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Original Article

The incidence and risk factors for new-onset diabetes after transplantation in kidney allograft recipients

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Abstract: Background: New-onset diabetes after transplantation (NODAT) of a kidney is a serious metabolic complication that can lead to graft dysfunction, cardiovascular disease, and death. The aims of this retrospective study were to determine the incidence of NODAT and the risk factors for its development in kidney allograft recipients at our institution. Methods: The records of patients free of previously known diabetes who received kidney transplants at the First Hospital of China Medical University from January 2005 to December 2012 were reviewed. NODAT was identified based on the criteria of the American Diabetes Association. Cox proportional hazards regression analysis was performed to identify the predictors of NODAT, using age, gender, and history of hypertension as covariates. Results: The patients were followed for a mean duration of 52.1±10.8 months. Among 197 patients, 20 (10.15%) developed NODAT. The cumulative incidence of NODAT was 7.6%, 8.6%, and 10.2% at 6 months, 1 year, and 3 years following transplantation, respectively. Patients developing NODAT after transplantation were significantly older (48.1±5.57 vs 43.36±11.37 years; P=0.004) and had a tendency to have a higher body mass index (22.26±2.89 vs 21.85±2.87 kg/m^2; P=0.544) than patients without NODAT. Multivariate analysis identified the following clinical factors as independent predictors of NODAT: higher pretransplantation levels of plasma glucose, alanine aminotransferase, and total cholesterol; a lower pretransplantation high-density lipoprotein cholesterol level; and a higher post-transplantation alkaline phosphatase level. Conclusions: Patients undergoing kidney transplantation should undergo risk assessment for development of NODAT.

Keywords: Kidney transplantation, diabetes mellitus, risk factors

Introduction

As the duration of survival of kidney recipients has increased greatly, long-term complications and the quality of life have received increasing attention. New-onset diabetes after transplantation (NODAT) is a serious metabolic complication of kidney transplantation that increases the risk of post-transplantation mortality, graft dysfunction, cardiovascular disease, and allograft failure [1-3]. Although NODAT was recognized more than 40 years ago, its true incidence has been difficult to establish because of the lack of standard criteria for the diagnosis of new-onset diabetes mellitus and the varied duration of post-transplantation follow-up. Estimates of NODAT cumulative incidence of one year vary widely, ranging from 2% to 50% [4]. In 2003, an International Expert Panel established the International Consensus Guidelines for the diagnosis and treatment of NODAT [5, 6]. Following the recommendations of the International Consensus Guidelines, clinicians have been using strict diagnostic criteria from the American Diabetes Association (ADA) in an attempt at an accurate estimate of the incidence of NODAT [7]. Single-center, observational, and case-control studies have identified several risk factors as independent predictors of the development of this disorder. These factors include older age, higher body mass index (BMI), ethnicity, positive hepatitis C virus (HCV) serology, donor source (live vs cadaver), and tacrolimus (Tac) treatment [8-12].

Most of the studies reporting risk factors used data from Caucasian recipients of kidneys. Compared with Caucasian recipients, Chinese recipients have a lower BMI, lower calcineurin inhibitor (CNI) level, and lower rate of HCV infection. This single-center retrospective study evaluated data from the organ transplant unit of the

First Hospital of China Medical University, with the aims of determining the incidence of NODAT in kidney allograft recipients and assessing potential risk factors for its development.

Materials and methods

Patient population

A total of 236 patients who received a deceased kidney transplant were consecutively enrolled in this study and followed by the organ transplant unit of the First Hospital of China Medical University between January 2005 and December 2012. Exclusion criteria included (1) diagnosis of diabetes mellitus prior to transplantation, (2) previous kidney transplantation. (3) kidney transplantation combined with other organ transplantation (s), and (4) graft failure within the first 14 days after surgery without subsequent restoration of graft function.

This study was approved by the ethics committee of our institution before it began, and the protocols conformed to the ethical guidelines the Declaration of Helsinki. Written informed consent was obtained from all the study patients.

