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Risk Factors and Outcomes of the Post-Liver Transplantation Diabetes Mellitus

ABSTRACT

Objective: We aimed to identify the risk factors for the development of diabetes mellitus after transplantation in liver recipients.

Methods: Two hundred twenty-seven patients with a follow-up period >8 months after liver transplantation were included in the study. The clinical and laboratory data of patients with post-liver transplantation diabetes mellitus and without post-liver transplantation diabetes mellitus were compared.

Results: Of the 227 patients, 61 patients were diagnosed with diabetes mellitus in the pretransplantation period. Twelve percent of the patients (20 patients) were diagnosed with post-liver transplantation diabetes mellitus and 146 patients were not diagnosed with diabetes mellitus. We found that post-liver transplantation diabetes mellitus was associated with advanced age (95% CI: 1.002-1.142). Male liver recipients were diagnosed with a higher rate of post-liver transplantation diabetes mellitus than female recipients (15.5% and 5.4%, respectively; $P = .045$). Pretransplantation fasting plasma glucose levels were higher in patients with post-liver transplantation diabetes mellitus than without post-liver transplantation diabetes mellitus, which was not statistically significant ($P = .097$). While 22.2% of patients with post-liver transplantation diabetes mellitus had complications after transplantation, 14.2% of the patients without post-liver transplantation diabetes mellitus had complications after transplantation ($P = .370$).

Conclusion: As post-liver transplantation diabetes mellitus is associated with graft failure and increased mortality and morbididy, candidates for liver transplantation should be screened for risk factors of diabetes, and blood work for diabetes mellitus should be done regularly in these patients. Since patients with advanced age, male gender, and higher fasting plasma glucose levels in the pretransplantation period have higher risk for the development of post-liver transplantation diabetes mellitus, these cases should be screened more carefully.

Keywords: Diabetes mellitus, graft failure, post-liver transplantation diabetes mellitus

Introduction

Liver transplantation plays an important role in the management of many liver diseases.[1] The cirrhosis secondary to viral hepatitis and alcohol abuse, primary liver tumors, and cholestatic disease are frequent indications for liver transplantation.[2] Developments in surgical techniques and usage of immunosuppressive therapy have led to improvement in the survival of the patients after liver transplantation.[3] Although the survival rate has been increased in liver transplant recipients, some complications such as hepatitis C infection, cardiovascular disease, and nonalcoholic fatty liver disease can be a risk factor for graft failure and mortality. Post-liver transplantation diabetes mellitus post-liver transplantation diabetes mellitus, is one of the serious complications which is commonly seen after liver transplantation.[4,5]

While the prevalence of pretransplant diabetes mellitus among liver transplant recipients ranges between 15% and 26%, new-onset diabetes mellitus after transplantation is expressed to be between 9% and 63.3%.[6-9] Both pretransplantation diabetes mellitus and PLTDM are associated with a risk of poor outcomes after transplantation.[10,11] According to studies, race, male gender, family history of diabetes mellitus, obesity-, alcohol-, and hepatitis C virus-induced cirrhosis, and immunosupressive agents are among the risk factors for PLTDM.[12-16] Corticosteroids may impair insulin secretion and insulin signaling pathway; moreover, they increase hepatic glucose output.[17-19] Calcineurin inhibitors also may cause deregulation of insulin secretion, apoptosis of insulin-producing beta cells, and induction of peripheral insulin resistance.[20]

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As most studies have documented a significant increase in mortality in cases with PLTDM, screening all liver recipients for risk factors and identifying impaired glucose metabolism are important. The development of PLTDM has been shown as an independent predictor of posttransplantation cardiovascular events in the literature.[20] Higher risk for graft failure and rejection episodes have been found in these cases.[21] Furthermore, infections and renal insufficiency have been shown with a higher incidence in cases with PLTDM.[22]

In this study, we intended to explore the risk factors for the development of PLTDM. We also investigated the outcomes of PLTDM.

