; PT=prothrombin time; INR=international normalized ratio; OGTT=oral glucose tolerance test; DM=diabetes mellitus; IGT=impaired glucose tolerance

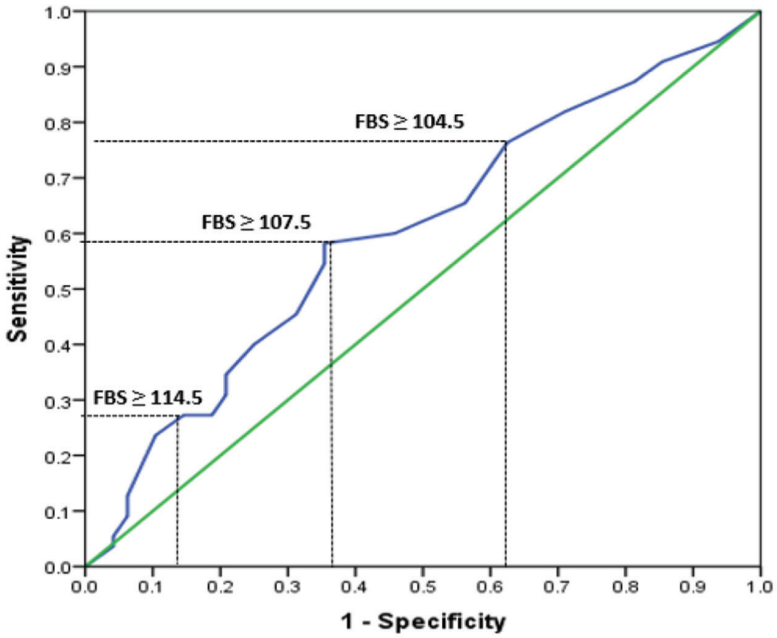

Figure 1 Receiver operating characteristic (ROC) curve of the FBS level during the 75-g OGTT, and the correlation with the diagnosis of diabetes mellitus by the 75-g OGTT (area under the curve=0.601)

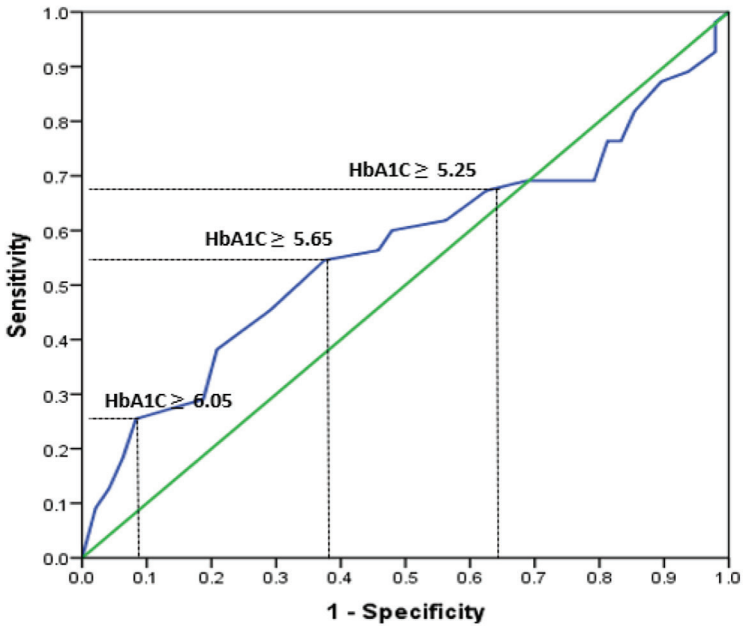

Figure 2 Receiver operating characteristic (ROC) curve of the HbA1c level during the 75-g OGTT, and the correlation with the diagnosis of diabetes mellitus by the 75-g OGTT (area under the curve=0.565)

Table 2 Logistic regression of the risk factors associated with the presence of T2DM in cirrhotic patients with IFG

Factor	Univariate		Multivariate	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
HCV infection	3.53 (1.18–10.53)	0.024	5.05 (1.45–17.61)	0.011
CTP score	2.01 (1.22–3.31)	0.006	1.93 (1.14–3.28)	0.014
Ascites	6.42 (1.34–30.35)	0.019	–	–
MELD score	1.15 (1.02–1.28)	0.020	–	–
FBS (before OGTT) (mg/dL)	1.08 (1.02–1.14)	0.014	1.11 (1.03–1.19)	0.005
Albumin (g/dL)	0.37 (0.18–0.75)	0.006	–	–
Globulin (g/dL)	2.42 (1.32–4.44)	0.004	–	–
Total bilirubin (mg/dL)	2.02 (1.11–3.68)	0.021	–	–

HCV=hepatitis C virus; CTP=Child–Turcotte–Pugh; MELD=model of end stage liver disease; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test

Regarding HbA1C, the level of HbA1c ≥5.25% had a sensitivity of 67.3%, 95% CI [53.3%, 79.3%], and a specificity of 37.5%, 95% CI [24.0%, 52.6%], with a PPV of 55.2% and an NPV of 50.0%. The level of HbA1c ≥5.65% had a sensitivity of 55.6%, 95% CI [41.4%, 69.1%] and a specificity of 59.1%, 95% CI [43.2%, 73.7%], with a PPV of 62.5% and an NPV of 52.0%. The level of HbA1c ≥6.05% had a sensitivity of 25.5%, 95% CI [14.7%, 39.0%] and a specificity of 91.7%, 95% CI [80.0%, 97.7%], with a PPV of 77.8% and an NPV of 51.8%.