Data collection

Hospitalization and outpatient data were collected retrospectively from transplantation charts and electronic medical records (EMRs), according to institutional ethical guidelines.

Pretransplantation information included the following: age, gender, BMI at the time of transplantation, smoking and alcohol history, hepatitis B antibody status at the time of transplantation, and presence or absence of hypertension (defined as any treatment for high blood pressure and/or a systolic value >140 mmHg or a diastolic value >90 mmHg within 2 years of transplantation). Data on the fasting plasma glucose (FPG) level 1 day prior to transplantation were also collected. The results of liver function testing at the time of transplantation were collected, which included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin, and direct bilirubin. Lipid metabolism was evaluated, which included total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein-cholesterol.

Information collected from the perioperative period included data on intraoperative induction immunosuppressive therapy and initial immunosuppressive regimen, acute rejection (AR), and recovery of renal function. Post-transplantation follow-up data included type and dosage of maintenance immunosuppressive therapy, CNI trough levels, rejection episodes, cytomegalovirus infection status, and lipid and liver function 1 month after transplantation. All FPG values, which consisted of tests performed on patient specimens taken at least weekly for 0 to 1 months post-transplantation, every 2 weeks for the subsequent 2 to 3 months, every month for 3 to 6 months, and every 3 months thereafter, were collected for evaluation.

Diagnosis of post-transplantation diabetes mellitus

NODAT was diagnosed retrospectively from the medical chart. The diagnosis was based on the 2014 ADA diagnostic criteria for diabetes, as follows: symptoms typical of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥11.1 mmol/L; or an FPG level ≥7.0 mmol/L; or a 2-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test after a glucose load of a solution of 75 g anhydrous glucose in water; or HbA1c ≥6.5% [13].

Immunosuppressive regimens

Initial immunosuppressive treatment consisted of a triple drug regimen that included a corticosteroid, CNI (cyclosporine [CsA] or Tac), and an antiproliferative agent (azathioprine or mycophenolate mofetil). Intravenous methylprednisolone (1000 mg) was administered on the day of surgery and on the first postoperative day, and 500 mg was administered on the second and third postoperative day. Then oral prednisone was administered in gradually decreasing doses to 15 to 20 mg/day by the third month, and 10 mg/day by the sixth month. Prednisone was withdrawn or used at a dose of 5 mg/day starting at 6 months.

Concentration (s) of CNI trough levels were monitored during the follow-up. The target trough concentrations of Tac and CsA for the first 3 postoperative months were 10-15 ng/mL and 200-300 ng/mL, respectively; and 5-10 ng/mL and 100-150 ng/mL, respectively, thereafter.