Materials and Methods

Two hundred twenty-seven patients who underwent liver transplantation between January 2005 and December 2019 were identified by medical records retrospectively in the study. All cases were aged more than 18 years. The recipients who were aged <18 years and had multi-organ transplants were excluded. Cases with a follow-up period >8 months after liver transplantation were included in the study to define diagnosis of diabetes mellitus.

The immunosuppression protocol used postoperatively consists of intravenous corticosteroids, tacrolimus/everolimus, and cyclosporine. Corticosteroid administration started with the regimen of 500 mg intravenous methylprednisolone preoperatively and then progressively tapered to a treatment stop by 4 months. So, when we evaluated the patients, doses of immunosuppressive agents had been tapered and the doses were stable.

All data (sociodemographic, laboratory data, and donor characteristics) were obtained via electronic medical records of the hospital. Model for End-Stage Liver Disease (MELD) score closest to the date of transplant was calculated for the patients.[23] Laboratory analysis of the patients in pretransplantation and posttransplantation periods was recorded.

Post-liver transplantation diabetes mellitus was defined by using the American Diabetes Association (ADA) and the World Health Organization guidelines as follows: glycated hemoglobin (HbA1C) ≥6.5% or fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis or random plasma glucose ≥200 mg/dL (11.1 mmol/L) before transplantation or during the posttransplant period.[24-26]

Patients were stratified as those without diabetes mellitus in the pre/after transplantation period (146 patients), those with pretransplant diabetes mellitus (61 patients), and the third group without diabetes mellitus in the pretransplantation period and diabetes mellitus in the postransplantation period (20 patients). We analyzed only pretransplant characteristics between these 3 groups (227 patients), but the majority of the analyses were conducted between only patients with PLTDM (20 patients) and patients without PLTDM (146 patients).

The study protocol was approved by Uludağ University Faculty of Medicine Ethics Committee with decision no 2021-1/12 (December 6, 2021).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences software version 23 (IBM Corp.; Armonk, NY, USA). Normally and non-normally distributed variables were described by using visual (histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test). Normally distributed quantitative variables were expressed as mean values ± standard deviation. Non-normally distributed variables were expressed as median values (range). Qualitative variables were expressed as proportions. To identify variables associated with patient outcome (development of diabetes mellitus after transplantation), univariate analysis was investigated using Chi-square test, Fisher's exact test, and Mann–Whitney *U*-test. For multivariate analysis, the possible factors identified with univariate analysis were further entered into a logistic regression analysis to determine independent predictors of patient outcome.

Results

Two hundred twenty-seven cases who underwent liver transplantation were included in the study. Demographic and clinical characteristics and laboratory analyses of the patients are shown in Table 1. The most common indication for liver transplantation was hepatitis B cirrhosis (40.5%). Cryptogenic cirrhosis and cirrhosis secondary to Wilson's disease are other common indications (13.7% and 10.1%, respectively) (Table 2). Liver transplantations with deceased donor were enrolled in 210 cases (92.5%) (Table 3). Right lobe recipients constitute 4.4% of the cases, left lobe recipients 0.9%, and whole lobe 92.5% of the cases.

All patients were treated with glucocorticosteroids and mycophenolate mofetil after transplantation. After intravenous methylprednisolone treatment, all patients were left on oral prednisolone. The other immunosuppressive agents used after liver transplantation were tacrolimus, everolimus, and cyclosporine (Table 3).

Biopsy-proven acute graft rejection was seen in 2 (0.4%) liver recipients. One of those had a history of diabetes mellitus in the pretransplantation period and 1 with acute graft rejection was diagnosed with PLTDM during follow-up. The most common complication seen after transplantation was bacterial infections (11.9%) (Table 3).

