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Original Article

INCIDENCES OF-AND RISK FACTOR FOR NEW ONSET DIABETES AFTER TRANSPLANTATION IN LIVE DONOR KIDNEY TRANSPLANTATION: A PROSPECTIVE SINGLE CENTRE STUDY

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ABSTRACT

Objective: The objective of present study was to evaluate incidence and risk factors for the development of new-onset diabetes after transplantation (NODAT) after kidney transplantation at our center.

Methods: A total 79 nondiabetic patients who underwent living donor kidney transplantation from January 2014 to August 2014 were prospectively enrolled. All the patients were followed for one year. All the patients received the same protocol of immunosuppressive therapy. NODAT was defined as if a patient had HbA1c≥ 6.5%, fasting venous plasma glucose ≥126 mg/dl, or was receiving diet or medical therapy for diabetes.

Results: The incidence of NODAT was 29.9% after one year. Risk factors associated with the development of NODAT included older age (OR: 1.07; p<0.05), family history (OR: 3.58; P<0.05), hepatitis C virus (HCV) positivity (OR: 11.15; p<0.05), obesity (OR: 4.28; p<0.05), pre-transplant triglycerides (OR: 1.01; p<0.005) and cholesterol level (OR: 1.01; p<0.005).

Conclusion: The prevalence of potentially modifiable risk factors in our study cohort was overweight recipients and pretransplant HCV infection, serum triglycerides, and cholesterol levels.

Keywords: New-onset Diabetes after transplantation, Kidney transplantation, Tacrolimus, Hepatitis C virus.

INTRODUCTION

New-onset diabetes after transplantation (NODAT) is a common and clinically important complication of solid organ transplantation including kidney transplantation. NODAT is associated with reduced long-term patient and graft survival [1, 2]. NODAT can increase the risk of cardiovascular disease by two to three fold compared with nondiabetic patients [3]. The incidence of NODAT after solid organ transplantation varies from 2% to 53% in the first transplant year [4]. The development of NODAT is a well-known complication of renal transplant patients with very much higher incidences of 15 to 25% in the first year after transplantation, compared with subsequent annual incidence(4-6%) [5]. Despite the apparently high incidence of NODAT after transplantation, transplant patients are not always routinely screened for hyperglycemia posttransplant and the condition is often underestimated [6]. There are various risk factors for NODAT, which include older age, recipient male gender, ethnicity, higher BMI, immunosuppressive use, family history of type 2 diabetes (T2DM), hepatitis C seropositivity, cytomegalovirus (CMV) infection, acute rejection (AR) history, male donor, and elevations in pretransplant fasting glucose and triglycerides [2, 7, 8].

The aim of the present study was to determine the incidence of NODAT and to assess modifiable risk factors for the development of NODAT at 12 mo in Indian population potentially.

MATERIALS AND METHODS

This single-center prospective observational study was carried out at the MuljibhaiPatel Urological Hospital, Nadiad, Gujarat, India. All the recipients, who underwent living donor renal transplantation from January 2014 to July 2014, were included for the analysis. A total of 104 patients was transplanted during this period. Seventy-seven patients were eligible for the study. Reasons for exclusion were pre-transplant diabetes Mellitus (n=25), death within the first month of transplantation (n=1) and graft loss within 2 w of transplantation (n=1). All the patients were followed up for at least one year. Ethical approval was obtained from the Institute Ethics Committee of Muljibhai Patel Society for Research in Nephro-Urology, and informed consent was obtained from all the patients.

NODAT definition[5]

NODAT was defined as if a patient had HbA1c ≥ 6.5%, fasting venous plasma glucose≥ 126 mg/dl, or was receiving diet or medical therapy for diabetes between 1 mo and one-year post transplant.