Table 1. Characteristics of patients by the development of NODAT

	NODAT	No NODAT	*P*-value
Numbers	20	177	
General characteristics			
Age (years)	48.1±5.57	43.36±11.37	0.004
Gender (men, %)	40.00	58.19	0.120
BMI (kg/m^2)	22.26±2.89	21.85±2.87	0.544
History of smoking (%)	10.00	12.99	0.978
History of alcoholism (%)	5.00	6.21	NS
Family history of diabetes (%)	20	5.65	0.040
Pretransplant characteristics			
Positive hepatitis B status (%)	5.00	5.65	NS
Hypertension (%)	60.00	40.68	0.098
Plasma glucose (mmol/L)			
Day-1 (fasting)	5.57±1.04	5.04±0.66	0.035
Liver function			
ALT (U/L)	22.5 (13.5-41.25)	18 (13-25)	0.122
AST (U/L)	24.3 (12.5-42.5)	21 (13.5-26.5)	0.123
ALP (IU/L)	78.75 (63.75-117.5)	72 (53-91.5)	0.107
GGT (IU/L)	24.00 (17.00-56.25)	19.00 (15.00-32.00)	0.121
T-BiL (μmol/L)	6.40 (5.03-9.63)	6.0 (4.05-7.78)	0.093
D-BiL (μmol/L)	1.95 (0.65-3.00)	1.80 (1.00-2.80)	0.919
Lipids metabolism			
Total cholesterol (mmol/L)	4.90 (4.28-5.65)	4.12 (3.38-5.21)	0.015
Triglycerides (mmol/L)	1.28 (0.86-1.92)	1.07 (0.76-1.63)	0.259
HDL-C (mmol/L)	1.36 (1.02-1.99)	1.38 (1.07-1.63)	0.921
LDL-C (mmol/L)	2.75 (2.06-3.68)	2.56 (2.07-3.25)	0.408
Posttransplant characteristics			
Cyclosporin (%)	90.00	89.27	NS
Tacrolimus (%)	15.00	10.73	0.842
Azathioprine (%)	20.00	25.99	0.560
Mycophenolate (%)	80.00	74.01	0.560
Acute rejection (%)	15.00	19.77	0.831
Positive CMV infection (%)	5.00	2.82	0.479
Liver function at 30 days posttransplant			
ALT (U/L)	19.5 (14.00-35.75)	21 (15-28)	0.864
AST (U/L)	25.5 (17.00-37.75)	23.44 (15.55-37.75)	0.841
ALP (U/L)	83.50 (49.75-93.50)	59 (44.00-86.50)	0.081
GGT (U/L)	43 (37.5-45.8)	41 (36.3-44.15)	0.255
T-BiL (μmol/L)	33.00 (23.00-42.00)	32.00 (32.00-51.00)	0.907
D-BiL (μmol/L)	11.95 (9.13-16.68)	11.10 (7.80-14.15)	0.243

ALP, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CMV, cytomegalovirus; D-BiL, direct bilirubin; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NODAT, new-onset diabetes after transplantation; T-BiL, total bilirubin.

AR episodes that were confirmed by biopsy of the allograft were initially treated by intravenous pulse methylprednisolone (500 mg/day for 3 consecutive days). Antithymocyte globulin was subsequently administered to cases resistant to pulse methylprednisolone.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile range, and discrete variables are expressed as a number and percentage. Comparisons

between 2 groups were performed using the unpaired Student *t* test for continuous normally distributed variables and the Mann-Whitney U-test for continuous non-normally distributed variables. The chi-square test or Fisher exact test was used for categorical data. The Kaplan-Meier method was used to estimate the cumulative incidences of NODAT, and the log-rank test was used to compare the incidences of NODAT between groups of patients. Univariate Cox proportional hazards regression analysis was used to evaluate candidate risk factors for developing NODAT. Multivariate Cox proportional hazards regression analysis was used to identify the independent risk factors of NODAT, with age, gender, and history of hypertension used as adjusted factors. All the tests were two tailed, and *P*-values <0.05 were considered statistically significant. All calculations were performed using SPSS software, version 20.0 (IBM Corporation, New York, NY).

Results

Characteristics of patients and incidence of NODAT

Of the 236 initially enrolled patients, 197 patients were eligible for the study. The excluded patients consisted of 26 with pre-existing diabetes mellitus (associated with kidney disease or comorbidity), 11 receiving a combined or simultaneous transplant (liver-kidney [n=3], pancreas-kidney [n=5], islet-kidney [n=3]), and 2 receiving a second kidney transplant.

The mean age of the eligible study patients at transplantation was 43.93±11.01 years, and 56.35% of the patients were men. 97.5% of the patients recieved dialysis before transplant. The average period of dialysis was 22 month. The mean BMI at transplantation was 21.89± 2.87 kg/m^2; only 22.8% of the 197 patients had a BMI ≥24 kg/m^2. The obesity rate of obesity was very low; only 6 (3.05%) patients had a BMI ≥28 kg/m^2.

The mean duration of follow up was 52.1±10.8 months. Twenty of 197 (10.15%) recipients were diagnosed with NODAT; the cumulative incidences of NODAT at 6 months, 1 year, and 3 years post-transplantation were 7.6%, 8.6%, and 10.2%, respectively.