Of the 227 patients, 61 patients were diagnosed with diabetes mellitus in the pretransplantation period. Twelve percent of the patients (20 patients) were diagnosed with PLTDM and 146 patients were not diagnosed with diabetes mellitus. When we compare the demographic, clinic, and laboratory parameters of the patients with PLTDM and patients without diabetes mellitus, it was seen that PLTDM was associated with advanced age (95% CI: 1.002-1.142) (Table 4). Furthermore, male liver recipients were diagnosed with a higher rate of PLTDM than female recipients 15.5% and 5.4%, respectively; $P = .045$) (Table 4). While 21.1% of the patients with living donors were diagnosed with PLTDM, 11.2% of patients with deceased donors were diagnosed with PLTDM ($P = .26$). There was no association between the MELD score of the recipients and the development of PLTDM (Table 4).

MAIN POINTS

- Many factors are mentioned to be predisposing to post-liver transplantation diabetes mellitus (PLTDM).
- Post-liver transplantation diabetes mellitus has an influence on liver transplantation outcomes.
- As most studies have documented a significant increase in mortality in cases with PLTDM, screening all liver recipients for risk factors and identifying impaired glucose metabolism are important.

Table 1. Baseline Characteristics and Laboratory Analysis of the Transplant Recipients

Parameters	Results (n = 227)
Age (median, years)	54 (18-76)
Male (n, %)	153 (67.4)
Pretransplant body mass index (mean, kg/m^2)	26.53 ± 4.34
Smoking status (n, %)	
Never smoke	145 (63.9)
Current smoker	67 (29.5)
History of alcohol use (n, %)	30 (13.2)
Family history of diabetes (n, %)	4 (1.8)
Preexisting diabetes mellitus (n, %)	61 (26.9)
Comorbidity (n, %)	
Hypertension	15 (6.6)
Coexistence of hypertension and hiperlipidemia	7 (3.1)
Atherosclerosis	6 (2.6)
Coexistence of atherosclerosis and hypertension	4 (1.8)
Chronic renal failure	3 (1.3)
Hyperlipidemia	2 (0.9)
COPD	2 (0.9)
Coexistence of hypertension and COPD	1 (0.4)
Coexistence of hyperlipidemia and coronary artery disease	1 (0.4)
Fasting plasma glucose (mg/dL)	118 (78-237)
Plasma HbA1c (%)	5.6 (4.7-8.6)
Plasma total cholesterol (mg/dL)	153.5 (42-239)
Plasma LDL (mg/dL)	83 (17-179)
Plasma triglyceride (mg/dL)	84 (25-335)
Plasma 25(OH) vitamin D (µg/L)	11 (8-33)
MELD score	24 (14-72)

COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin;
LDL, low-density lipoprotein; 25(OH) vitamin D, 25-hydroxy vitamin D; MELD, Model For End-Stage Liver Disease.

In addition, pretransplantation fasting plasma glucose levels were higher in patients with PLTDM than without PLTDM, which was statistically insignificant (P = .097). The age and gender of the donors were not associated with the development of PLTDM. Also, analysis of the data indicated no significant association between hepatitis B, hepatitis C, or other etiologies requiring liver transplantation and PLTDM. Also, there was no association between the family history of diabetes mellitus, types of immunosuppressive agents used after transplantation, and PLTDM.

While 22.2% of the patients with PLTDM had complications after transplantation, in 14.2% of the patients without PLTDM, complications were seen (P = .370). The complications seen in patients with PLTDM were renal failure (10%) and bacterial infections (10%). Cardiovascular events were not seen in patients with PLTDM.

Median HbA1c levels of the patients with PLTDM was 7.5% (4.6-10.4). Eighty-one percent of the patients (17 cases) with PLTDM were treated with insulin, and 14.3% of them were treated with oral antidiabetic agents. Also, 1 case was treated with the combination of oral antidiabetic agents and insulin.

