Elevated Fasting Plasma Glucose before Liver Transplantation is Associated with Lower Post-Transplant Survival

Emi Katsura
Tatsuki Ichikawa
Naota Taura
Hisamitsu Miyaaki
Satoshi Miuma
Hidetaka Shibata
Takuya Honda
Masaaki Hidaka
Akihiko Soyama
Masaaki Hidaka
Fuminao Takeshima
Susumu Eguchi
Naota Taura
Hidetaka Shibata
Tatsuki Ichikawa
Emi Katsura

Background: The risk of liver cirrhosis is higher among individuals with diabetes mellitus, and a cirrhotic patient with diabetes may have a poorer prognosis after liver transplantation compared to a patient without diabetes. Thus, we evaluated whether fasting plasma glucose prior to receiving a liver transplant was a prognostic factor for post-transplant survival.

Material/Methods: Ninety-one patients received a living donor liver transplant between November 2005 and December 2012. Patients were considered diabetic if they were prescribed diabetes medications or had impaired glucose tolerance as measured by an oral glucose tolerance test. Each patient was monitored through December 31, 2013, to evaluate prognosis.

Results: Fasting plasma glucose of at least 100 mg/dL significantly decreased survival following transplant (52% in the high FPG group compared to 78% in the control group, p=0.04), while postprandial hyperglycemia had no effect on survival. Additionally, overall mortality and the incidence of vascular disease were significantly higher among patients with uncontrolled plasma glucose. Impaired fasting plasma glucose was significantly and inversely associated with overall survival in the univariate and multivariate analyses, while creatinine (at least 1 mg/dL) was inversely associated with survival in the univariate analysis.

Conclusions: Elevated fasting plasma glucose prior to liver transplantation was inversely associated with post-transplant survival. This effect may be due to underlying microangiopathy as a result of uncontrolled diabetes before transplantation. Our data demonstrated the importance of controlled blood glucose prior to liver transplantation.

MeSH Keywords: Diabetes Mellitus, Type 2 • Liver Cirrhosis • Liver Transplantation

Abbreviations: BMI – body mass index; WBC – white blood cells; Hb – hemoglobin; Plt – platelet; PT – prothrombin time; CRP – C-reactive protein; BUN – blood urea nitrogen; Cre – creatinine; eGFR – estimated glomerular filtration rate; TP – total protein; Alb – albumin; T-Bil – total bilirubin; ALT – alanine aminotransferase; γ-GTP – γ-glutamyltranspeptidase; ChE – cholinesterase; TG – triglyceride; TC – total cholesterol; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; FPG – fasting plasma glucose; HOMA-R – homeostasis model assessment ratio; CP-S – Child-Pugh score; MELD – Model for End-Stage Liver Disease; HAT – hepatic artery thrombosis; PVT – portal vein thrombosis; NOMI – nonocclusive mesenteric ischemia; TMA – thrombotic microangiopathy; HD – hepatogenous diabetes; LC – liver cirrhosis; DM – diabetes mellitus; T2DM – type 2 DM; IGT – impaired glucose tolerance; HCC – hepatocellular carcinoma; SU – sulfonylurea; DPP4I – dipeptidyl peptidase-4 inhibitor; NEFA – non-esterified free fatty acid; BTR – branched chain amino acid tyrosine molar ratio
Liver cirrhosis (LC) and diabetes mellitus (DM) are closely related clinical conditions. Type 2 DM (T2DM) patients are at risk for onset of non-alcoholic liver disease, hepatocellular carcinoma, and death by hepatobiliary disease [1,2]. The risk of chronic liver disease and cirrhosis are also increased by DM [3]. Therefore, T2DM may predict the onset and progression of liver disease. Diabetes, as a coexisting disease with cirrhosis, is called hepatogenous diabetes (HD) and differs from type T2DM. HD is characterized by later onset than cirrhosis, negative family history for DM, lower body mass index (BMI), reduced frequency of diabetic complications (retinopathy, cardiovascular disease, and renal disease) and insulin resistance, and the common causes of death from HD are related to liver disease [4]. Influence of HD in cirrhosis is not clear. For example, Japanese patients with Child-Pugh grade A and B disease who had not been diagnosed with T2DM were found to have an evaluated OGTT (by a 75 g oral glucose tolerance test), and a DM pattern associated with a worse prognosis than normal glucose tolerance [5]. However, German patients with a DM pattern identified by OGTT were found to have a similar prognosis to patients who had an impaired glucose tolerance (IGT) pattern [6]. It has been reported that DM complicated with cirrhosis was not a prognostic factor for in-hospital death in Taiwan [7], but DM complicated with decompensated cirrhosis was a prognostic factor for mortality in Italy [8]. The associations between cirrhosis and diabetes have not been fully characterized.

