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Original Research

Higher tacrolimus blood concentration is related to increased risk of post-transplantation diabetes mellitus after living donor liver transplantation

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ABSTRACT

Background/Aims: To investigate the association between tacrolimus (TAC) blood concentration and the risk of post-transplantation diabetes mellitus (PTDM) development after living donor liver transplantation (LDLT).
Methods: This study reviewed the clinical data of 158 adult LDLT recipients. A cut-off of mean trough concentration of TAC (cTAC) value at the sixth month postoperatively was identified using a receptor operating characteristic curve. Other clinical complications rates were compared between different cTAC groups.
Results: Thirty-four (21.5%) recipients developed PTDM during follow-up period. Recipients with PTDM suffered lower 1-, 5- and 10-year overall survival rates (85.2%, 64.9%, and 55.6% vs 92.4%, 81.4%, and 79.1%, $p < 0.05$) and allograft survival rates (87.9%, 76.9%, and 65.9% vs 94.1%, 88.5%, and 86.0%, $p < 0.05$) than those without PTDM. The best cut-off value of mean cTAC was 5.9 ng/mL. Recipients with higher cTAC (> 5.9 ng/mL) were more likely to develop hyperlipidemia (39.6% vs 21.9%, $p < 0.05$), cardio-cerebral events (7.5% vs1.0%, $p < 0.05$), and infections (37.7% vs19.0%, $p < 0.05$) than recipients exposed to low cTAC (≤5.9 ng/mL). However, the two groups showed no difference in the incidence of acute and chronic rejection.
Conclusion: Higher mean cTAC at the sixth month postoperatively is related to increased risk of PTDM in LDLT recipients.

1. Introduction

Liver transplantation (LT) is a curative treatment for end-stage liver disease, and living donor liver transplantation (LDLT) expands the donor pool and remedy the organ shortage [1]. However, improved long-term survival after transplantation is accompanied by increasingly prevalent post-operative chronic complications [2]. Post-transplantation diabetes mellitus (PTDM) is a serious metabolic complication due to its negative impact on allograft and recipient survival [3]. Recent studies have shown that the prevalence of PTDM after transplantation is approximately 16%–61% [4,5], depending on the medical centers. PTDM is associated with an increased cardiovascular adverse events, rejection episodes, susceptibility to infection, allograft loss and all-cause mortality [6,7]. Previous studies have determined that older recipient age, obesity, non-white ethnicity, family history, hepatitis C virus infection and calcineurin inhibitors (CNI) are risk factors for the incidence of PTDM in liver transplant recipients [8].

Cyclosporine and tacrolimus (TAC) are still mainstream immunosuppressant indicated for liver transplant recipients in the last decades [9]. Compared to cyclosporine, TAC could effectively reduce the episodes of acute rejection (AR) and increases allograft survival in liver transplantation recipients [10]. However, prolonged exposure to TAC leads to nephrotoxicity, neurotoxicity, and diabetogenicity [11]. Several reports suggested that recipients can benefit from early minimizing CNI strategy with low complications rates [12]. However, there are no studies investigating the association between cTAC level and PTDM risk in LDLT recipients. In this study, we aim to explore the impact of cTAC level on metabolic complications and identify the risk factors for PTDM after LDLT.

Abbreviations: LT, liver transplantation; LDLT, living donor liver transplantation; PTDM, post-transplantation diabetes mellitus; CNI, calcineurin inhibitors; TAC, tacrolimus; AR, acute rejection; cTAC, trough concentration of tacrolimus; MMF, mycophenolate mofetil; BMI, body mass index; FPG, fasting plasma glucose; RPG, rapid plasma glucose; OGTT, oral glucose tolerance test; HbA1c, glycohemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CKD, chronic kidney disease; CR, chronic rejection; IQR, inter quartile range; ROC, receiver operating characteristic

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2. Materials and methods

2.1. Study population

We retrospectively analyzed the data of all the consecutive adult patients receiving LDLT between April 2002 and January 2015 at the Liver Transplantation Center of West China Hospital. The recipients were followed until July 2015. We excluded the recipients who were younger than 18 years old at the time of transplantation, diagnosed as diabetes mellitus before liver transplantation, followed up less than 6 months, and administrated with cyclosporine after LDLT. Finally, we enrolled 158 LDLT recipients in this study. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the West China Hospital of Sichuan University and with the Helsinki declaration. Written informed consent was obtained from all the patients prior to their surgery, and was in accordance with the ethical guidelines of the Helsinki declaration.

2.2. Adjustment of immunosuppression regimens

All the recipients in our center were initially given the standard triple therapy of glucocorticoids, TAC and mycophenolate mofetil (MMF) following transplantation. The methylprednisolone was intravenously given at the first day after transplantation, then gradually reduced daily and discontinued after the first week. Then oral prednisone was also tailored and discontinued within the first 3 months after transplantation. The dosage of MMF was given 1.0 g/d or 1.5 g/d initially and was withdrew when severe side effects occurred. Rapamycin was given with a dose of 1 mg per day, as a substitute of MMF or auxiliary treatment for liver malignancy recipients.