Table 2. Etiologies of the Acute Liver Failure, Cirrhosis, and Metabolic Disorders That Were Indications for Liver Transplantation

Etiologies	n (%)
Hepatitis B cirrhosis	92 (40.5)
Cryptogenic cirrhosis	31 (13.7)
Cirrhosis in Wilson's disease	23 (10.1)
Hepatitis C cirrhosis	18 (7.9)
Alcohol-related cirrhosis	13 (5.7)
Budd–Chiari syndrome	11 (4.8)
Cirrhosis in autoimmune hepatitis	10 (4.4)
Cirrhosis in nonalcoholic fatty liver disease	7 (3.1)
Primary sclerosing cholangitis	6 (2.6)
Primary biliary cirrhosis	5 (2.2)
Cirrhosis in intoxications	4 (1.8)
Echinococcosis infection	3 (1.3)
Coexistence of hepatitis B and alcohol-related cirrhosis	1 (0.4)
Crigler–Najjar syndrome	1 (0.4)
Alström syndrome	1 (0.4)
Coexistence of hepatitis C and hepatitis B cirrhosis	1 (0.4)

Discusssion

Post-liver transplantation diabetes mellitus with a reported average yearly incidence of 3.3%-30.8% has an influence on liver transplantation outcomes.[20] In our study, 12% of the patients were diagnosed with PLTDM (20/166), which is consistent with the literature.

Older age and male gender are stated to be risk factors for PLTDM in the literature.[27,28] Consistent with the literature, it was seen that PLTDM was associated with advanced age (odds ratio: 1.066, 95% CI: 1.002-1.142, P = .004) and male liver recipients were diagnosed with a higher rate of PLTDM than female recipients in our study (P = .045).

Table 3. Donor- and Procedure-Dependent Factors and Liver Transplantation-Specific Characteristics and Complications Seen in Posttransplantation Period

Parameters	Results (n = 227)
Deceased donor (n, %)	210 (92.5)
Age of the recipient (years)	47 (1-89)
Time of cold ischemia (median, hours)	5 (1-12)
Usage of induction therapy (n, %)	7 (3.1)
Usage of immunosuppressive agents (n, %)	
Tacrolimus	178 (78.4)
Tacrolimus and everolimus	31 (13.7)
Cyclosporine	9 (4)
Everolimus	7 (3.1)
Postransplantation intensive care unit stay (days)	3 (1-6)
Acute graft rejection	2 (0.4)
Complications (n, %)	
Bacterial infections	27 (11.9)
Renal failure	6 (2.6)
Hematoma	3 (1.3)
Dysfunctions of anastomoses	1 (0.4)
Cardiovascular events	7 (3.1)

Table 4. Comparison of the Parameters of Patients with Post-liver Transplantation Diabetes Mellitus and Without Diabetes Mellitus

Parameters	Patients with Posttransplantation Diabetes Mellitus (n = 20)	Patients Without Posttransplantation Diabetes Mellitus (n=146)	*P*
Age of the recipient (years)	59.5 (32-72)	50 (18-76)	**.002**
Male gender (n)/female gender (n)	17/3	92/54	**.0045**
Pretransplantation body mass index (kg/m^2)	25.68 (22.7-38.6)	25.8 (12.8-35.5)	.543
MELD score	22 (16-59)	23 (14-39)	.694
Age of the donor (years)	46 (18-83)	45.5 (1-85)	.710
Time of cold ischemia (hours)	6 (1-10)	5 (1-12)	.838
Intensive care unit stay (days)	3.5 (3-5)	3 (1-22)	.105
Pretransplantation fasting plasma glucose (mg/dL)	106 (61-291)	95 (60-199)	.097
Pretransplantation 25 (OH) vitamin D	12.4 (7-18)	11.9 (8-33)	.461
Pretransplantation plasma calcium (mg/dL)	8.95 (8-10)	8.9 (7-10.4)	.749
Pretransplantation magnesium (mg/dL)	1.75 (1.4-2.3)	1.7 (1.2-2.6)	.783

MELD, Model For End-Stage Liver Disease; 25(OH) vitamin D, 25-hydroxy vitamin D.