Table 1 shows the characteristics of the patients who developed NODAT compared with those who did not. Patients who developed NODAT were significantly older, and had higher pretransplantation levels of total cholesterol and FPG. Tac was administered as the CNI to 11.6% of patients and CsA to 89.3% (N=197). NODAT developed in 13.6% of patients treated with Tac and 10.2% of those treated with CsA (*P*=0.232). During the follow-up period, CsA was changed to Tac for 3 patients who had adverse reactions to CsA, although they subsequently developed NODAT. Two of the patients were changed back to CsA from Tac after the diagnosis of post-transplantation diabetes mellitus, but their NODAT did not resolve. None of the patients had to discontinue the CNI. NODAT developed in 9.9% of patients with BMI <24 kg/m^2 and 11.1% of overweight patients (*P*=0.499). Two patients were immunopositive for HCV, and neither developed NODAT.

Risk factors for NODAT

Univariate analysis identified the following pretransplantation risk factors to be associated with the development of NODAT: family history of diabetes, elevated 1-day preoperative FPG level, elevated levels of ALT and total cholesterol, and decreased level of HDL-C. An elevated ALP level 30 days after transplantation was the only post-transplantation risk factor. Factors with a *P*-value <0.1 in the univariate analysis were tested by the multivariate model. Multivariate analysis found that all the risk factors identified by univariate analysis were independent predictors of NODAT (**Table 2**).

Patient and graft survival

Overall patient survival at 1 month, 3 months, and 5 years post-transplantation was 98%, 97.5%, and 97%, respectively. The difference in patient survival between the patients with and without NODAT was not significant (*P*=0.369). Graft survival at 1 month, 3 months, and 5 years post-transplantation was 97%, 96.4%, and 95.9%, respectively. There was no significant difference in graft survival between patients with and without NODAT (*P*=0.369).

Discussion

Recipients of renal transplants frequently develop new-onset diabetes mellitus. A meta-analysis study report found that 1-year post-transplantation cumulative incidences of NODAT

Table 2. Predictors of NODAT Defined by Univariate/multivariate Analysis

Variable	*Univariate*			*Multivariate*		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age (years)	1.038	0.995-1.083	0.087	1.043	0.988-1.100	0.128
BMI at transplantation (≥25 vs <25)	1.160	0.422-3.193	0.773	-	-	-
Family history of diabetes	4.425	1.607-12.180	0.004	5.673	1.917-16.789	0.002
Hypertension	2.090	0.854-5.113	0.106	-	-	-
HBV infection	0.905	0.121-6.759	0.922	-	-	-
FPG day-1 (pretransplant) (mmol/L)	2.184	1.382-3.452	0.001	1.800	1.190-2.722	0.005
Urine glucose	1.006	0.398-2.855	0.899	-	-	-
Liver function at pretransplant						
ALT (U/L)	1.025	1.012-1.039	<0.001	1.022	1.008-1.036	0.002
AST (U/L)	1.002	0.996-1.004	0.697	-	-	-
ALP (U/L)	1.001	0.997-1.005	0.729	-	-	-
GGT (U/L)	1.008	0.998-1.018	0.135	-	-	-
T-BiL (μmol/L)	1.059	0.959-1.169	0.256	-	-	-
D-BiL (μmol/L)	0.968	0.784-1.196	0.765	-	-	-
Lipids at pretransplant (mmol/L)	1.169	0.840-1.626	0.354	-	-	-
Total cholesterol at pretransplant (mmol/L)	1.317	1.046-1.659	0.019	1.460	1.073-1.986	0.016
HDL-C at pretransplant (mmol/L)	1.618	1.015-2.578	0.043	2.228	1.260-3.939	0.006
LDL-C at pretransplant (mmol/L)	1.284	0.845-1.952	0.242	-	-	-
Liver function at 30 days posttransplant						
ALT (U/L)	1.006	0.987-1.026	0.519	-	-	-
AST (U/L)	1.002	0.977-1.030	0.714	-	-	-
ALP (U/L)	1.004	0.001-1.007	0.004	1.004	1.000-1.007	0.036
T-BiL (μmol/L)	1.035	0.956-1.120	0.393	-	-	-
D-BiL (μmol/L)	0.969	0.861-1.091	0.969	-	-	-
GGT (U/L)	1.002	0.995-1.008	0.573	-	-	-
Sirolimus (yes vs no)	1.067	0.247-4.597	0.931	-	-	-
Tacrolimus (yes vs no)	1.458	0.427-4.975	0.547	-	-	-
Acute rejection (yes vs no)	0.730	0.214-2.492	0.616	-	-	-
CMV infection (yes vs no)	1.613	0.216-12.053	0.641	-	-	-