Risk factors

A logistic regression analysis was conducted to identify the predictors of T2DM in cirrhotic patients with IFG, as definitely diagnosed by 75–g OGTT. The risk factors studied were chronic HCV infection, high Child–Pugh score, high MELD score, low serum albumin level, high serum globulin level, and high FPG before the 75–g OGTT as shown in Table 2.

Multivariate logistic regression analysis indicated HCV infection, high Child–Pugh score, and high level of FPG before the 75–g OGTT were significantly associated with the presence of T2DM.

DISCUSSION

In this study, we used the 75–g OGTT to diagnose T2DM in cirrhotic patients with IFG. We found an unexpected result in that 53.4% of IFG patients with cirrhosis had T2DM. A previous study (No. 1) showed that the mean prevalence of diabetes diagnosed via OGTT criteria in patients with cirrhosis was 35.1%, 95% CI [22.8%, 47.4%], and the prevalence of IGT was 27.8%, 95% CI [21.2%, 34.4%]. Another study[21] reported that 28.5% of Thai individuals with IFG had T2DM according to 75–g OGTT criteria.

These results suggest that using HbA1c levels to detect T2DM in IFG individuals is less accurate than using the 2–hour plasma glucose level. The lower efficacy of using the HbA1c level compared to the 2–hour plasma glucose level probably resulted from postprandial hyperglycemia and increased insulin resistance in patients with chronic liver disease or cirrhosis. Moreover, the Thai population has a high prevalence of the thalassemia trait, resulting in physiologically lower HbA1c levels[35].

The results of this study suggest that the optimal cut–off level of FPG is ≥104.5 mg/dL, with a sensitivity of 76.4% and specificity of 37.5% for prediction of T2DM. The optimal cut–off level of HbA1c was ≥5.25%, with a sensitivity of 67.3% and specificity of 37.5%.

The FPG level of ≥104.5 mg/dL and the HbA1c level of ≥5.25% were chosen as the optimal cut-off levels because they demonstrated high sensitivity for detection of T2DM; as definitely diagnosed by the 2-hour plasma glucose level after a 75-g OGTT. The cut-off level of HbA1c in our study was lower than the optimal cut-off levels in previous studies[17,21,24,25,36] on non-cirrhotic participants that reported optimal HbA1c cut-off levels of around 6.0%–6.3%. These findings may be associated with an increased red blood cell turnover rate in patients with cirrhosis.

Our study indicated that the Child-Pugh score, MELD score, globulin level, and prevalence of ascites in the T2DM group were significantly higher than in the non-DM group. The T2DM group also reported lower albumin levels compared to the non-DM group. These findings suggest that the increasing prevalence of diabetes correlated with the severity of liver cirrhosis. This finding was in accordance with a previous study[14], which showed hepatogenous diabetes and insulin resistance significantly correlated with portal hypertension and variceal hemorrhage, and postprandial hyperglycemia significantly correlated with variceal hemorrhage. In our study, more participants with T2DM, diagnosed by OGTT, had a history of variceal bleeding compared to participants in the IGT and normal OGTT groups; however, this difference was not significant. Moreover, regarding the association between OGTT and prognosis of patients with liver cirrhosis, previous studies[7,27] reported that the 5-year survival rate of cirrhotic patients with normal OGTT results was 94.7%, that of patients with IGT was 68.8%, and that of patients with DM was 56.6%.

Multivariate logistic regression analysis found that HCV infection was associated with T2DM. Recent meta-analysis studies[36–38] reported similar findings, suggesting that HCV itself increased insulin resistance.

There were some limitations to this study. First, its limited number of participants resulted in small numbers of participants within each subgroup. Second, the participants were diagnosed with cirrhosis by imaging; not by liver biopsy, which is the gold standard for diagnosis of liver cirrhosis.

CONCLUSION

More than half of the cirrhotic patients with IFG had T2DM diagnosed by 75-g OGTT. An FPG level of ≥104.5 mg/dL and an HbA1c level of ≥5.25% were the optimal cut-off levels for the prediction of T2DM in cirrhotic patients with IFG. These patients should be advised to undertake a 75-g OGTT, so as to detect T2DM. HCV infection, high Child-Pugh score, and high FPG levels before a 75-g OGTT, as they are significantly associated with the presence of T2DM.

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CONFLICT OF INTEREST

Non declared.

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