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Original Article

New onset of diabetes after transplantation is associated with improved patient survival after liver transplantation due to confounding factor

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ABSTRACT

Background: The influence of NODAT on survival of liver transplant recipients has not been clarified. Therefore, we evaluated the effect of NODAT on survival in LT recipients.
Methods: Data from 352 LT patients were totally analyzed. 97 patients with pretransplant diabetes mellitus were excluded, and 255 patients without diabetes mellitus at time of transplantation were included.
Results: NODAT was diagnosed in 41 patients (16.1%). There was no difference in frequency of NODAT according to the etiology of liver cirrhosis. NODAT was associated with a higher body weight ($p = 0.004$) and BMI ($p = 0.002$) 5 years after LT, but not with weight gain ($p = 0.201$) or increase in BMI ($p = 0.335$) 5 years after LT. HbA1c 5 years after LT was significantly higher in patients with NODAT ($p = 0.001$), but mean HbA1c still remained lower than 6.5% (6.4(±1.2) %). Patients with NODAT showed better survival rates (log rank: $p = 0.002$) compared to LT recipients without diabetes. According to all existing knowledge of diabetes mellitus (DM) better survival cannot be a direct effect of this disease. Our results are rather influenced by an not known confounding factor (possibly recovery from cachexia) associated with better survival and NODAT, while complications of NODAT will not appear during the relatively short postoperative time and observation period (mean follow up 6.08 (±2.67) years).
Conclusion: NODAT is frequently diagnosed in LT recipients and is associated with an improved 5 year survival after LT due to a not exactly known confounding factor.

1. Introduction

Over the last decades liver transplantation (LT) developed and became the final therapeutic option for patients suffering from end stage liver disease (ESLD). Perioperative complications and problems of rejection decreased, therefore comorbidities become increasingly important for long-term survival after LT. Increased mortality has been described for many diseases associated with liver cirrhosis.

Diabetes mellitus (DM) is a frequent disease in Western countries responsible for significant morbidity and mortality in general population [1].

New onset of diabetes after transplantation (NODAT) is defined as new onset of DM (according to diagnostic criteria in general population) that develops after solid organ transplantation and persists for more than 30 days [2]. Most studies published are difficult to compare because of different definitions used for NODAT, different effectivity of glycemic control and different immunosuppressive treatment regimens. Furthermore, many data concerning NODAT after organ transplantation were obtained from kidney transplant recipients.

Aims of this study were to define the prevalence of NODAT in our liver transplant cohort, to look for correlations with patient characteristics and to investigate the impact of NODAT on survival after LT.

2. Patients and methods

A total of 616 liver transplantations (performed at the Clinic for General, Visceral and Transplantation Surgery of the University of Mainz until June 1st, 2011) were evaluated. Patients were identified from an administrative transplant database and all data were retrieved from patients' charts and reports. Patients with less than 6 months of follow-up were excluded from the study. In case of missing clinical

Abbreviations: BMI, body mass index; BPAR, biopsy proved acute rejection; CNI, calcineurin inhibitor; DM, diabetes mellitus; ESLD, end stage liver disease; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model of end stage liver disease; MMF, mycophenolate mofetil; NODAT, new onset of diabetes after transplantation; RAI, rejection activity index.

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data patients were also excluded. In patients who underwent retransplantation only the first transplantation was included in the study. 97 patients with pretransplant DM out of 352 (27.6%) were excluded from the study. Finally, 255 patients met the inclusion criteria.

In addition to usual patient demographics, we reviewed the etiology of liver failure, ascites, hepatocellular carcinoma (HCC) status, and prevalence of hypertension. Pretransplant data about patients' body mass index (BMI), blood pressure, cholesterol and triglycerides were collected as a part of baseline information. In case of persisting nicotine abuse after LT patients were stated as smokers. Former nicotine abuse was not taken into account.

Patients treated with oral hypoglycemic agents and/or insulin before transplantation were diagnosed as pretransplant diabetes mellitus. Patients obtained immunosuppression according to individual risk factors and comorbidities [3]. A common immunosuppressive regimen was the combination of mycophenolate mofetil (MMF) with a calcineurin inhibitor (Tacrolimus or Cyclosporine). Target through levels were 5–7 ng/ml for tacrolimus during the first year and 3–5 ng/ml after one year. For cyclosporine target through levels were 70–90 ng/ml during the first year and 40–60 ng/ml thereafter. All patients received steroids until 3 months post LT. Methylprednisolone was reduced from 1.5 mg/kg on day one and two post LT to 1.0 mg/kg on day three and four, 0.5 mg/kg on day five to 14 and 0.2 mg/kg on day 15 till three months. Acute rejection episodes were treated with steroids (methylprednisolone 500 mg/d i.v. for 3 days) whenever a biopsy proved acute rejection (BPAR) was diagnosed with a rejection activity index (RAI) > 4.

NODAT was diagnosed (in case of missing pretransplant diabetes) according to international consensus guidelines: casual plasma glucose ≥200 mg/dl plus symptoms of diabetes, in case of fasting plasma glucose ≥126 mg/dl or in case of 2 hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test [4]. Therapy of diabetes was initiated according to international guidelines [5].

All the patients were followed up at least every three to six months at the outpatient clinic. Follow-up and the primary endpoint mortality (from all causes) were documented. The observation period ends on 31st December 2011.

Categorical variables were expressed as means (± standard deviations (SD)). Observations between groups were compared using the chi-square test for categorical variables and the unpaired t-test for continuous variables. P-values less than 0.05 were considered significant. Univariate logistic regressions were fitted to our data to detect any effect of each of patients' important demographic and medical information.