DM in cirrhotic patients is an important consideration for prognosis after liver transplantation (LT). One study found HD was resolved after LT, thereby improving insulin sensitivity, but decreased insulin secretion was not recovered following LT [9]. Research has shown that DM in pre-LT patients predicted mortality after LT [10], and recently, it was reported that DM in pre-LT increased mortality after LT [11,12]. However, DM has also been associated with adverse events and longer hospital stay without directly affecting survival after LT [13], and other studies concluded that DM in pre-LT was not related to mortality after LT [14–16]. These conflicting results may be due to different diagnostic criteria for DM between studies, or due to studies varying in objective measurements of blood glucose control.

Patients with cirrhosis awaiting a living donor LT (LDLT) in our hospital completed OGTTs beginning in November 2005, prior to which time patients did not receive diabetic treatments (insulin and/or oral medications). Blood glucose control was evaluated by fasting plasma glucose (FPG) level, hemoglobin A1c (HbA1c), and glycoalbumin (GA) before and after LDLT. Thus, we evaluated whether glucose levels in pre-LDLT patients was a prognostic factor for post-LDLT survival.

Materials and Methods

Patients

Study participants were recruited from liver cirrhosis patients who were admitted for LDLT at Nagasaki University Hospital in Nagasaki, Japan, between November 2005 and December 2012. Patients were observed for complications and/or mortality until December 31, 2013. Study inclusion criteria were as follows: first LDLT for patient, adult (at least 20 years of age), chronic liver disease diagnosis, and evaluation of blood glucose level before LDLT (Table 1). Ninety-one patients who received LDLT were included. Informed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by the approval by the Nagasaki University Hospital Human Research Committee. Written consent was obtained from each patient.

Laboratory measurements

Laboratory data and anthropometric measurements were obtained on the day of entry for each participant. Body mass index (BMI) was calculated pre-LDLT as weight (kg) divided by the square of height (m). Laboratory measurements included white blood cells (WBC), hemoglobin (Hb), platelet counts (Plt), prothrombin time (PT), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine (Cr), estimated glomerular filtration rate (eGFR), total protein (TP), albumin (Alb), total bilirubin (T-Bil), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (γ-GTP), cholinesterase (ChE), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), FPG, HbA1c, GA, and homeostasis model assessment ratio (HOMA-R). HbA1c in pre-LDLT was measured using the Japan Diabetes Society method.

Diagnosis of diabetes mellitus (DM) in pre-LT

DM was diagnosed in patients admitted for LDLT if (1) the patient was prescribed at least one medication for DM or (2) the patient had FPG of at least 126 mg/dL. Patients without DM at admission completed a 75 g oral glucose tolerance test (OGTT) and were diagnosed with DM if plasma glucose was 126 mg/dL or greater at fasting or 200 mg/dL or greater at 120 minutes. Patients with plasma glucose of 110 mg/dL or less at fasting and 140 mg/dL or less at 120 minutes were considered DM-free. Impaired glucose tolerance (IGT) is expected for patients with DM and the normal pattern.