Moreover, many studies have emphasized that hepatitis C virus is an important risk factor for PLTDM. A meta-analysis interpreted by White et al[29] showed that hepatitis C infection increased diabetes mellitus by 1.7-fold. However, it is important to recognize that hepatitis C virus infection is the most common cause of liver transplantation in the region where the meta-analysis was done. In our study, cirrhosis secondary to hepatitis B infection was the leading cause for liver transplantation (40.5%). Region differences and race are important variables for PLTDM.

Impaired fasting plasma glucose has been shown to a be a risk factor for PLTDM in some studies.[26] In our study, it was found that pretransplantation fasting plasma glucose levels were higher in patients with PLTDM than without PLTDM. We evaluated the patients with pretransplantation diabetes mellitus separately to avoid false results.

Donor characteristics are also important risk factors for PLTDM. In our study, it was stated that patients with living donor had a higher rate of PLTDM than others. Also, we could not find any association between the donor age, gender, and development of PLTDM.

Types and doses of immunosuppressive agents are important risk factors for PLTDM. Corticosteroids and calcineurin inhibitor drugs are associated with PLTDM by several mechanisms.[30] Treatment with tacrolimus is associated with a higher risk of PLTDM than cyclosporine.[30] In our study, tacrolimus was the most commonly used immunosuppressive agent (78.4%) after corticosteroids and mycophenolate mofetil. No association was found between the development of PLTDM and the use of immunosuppressive agents.

In a multicenter prospective study, Moon et al[31] showed an increased risk for graft failure in cases with PLTDM. Also, in 1 cohort study, PLTDM and acute rejection were found to have increased risks for graft failure.[20] In our study, while 22.2% of patients with PLTDM had complications after transplantation, in 14.2% of the patients without PLTDM, complications were seen. Biopsy-proven acute graft rejection was seen in 1 patient with a history of pretransplant diabetes mellitus, and 1 patient with PLTDM was diagnosed with acute graft rejection during the follow-up in this study. In our study, complications seen in patients with PLTDM were renal failure (10%) and bacterial infections (10%). Cardiovascular events were not seen in patients with PLTDM. Furthermore, infections, infection-related complications, renal insufficiency, and cardiovascular disease are more common among patients with PLTDM in the literature.[30]

This study had some limitations. Firstly, the study had retrospective design and also had a relatively short length of follow-up period to observe the complications. Also, we could not evaluate all complications associated with PLTDM because of the relatively short length of follow-up. Secondly, we did not include data about the severity and duration of diabetes mellitus in our analysis. Future studies should focus on the control of pre- and post-liver transplantation glucose control so that the complications can be reduced in the posttransplantation period.

Conclusion

Post-liver transplantation diabetes mellitus can impair survival of the graft. It can cause increased risk for morbidity and mortality. Prevention strategies should be planned. Realizing the patients with high risk factors and screening the liver recipients regularly are important measures. Since patients with advanced age, male gender, and higher fasting plasma glucose levels in the pretransplantation period have higher risk for the development of PLTDM, these cases should be screened more carefully.

Ethics Committee Approval: The study was approved by the medical ethics committee of Uludağ University Faculty of Medicine (No: 2021-1/12).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G.; Design – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G., S.C., C.Ö.E., E.A., C.A., O.Ü., M.K.; Supervision – Y.A.Ü., Ö.Ö.Ö., E.E.; Resources – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G.; Materials – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G., S.C., C.Ö.E., E.A., C.A., O.Ü., M.K.; Data collection and/or Processing – Y.A.Ü., M.R.G., Ö.Ö.Ö.; Analysis and/or Interpretation – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G., S.C., C.Ö.E., E.A., C.A., O.Ü., M.K.; Literature Search – Y.A.Ü., Ö.Ö.Ö., E.E., M.R.G.; Writing Manuscript –Y.A.Ü., Ö.Ö.Ö., E.E.; Critical Review – Y.A.Ü., Ö.Ö.Ö.

Declaration of Interests: The authors declare that they have no competing interest.

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