Cumulative survival curves were generated using the Kaplan–Meier method, and survival between groups was compared by log-rank test. In this analysis, death was considered a censoring event. In order to reduce bias patients who died in first six months after LT were excluded from survival curves and log-rank test.

All statistical analysis was performed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, IL, USA). This study followed the ethical guidelines of the Declaration of Helsinki 1975.

3. Results

Two hundred fifty-five patients who underwent liver transplantation for different reasons were included in this study. Baseline patient characteristics are listed in Table 1. Most patients were middle-aged men. The cause of ESLD was predominantly alcohol related (33.3%) and viral (hepatitis C 26.7%; hepatitis B 16.5%). In all patients there was a high prevalence (33.7%) of hepatocellular carcinoma (HCC). Most patients received an immunosuppressive therapy with tacrolimus (74.9%) and mycophenolate mofetil (MMF; 72.5%). BPAR was diagnosed (and treated with methylprednisolone) in 28.2% (72/255) of all LT recipients. In the first year after LT a loss of weight (−3.6 kg) was diagnosed, while after five years patients showed higher weight (+1.1 kg) than at the time of LT.

Table 1
Patient characteristics.

Table 1: Demographic information on cohort (n = 255)	
Follow-up (years), mean (±SD)	4.21 (±3.1)
Age (years),mean (±SD)	53.67(±10.4)
Gender, % (n)	
- Male	64.3 (164)
- Female	35.7 (91)
Ethnicity, % (n)	
- Caucasian	98.4 (251)
- Others	1.6 (4)
Etiology of liver disease, % (n)	
- ETOH	33.3 (85)
- Hepatitis B	16.5 (42)
- Hepatitis C	26.7 (68)
- Autoimmune, PBC, PSC	8.2 (21)
- Amyloidosis	5.5 (14)
- Cryptogenic	5.9 (15)
- Acute liver injury	4.3 (11)
-Other causes	5.1 (13)
Hepatocellular carcinoma, % (n)	33.7 (86)
Body height (cm), mean (±SD)	172.7 (±8.4)
Body weight (kg), mean (±SD)	77.0 (±17.3)
Body weight (kg) 1 year post LT, mean (±SD)	73.08 (±15.2)
Body weight (kg) 5 years post LT, mean (±SD)	78.7 (±15.9)
Weight gain 1st year [kg], mean (±SD)	- 3.6 (±10.9)
Weight gain 5 years [kg], mean (±SD)	1.1 (±10.8)
BMI (kg/m^2), mean (±SD)	25.7 (±5.0)
BMI (kg/m^2), 1 year post LT, mean (±SD)	24.4 (±4.2)
BMI (kg/m^2), 5 years post LT, mean (±SD)	26.2 (±4.5)
BMI difference 1st year [kg/m^2], mean (±SD)	- 1.3 (±1.3)
BMI difference 5 years [kg/m^2], mean (±SD)	0.32 (±3.7)
Baseline cholesterol (mg/dl), mean (±SD)	138.9 (±61.0)
Baseline triglycerides (mg/dl), mean (±SD)	100.0 (±64.3)
Glucose (mg/dl), mean (±SD)	107 (±39)
Hypertension, % (n)	55.7 (142)
Nicotin, % (n)	24.7 (63)
labMELD-Score (±SD)	20(±10)
Ascites, % (n)	60.4 (154)
Dialysis, % (n) (at time of LT)	13.7 (35)
LVH, % (n)	36.1 (92)
Diastolic dysfunction, % (n)	40.0 (102)
Tacrolimus, % (n)	74.9 (191)
Cyclosporine, % (n)	31.8 (81)
MMF, % (n)	72.5 (185)
HbA1c [LTX], mean (±SD)	4.8 (±0.9)
HbA1c [6 months], mean (±SD)	5.2 (±0.9)
HbA1c [12 months], mean (±SD)	5.2 (±0.8)
HbA1c [18 months], mean (±SD)	5.4 (±0.7)
HbA1c [24 months], mean (±SD)	5.4 (±0.8)
HbA1c [60 months], mean (±SD)	5.5 (±1.0)
Time to NODAT, months (±SD)	27.2 (±27.6)
BPAR, % (n)	28.2 (72)

Abbreviations: ETOH = ethyltoxic etiology of liver cirrhosis, BMI = body mass index, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis, LVH = left ventricular hypertrophy, MMF = mycopehnolate mofetile, HbA1c = glycated hemoglobin, NODAT = new-onset diabetes mellitus after transplantation, BPAR = biopsy proven acute rejection.

NODAT was present in 16.1% of all LT recipients as shown in Table 2. NODAT was diagnosed 27.2 months (±27.6) after LT. There were no significant differences in etiology of liver cirrhosis, age ($p = 0.631$), gender ($p = 0.722$), body weight at LT ($p = 0.303$), type of immunosuppression or casual plasma glucose (at time of LT; $p = 0.068$) between patients with and without NODAT. Patients with NODAT had higher weight ($p = 0.004$) and BMI ($p = 0.002$) five years after LT and more often ascites ($p = 0.048$). They showed higher HbA1c levels 6 months ($p = 0.003$), 12 months ($p = 0.019$), 18 months ($p < 0.001$), 24 months ($p < 0.001$) and 60 months ($p = 0.001$) after LT, but there was no difference in HbA1c at time of LT ($p = 0.637$) between patients who will develop NODAT and those who won't (as shown in Fig. 1). There was no difference in frequency of BPAR (and treatment with