Statistical analysis

Data were analyzed using the StatView 5.0 software program (SAS Institute, Inc., Cary, NC, USA). Laboratory variables were...
compared for DM and DM-free patients using t-tests and χ²-square tests, and survival curves were prepared using the Kaplan Meier method. Survival between groups was measured via log-rank tests. Multivariate and univariate analyses were performed with logistic regression. A p value <0.05 was considered statistically significant.

Results

Patients with type 1 DM were not found in this study. Thirty pre-LDLT patients (33%) were treated with the T2DM medications insulin (n=25), sulfonylurea (SU) (n=3), dipeptidyl peptidase-4 inhibitor (DPP4I) (n=1), and glinide (n=1). Thirty-two patients (52%) who completed the OGTT (n=61) were diagnosed with T2DM. The hospital diabetes specialist managed DM treatment, and patients with fasting and postprandial plasma glucose greater than or equal to 250 mg/dL were treated with insulin. DM treatment was considered successful if blood glucose levels were maintained below 300 mg/dL.

Initially, we evaluated the extent to which DM in pre-LDLT patients influenced survival after LDLT. Individuals diagnosed with DM prior to LDLT (diabetes group, n=30) had a poorer 5-year survival rate compared to the control group (n=61); 48% and 70%, respectively, p=0.03, Figure 1A. DM patients treated with insulin (insulin group, n=25) demonstrated borderline significantly poorer survival compared to the control group (n=66); 49% and 70%, respectively, p=0.05, Figure 1B. Next, we evaluated whether DM diagnosed at 120 minutes of OGTT influenced post-LDLT survival. Figure 1C shows the similar survival rates between patients with DM diagnosed either via medication

Table 1. Clinical characteristics of LDLT patients with high or normal FPG.

| Characteristic (unit) | High FPG (n=41) | Normal FPG (n=50) | p-value for difference |
|----------------------|----------------|------------------|------------------------|
| Observation time (days) | 1086.5 (926) | 1150 (773) | NS |
| BMI (kg/m²) | 23.7 (3.56) | 24.9 (4.23) | NS |
| Age (y) | 58.1 (6.76) | 56.2 (9.39) | NS |
| Gender (female, n) | 17 | 24 | NS |
| HCV (n) | 26 | 21 | 0.05 |
| MELD | 13.3 (8.24) | 13.6 (7.44) | NS |
| Cr (mg/dL) | 1.06 (0.95) | 0.83 (0.25) | NS |
| eGFR (ml/min/m²) | 5.67 (1.32) | 4.36 (0.56) | NS |
| HbA1c (%) | 5.67 (1.32) | 4.36 (0.56) | <0.0001 |
| GA (%) | 23.9 (6.21) | 17.9 (4.02) | <0.0001 |
| LDL-C (mg/dL) | 52.4 (22.0) | 57.3 (25.5) | NS |
| HDL-C (mg/dL) | 32.3 (17.3) | 29.9 (18.2) | NS |
| TG (mg/dL) | 99.8 (64.9) | 76.1 (53.6) | 0.06 |
| NEFA | 0.68 (0.23) | 0.69 (0.37) | NS |
| BTR | 3.16 (1.43) | 3.16 (1.91) | NS |
| Deaths (n) | 18 | 11 | 0.04 |
| Cause of death (n) | | | |
| Graft failure | 5 | 5 | NS |
| Infection | 4 | 4 | NS |
| Vascular complication | 5 | 0 | 0.05 |
| Other (HAT, PVT, TMA, NOMI, Stroke) | 4 | 2 | NS |