The initial dosage of TAC was given 0.05–0.1 mg/kg per day and allograft function and cTAC were monitored daily during the first week, weekly during the first month, monthly during the first 3 months and every 3–6 months thereafter post-LDLT. The ideal range of cTAC was 5–10 ng/mL during the first 3 months post-LDLT. If rejection episodes diagnosed by allograft biopsy, the previous dosage of TAC was reinstated, together with the high-dose steroid pulse therapy. After 6 months post-LDLT, we reduced the TAC dosage very slowly and carefully with closely monitoring allograft function in stable recipients, to keep the cTAC as low as possible. Therefore, we collected the mean cTAC at the sixth month following transplantation to measure the exposure of TAC.

2.3. Definition of clinical parameters

PTDM was defined as newly diagnosed diabetes after transplantation according to the American Diabetes Association guidelines [13] as follows: Symptoms of diabetes with a rapid plasma glucose ≥ 11.1 mmol/L; a fasting plasma glucose ≥ 7.0 mmol/L; a two-hour plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test or a plasma HbA1c ≥ 6.5%. Obesity was defined as a body mass index (BMI) ≥ 25. Hypertension was defined as a systolic blood pressure > 140 mmHg or a diastolic pressure > 90 mmHg twice at different time [14]. Hyperlipidemia was defined as a total plasma cholesterol ≥6.22 mmol/L or a triglyceride ≥2.26 mmol/L [14]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 for at least 3 consecutive months [15]. AR was diagnosed by liver biopsy or while liver function recovered via a single high-dose methylprednisolone pulse therapy. If chronic rejection (CR) was suspected, liver biopsy was performed for a conformed diagnosis.

2.4. Statistical analysis

Quantitative variables were expressed as the mean ± standard deviation or median (inter quartile range, IQR). Comparable analysis using Chi-square test were performed for categorical variables. Quantitative descriptive variables were compared by independent sample Student's *t*-test. Survival curves were analyzed using the Kaplan-Meier method. The best cut-off of mean cTAC at the sixth month post-LT related to PTDM was determined using a receiver operating characteristic (ROC) curve. Independent risk factors for PTDM were identified by a stepwise forward multivariate Cox regression model. Statistical analysis was performed using SPSS version 21.0 statistical software (SPSS Company, Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

3. Results

3.1. Recipient and donor characteristics

A total of 245 adult recipients received LDLT between April 2002 and January 2015 at the Liver Transplantation Center of West China Hospital. Eventually, 158 recipients were enrolled in this study. The median follow-up period was 40 months (range, 6–125 months). Recipients were 42.1 ± 7.8 years (range, 19–65 years) old and were predominantly male (86.1%). Hepatitis B virus infection (78.5%) was the most common etiology of liver disease; only 1 recipient had hepatitis C virus infection (0.6%), 3 recipients (1.9%) had alcoholic cirrhosis and more than half of the recipients (55.7%) had liver malignancy. The pre-LDLT baseline comorbidities included obesity in 36 (22.8%) recipients, hypertension in 1 (0.6%) recipient, and hyperlipidemia in 7 (4.4%) recipients. The median MELD score of all recipients was 13 (IQR, 9–18). MMF was administered in 103 (65.2%) recipients, and 45 (28.5%) recipients were also prescribed with Rapamycin. Donors were 35.9 ± 9.7 years (range, 19–63 years) old and were more likely to be male (60.1%). The median graft to recipient weight ratio (GRWR) was 0.92% (IQR, 0.80%–1.04%).

3.2. Prevalence of PTDM and other complications

Eventually, 34 recipients (21.5%) developed PTDM over the course of the follow-up period. The cumulative incidence of PTDM increased over time, and the 0.5-, 1-, 3-, 5- and 10-year incidence rates were 13.9%, 16.8%, 23.2%, 25.8% and 25.8%, respectively (Fig. 1). We compared the demographical and clinical variables between recipients with and without PTDM, as shown in Table 1. Common TAC-related complications included obesity in 42 (26.6%) recipients, hypertension in 11 (7%) recipients, hyperlipidemia in 44 (27.8%) recipients, and CKD in 21 (13.3%) recipients. Moreover, 17 (10.8%) and 8 (5.1%) recipients occurred AR and CR, respectively. Predictably, the recipients with PTDM were more likely to experience cardio-cerebral vascular events (11.8% vs 0.8%, $p < 0.05$), CR (14.7% vs 2.4%, $p < 0.05$), and

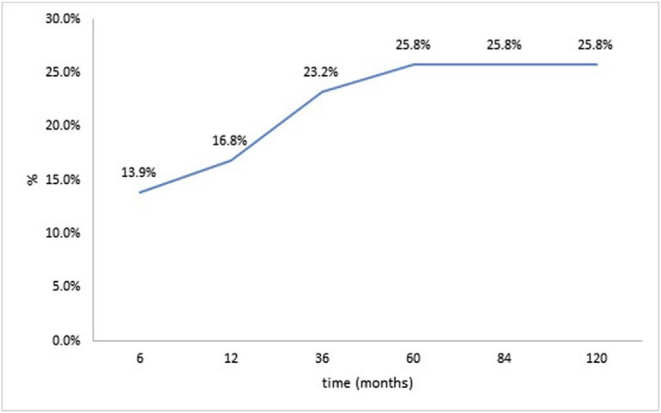

Fig. 1. Cumulative incidence of post-transplantation diabetes mellitus during 10 years after living donor liver transplantation.