ALP, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CMV, cytomegalorvirus; D-BiL, direct bilirubin; FPG = fasting plasma glucose; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; T-BiL, total bilirubin.

ranged from 2% to 50% [4]. The wide range in estimates is largely attributed to the varied diagnostic criteria for diabetes mellitus, the varied duration of post-transplantation follow-up, the different types and dosages of immunosuppressive therapy, and the types of pretransplantation risk factors. This study found that NODAT developed in 20 of 197 (10.15%) allograft recipients, with cumulative incidences of NODAT after 6 months, 1 year, and 3 years post-transplantation of 7.6%, 8.6%, and 10.2%, respectively. Potential risk factors were also analyzed in this study, because identification of the risk factors for NODAT can aid in determining a patient's degree of risk of developing NODAT after receiving a kidney transplant.

The 1-year cumulative incidence of NODAT in this study (8.6%) was slightly lower than the incidence reported from studies of Caucasian renal recipients. The initial immunosuppressive therapy used at our center is a triple drug regimen that consists of a corticosteroid, a CNI, and an antiproliferative agent (azathioprine or mycophenolate mofetil). The target concentrations were lower than those used for Caucasian

renal recipients. The lower rates of older recipients and obese recipients in our study might be attributed to the low incidence of NODAT. The mean BMI in our study was 22.26 kg/m^2, and only 3.05% of patients had a BMI ≥30 kg/m^2. The age of our study patients was 43.91±11.01 years; only 2 patients were older than 65 years at the time of renal transplantation.

The risk factors for NODAT after transplantation vary between studies; the commonly reported predisposing factors include obesity, older age, family history of diabetes, impaired glucose tolerance before transplantation or presence of other components of the metabolic syndrome, hepatitis C virus infection, and immunosuppressive therapy [14-17]. Elevated FPG, impaired liver function, and dyslipidemia before transplantation were identified in this study as independent risk factors for NODAT. An elevated ALP level was the only independent post-transplantation risk factor.

Our study found that elevated 1-day pretransplantation levels of FPG predicted the development of NODAT. Cosio et al. [2] analyzed a database of 490 adult kidney transplant recipients in the United States. They found that the statistically strongest predictor of NODAT at 1 year post-transplantation was the development of hyperglycemia during the first postoperative week. An elevated plasma glucose level on post-tranplantation day 1 is generally thought to be a result of the use of high-dose corticosteroids and surgical stress. However, an elevated pretransplantation FPG level 1 day before surgery may reflect a patient's actual glucose metabolism and be a very early indicator of glucose intoleranc.

Previous diabetes studies have found that participants with insulin resistance and metabolic syndrome have high circulating levels of GGT, ALT, and AST [18, 19]. These liver enzymes have been shown to be positively associated with the risk of type 2 diabetes. Our study found that an elevated ALP level was a significant postoperative risk factor for NODAT. Although the GGT level of our patients with NODAT was higher than the GGT level of patients without NODAT, the difference was not significant. An increased post-transplantation ALP level in the patients who developed NODAT might have been related to abnormal bone metabolism.