* Values are presented as mean (SD) unless otherwise indicated. NS is not significant.
Figure 1. Patients with DM had poorer post-LDLT prognoses than patients without DM. Survival was measured until each patient’s death and graft loss or the end of the observation period, whichever occurred first. (A) The diabetes group included patients who used DM medications (insulin and oral medications) (black circle is the control group and white circle is the diabetes group). (B) The insulin group included insulin users only (black circle is the control group and white circle is the insulin group). (C) The clinical and OGTT diabetes group included patients who used DM medications (n=30) and diabetes diagnosed by OGTT (n=32). (Black circle is the control group and white circle is the clinical and OGTT diabetes group). (D) The high FPG group included patients with FPG ≥100 mg/dL, measured in the morning (n=30) or during an OGTT (n=11). (Black circle is the control group and white circle is the clinical and high PG at fasting group). (E) Patients were divided into 3 groups based on FPG. “<100” is 100 or less mg/dL of FPG (black circle). “100–110” is 100 to 110 mg/dL of FPG (gray circle). “>111” is 111 or more mg/dL of FPG (white circle). Y-axis is survival rate and X-axis is observation time (day).
Table 2. The associations of high FPG and Cr with short- and long-term prognosis following LDLT in univariate and multivariate logistic regression analyses.

| Variable       | Univariate | Multivariate* |
|----------------|------------|---------------|
| Overall survival |            |               |
| High FPG (≥100 mg/dL) | 0.028 | 0.36 | 0.15–0.90 | 0.047 | 0.39 | 0.15–0.99 |
| High Cr (≥1 mg/dL) | 0.033 | 0.32 | 0.11–0.92 | 0.059 | 0.35 | 0.15–0.99 |
| 6-month survival |            |               |
| High FPG (≥100 mg/dL) | 0.30 | 0.59 | 0.21–1.67 | 0.50 | 0.69 | 0.23–2.34 |
| High Cr (≥1 mg/dL) | 0.009 | 0.22 | 0.072–0.69 | 0.010 | 0.23 | 0.075–0.73 |
| 3-year survival |            |               |
| High FPG (≥100 mg/dL) | 0.04 | 0.36 | 0.27–0.99 | 0.090 | 0.41 | 0.14–1.17 |
| High Cr (≥1 mg/dL) | 0.002 | 0.18 | 0.060–0.54 | 0.004 | 0.19 | 0.064–0.73 |

*p* Adjusted for FPG (100 or more mg/dL), Cr (1 or more mg/dL), gender, age at transplantation (60 or more years), original disease (HCV), MELD (12 or more), BMI (30 or more), and HCC.

Patients with high FPG had significantly increased HbA1c and GA relative to the control group (*p*<0.0001, Table 2). The prevalence of hepatitis C (HCV) was higher among patients with high FPG (*p*=0.05), but BMI, age, MELD, CP-S, and renal function were not different between groups. The number of patients who died during the observation period was greater among the high FPG group compared to the normal FPG group, but there were no differences between the number of graft failures between the two groups, and no difference in infections as a cause of death between the two groups. Causes of death among patients with high FPG included graft failure (*n*=5, including small for size), infection (*n*=4), chronic rejection (*n*=2), hepatic artery thrombosis (HAT, *n*=1), portal vein thrombosis (PVT, *n*=1), nonocclusive mesenteric ischemia (NOMI, *n*=1), thrombotic microangiopathy (TMA, *n*=1), stroke (*n*=1), recurrence of cirrhosis (*n*=1), and recurrence of HCV (*n*=1). Among patients with normal FPG, causes of death included graft failure (*n*=5, including small for size), infection (*n*=4), and chronic rejection (*n*=2). The prevalence of vascular disease (including TMA, PVT, NOMI, and stroke) as a cause of death was higher among patients with high FPG than among patients with normal FPG (*p*=0.05).

Using logistic regression, we analyzed the influence of covariates (including the clinical characteristics presented in Table 1) on the association between pre-LDLT FPG and post-LDLT prognosis (Table 2). High serum Cr (1 or more mg/dL) at 6 months,
1 year, and 3 years significantly decreased survival rates among all patients. However, for overall 5-year survival, high FPG and high Cr were significantly associated with poorer prognoses in the univariate analyses, and high FPG alone remained a significant negative predictor of survival in the multivariate analyses. Patients with high Cr had a shorter mean observation time and poorer average MELD scores than patients with normal Cr (Table 3). Mean FPG, the number of patients treated for DM, and the number of patients with high FPG were similar between patients with high or normal Cr.

The 5-year survival rates were 46% and 71% in the high Cr (n=19) and control group (n=72), respectively (p=0.002, Figure 2A). Patients with low eGFR (45 or less mL/min/m² based on Cr) demonstrated similar 5-year survival rates compared to patients with high Cr (70% in control group (n=74) versus 45% in low eGFR group (n=17), p=0.003, Figure 2B). Patients were assigned to four groups based on Cr and FPG (low/low, low/high, high/low, or high/high) to assess prognosis after LDLT. Among the four groups, survival rates were best among patients with low Cr and low FPG (n=42) and worst among patients with high Cr and high FPG (n=11); patients with either high Cr and low FPG (n=30) or low Cr and high FPG (n=8) demonstrated poorer prognoses than the low Cr and low FPG group; the 5-year survival rates were 82%, 55%, 60% and 37%, respectively, p=0.04, Figure 2C. When patients with either high Cr and low FPG (high/low group) or low Cr and high FPG (low/high group) were collapsed into a single group (risk=1; n=38), survival rates differed significantly between this group and the low/low group (risk=0; n=42), and the high/high group (risk=2; n=11), p=0.001, Figure 2D). Patients classified as risk=0 had a 5-year survival rate of 82%, patients classified as risk=1 had a 5-year survival rate of 55%, and patients classified as risk=2 had a 5-year survival rate of 37%.

Discussion

Patients diagnosed with DM prior to LDLT have a significantly poorer prognosis following LDLT compared to patients without DM. In addition, FPG greater than or equal to 100 mg/dL before LDLT significantly decreases survival after LDLT. The mortality

| Table 3. Clinical characteristics of LDLT patients with high or normal Cr. |
|-----------------|-----------------|-----------------|-----------------|
| Characteristic (unit)* | High Cr (n=19) | Normal Cr (n=72) | p-value for difference |
| Observation time (days) | 594 (691) | 1260 (826) | 0.001 |
| BMI (kg/m²) | 23.6 (3.39) | 24.5 (4.1) | NS |
| Age (y) | 55.3 (8.13) | 57.6 (8.36) | NS |
| Gender (female, n) | 5 | 36 | 0.077 |
| HCV (n) | 8 | 37 | NS |
| MELD | 21 (8.24) | 11.5 (7.44) | <0.0001 |
| CP-S | 10.6 (2.03) | 9.44 (2.49) | 0.09 |
| FPG (mg/dL) | 122.4 (68) | 100 (44.1) | NS |
| DM (n) | 9 | 21 | NS |
| High FPG (n) | 11 | 30 | NS |
| HbA1c (%) | 4.98 (1.13) | 4.92 (1.2) | NS |
| GA (%) | 19.7 (4.2) | 21.1 (6.34) | NS |
| LDL-C (mg/dL) | 50.5 (26.8) | 56.3 (23.3) | NS |
| HDL-C (mg/dL) | 24.8 (19.8) | 32.5 (16.9) | NS |
| TG (mg/dL) | 114.7 (93.2) | 80 (46.6) | 0.03 |
| NEFA | 0.64 (0.29) | 0.69 (0.33) | NS |
| BTR | 3.34 (1.45) | 3.11 (1.76) | NS |
| Deaths (n) | 10 | 19 | 0.05 |
| Cause of death (n) | | | |
| Graft failure | 3 | 7 | NS |
| Infection | 4 | 4 | NS |
| Other | 7 | 11 | NS |

* Values are presented as mean (SD) unless otherwise indicated.
rate among patients with high FPG was greater compared to patients with normal FPG during the observation period, and vascular disease was a more prominent cause of death in the high FPG group compared to the normal FPG group. Regarding overall survival rates, high FPG and Cr were associated with significantly poorer prognoses in the univariate analyses, while FPG was significantly associated with decreased survival in the multivariate analyses.