The results of many studies have suggested that dyslipidemia is associated with visceral obesity, metabolic syndrome, and diabetes [20, 21]. Previous studies have identified a high triglyceride level as a risk factor for the development of type 2 diabetes in individuals with normal or impaired fasting glucose [22]. The dysregulation of lipoprotein metabolism, characterized by such findings as low levels of HDL-C, is an early event in the development of type 2 diabetes mellitus, accompanying insulin resistance and preceding beta cell failure [23]. Our study found that a high level of total cholesterol and low level of HDL-C before transplantation were independent risk factors of NODAT. The patients with NODAT also had a higher pretransplantation level of triglycerides, but the difference was not significant.

Our findings were notable in that several risk factors that have been well established to be associated with NODAT were not identified by our study. Multivariate analysis did not find that BMI was a predictor of NODAT, in contrast to previous studies showing an association between obesity and NODAT [1, 24]. However, our result is probably accounted for by the low obesity rate in our cohort.

Old age has been consistently found to be an important factor contributing to the development of NODAT. Retrospective single-center studies have found that older kidney recipients more frequently develop NODAT than younger recipients [1]. Cosio et al. [2] reported that transplant recipients aged older than 45 years at the time of surgery were 2.2-fold more likely to develop NODAT than younger recipients. Although our study patients who developed NODAT were significantly older than those who did not develop NODAT (48.1±5.57 vs 43.36± 11.37 years; P=0.004), age was not found to be a risk factor. This result might be due to the relatively low incidence of NODAT and the small number of patients in our study.

HCV infection is strongly associated with insulin resistance and an increased risk of new onset diabetes mellitus in solid-organ transplant recipients. Accumulating evidence indicates that patients immunopositive for HCV have an increased incidence of type 2 diabetes mellitus [24]. The current theory regarding the pathogenesis of glucose intolerance in patients infected with HCV is that the iron overload,

hepatic steatosis, and elevated levels of proinflammatory cytokines that are associated with the infection impair the ability of the body to decrease the production rate of hepatic glucose and stimulate the uptake of glucose in the peripheral tissues. The eventual result is abnormal glucose metabolism. Only 2 of our study patients were infected with HCV, and neither developed diabetes. Further studies of the impact of HCV infection on the development of NODAT are needed.

Immunosuppression is strongly associated with the development of NODAT [25]. Glucocorticoids, CsA, and Tac have been shown to impair the secretion and action of insulin through dose-dependent, complex mechanisms [25, 26]. Immunosuppression was not found to be a risk factor in our study. The concentrations of CsA and Tac in were slightly higher in the patients with NODAT, but the difference was not significant. The reasons accounting for our results include the early withdrawal of glucocorticoids and the relatively low CNI concentrations.

Studies on the effect of NODAT on graft survival have yielded conflicting results. Kasiske et al. [1] found that patients with NODAT had a 63% increased risk of graft failure ($P<0.001$) and 46% increased risk of death-censored graft failure ($P<0.001$). Other studies did not find increased risk of graft failure in patients with NODAT, [25, 27] and our study did not find that NODAT significantly reduced patient and graft survival after transplant surgery.

There are some limitations to this study. First, it was a retrospective study with a small sample size and relatively short follow up. Second, pretransplantation OGTT was not systematically performed to determine the existence of preoperative glucose intolerance in the patients of our study cohort. Third, post-transplantation OGTT was also not formally administered to the patients of our study cohort to assess glucose tolerance, which might have led to the underestimation of the incidence of NODAT. Nevertheless, our analysis was based on careful follow-up of a patient cohort at a single transplant center, and included the individual review of each patient's transplantation chart and EMR.

Conclusions

The following significant risk factors for developing NODAT were found in Asian patients undergoing kidney transplantation; an elevated fasting plasma glucose level 1 day before transplant surgery, elevated pretransplantation plasma ALT and total cholesterol levels, a low pretransplantation HDL-C level, and an elevated post-transplantation ALP level. These factors might be useful for identifying high-risk patients. In addition, appropriate immunosuppressive therapy and timely lifestyle modifications should be implemented to prevent the development of NODAT in high-risk patients.

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Disclosure of conflict of interest

None.

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