In our study, the use of DM medications or high FPG in pre-LDLT patients influenced survival rate after LDLT. In patients receiving OGTT (n=61), postprandial hyperglycemia was not a prognostic marker after LDLT. However, postprandial hyperglycemia was not measured in patients with treated DM. Our study showed that FPG was a better marker for prognosis than HbA1c. Although DM has been reported as a poor prognosis marker for LT [10–12], there are only a few reports of FPG as a prognostic indicator after LT. One previous study concluded that FPG greater than or equal to 110 mg/dL in pre-LDLT patients significantly decreased survival post-LT [17]. Our results indicated that FPG of at least 100 mg/dL significantly decreased survival for patients with or without treated DM prior to LDLT. HbA1c and GA are considered useful clinical markers for blood glucose control, but are not useful in cirrhotic patients [18]. Consequently, FPG might be a more accurate indicator of blood glucose control in cirrhotic patients than HbA1c and GA. It has been reported that hypoglycemia (FPG less than 90 mg/dL), more than normal blood glucose or hyperglycemia, was a poor prognostic marker in decompensated cirrhotic patients who visited emergency rooms [19]. Although hypoglycemia has been
shown to be an indicator of blood glucose control among patients with DM, the 5-year survival rate among patients with FPG levels no greater than 90 mg/dL was similar to control patients in our data and in a previous study [17]. Our results confirm that FPG should be maintained between 90 to 100 mg/dL in pre-LT cirrhotic patients.

The causes of death among our study patients were similar between patients with high or normal FPG, but vascular disease was a more prominent cause of death among patients with high FPG. Previous studies reported that a major cause of death in diabetic patients with and without LT was liver disease [3,11]. However, one study found the risk of vascular events, including cardiovascular disease, was increased in patients with DM [20], and in another study, coronary artery calcification in patients with cirrhosis was associated with high FPG [21]. In cystic fibrosis-related diabetes, microvascular complications can occur in fasting hyperglycemic patients [22]. In addition, thrombotic angiopathy in a patient in a diabetic state has been associated with the oxidative modification of von Willebrand factor [23]. Studies have found HAT [24], PVT [25], NOMI [26], and TMA [27] are related to DM and high plasma glucose. Thus, patients with high FPG prior to LT should be monitored closely for vascular complications, including HAT, PVT, NOMI, TMA, and stroke after LT.

Elevation of FPG indicates greater abnormality in blood glucose control compared to postprandial hyperglycemia in T2DM [28]. β cell dysfunction begins during pre-DM [29], and LT cannot improve β cell dysfunction but can improve insulin resistance [9]. Although we could not establish distinct diabetes criteria in our study, high FPG in pre-LDLT patients significantly decreased survival following LDLT compared to patients with normal FPG. Regardless of diabetes criteria, high FPG in pre-LDLT may indicate an advanced stage of DM, and severe vascular disease may be more prevalent among patients with high FPG compared to patients with normal FPG after LT.

Our study found that high serum Cr was a prognostic marker in short-term survival following LDLT. Additionally, a combination of high Cr and high FPG decreased overall survival. High Cr was related to liver failure (MELD and CP-S), but not HbA1c, GA, DM, and FPG (Table 4). In a previous report, serum Cr was shown to be related to DM [7]. Additionally, serum Cr in cirrhotic patients who have less muscle volume than healthy controls was not shown to accurately reflect renal function [30,31]. However, renal dysfunction can predict progressive mortality in cirrhotic patients [30,31], and poor pre-transplant renal function can predict chronic kidney disease after LT [32]. It has not been previously shown that a small elevation of Cr in cirrhotic patients in pre-LT is a prognosis factor after LT. Our study suggests that a low serum level of Cr can be a useful predictor of survival after LT and may reflect liver function more accurately than renal function before LT.

Conclusions

High FPG in pre-LT decreases survival after LT, possibly due to diabetes-induced underlying microangiopathy before LT. Unlike serum Cr, FPG can be maintained at less than 100 mg/dL by medication in patients prior to LT. To improve the survival rate after LT, clinicians must carefully evaluate blood glucose control and DM complications before LT.

Conflicts of interest

The authors declare no conflicts of interest.

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