Immunosuppressant

A total of 63 (81.8%; table 1) patients had been offered either basiliximab or anti-thymocyte globulin (ATG) as induction therapy. Basiliximab was administered in a dose of 20 mg intravenously 2 h before transplantation and on day four after the operation. Treatment with ATG was initiated intraoperatively, before graft reperfusion. The dose of ATG varied from 1.5 mg/kg to 6 mg/kg and was administered either as a bolus or as divided doses. Throughout the study, all patients received a triple immunosuppressive regimen consisting of tacrolimus, steroids, and mycophenolate mofetil (MMF) as, maintenance therapy. Pulse methylprednisolone (1g) was given intravenously to all patients on day 0. Oral prednisolone was subsequently prescribed, starting at 1.0 mg/kg and tapered to 7.5–10 mg/d. MMF (2000 mg/d) was administered orally from the day-2. MMF was continued throughout the study if possible, but the dose was reduced or discontinued in the event of suspected toxicity, according to clinical judgment. Tacrolimus trough levels of 5–10 ng/ml were targeted for the initial two months and levels of 3–7 ng/ml was targeted thereafter in both groups. All the recipients received prophylaxis for CMV, i.e., Oral valganciclovir for 3-6 mo and for *Pneumocystis Pneumonia,* i.e., cotrimoxazole for 6–12 mo.

Clinical evaluation

The demographic and baseline data gathered included the age, weight, genders of the recipient and donor, HLA (Human leukocyte antigen) mismatch, baseline serum creatinine level, native kidney disease, the number of transplantation and type of living donor (related or Other than related). Tacrolimus trough level and serum creatinine level were

recorded on days 0 and 7 and months 1, 3, 6, 9 and 12. AR was diagnosed either clinically or through biopsies. AR episodes were treated either with intravenous courses of methylprednisolone (500–1000 mg) or with monoclonal antibodies, depending on the severity of rejection.

Table 1: Baseline demographic characteristic of study population (n=77)

Recipient	
Age	35.97±7.86
Gender	
Male	58 (75.3)
Female	19 (24.7)
Weight	54.9±10.9
Time on dialysis (in month)	4.4
Preemptive transplantation	18(23.4)
Second Transplantation	8 (10.1)
Donor	
Age	50±10.7
Gender	
Male	27 (35.1)
Female	50 (64.9)
Living other than related	20 (25.9)
Native kidney disease	
CGN	14 (18.2)
Polycystic kidney disease	4 (5.2)
Interstitial nephritis	6 (7.8)
Undetermined	53 (68.8)
HLA mismatch	
0	3
1-3	50
4-6	24
Induction therapy	
Basiliximab	28(44.4)
Antithymocyte globulin	35(55.6)
Mean baseline Serum creatinine (mg/dl)	4.11±1.7

Data are expressed as mean values, with Plus–minus values as standard deviation (SD), or as numbers, with percentages in parentheses

Statistical analysis

Statistical analysis was performed using MedCalc15.4. Categorical variables were summarized as total number and percentages, and continuous variables were summarized as means with standard deviations. Categorical data were compared using Fisher's exact test, and continuous variables were compared using the unpaired Student t-test. $P<0.05$ was considered statistically significant.

RESULTS

The baseline demographic characteristics of the recipients are presented in table 1. The mean age of patients at transplantation was 35.97 y, including 64.5% below 40 y and 35.5% above 40 y of age. There were 58 males and 19 females in the study cohort. Five patients were hepatitis C virus (HCV) positive before transplantation. The majority of donors were females (64.9%) and only 27 (35.1%) donors were males. The mean age of living donor was 50. A total of twenty patients (25.9%) underwent living other than related transplantation while the rest of all recipients received living-related transplantation. Haemodialysis was the pretransplant modality in all the patients, whereas eighteen patients (23.4%) received pre-emptive transplantation. During the study period, ten patients had acute rejection episodes, which were successfully treated with IV methylprednisolone and monoclonal antibodies.

At 12 mo, 23 (29.9%) patients developed NODAT. Among which 13 patients were given oral hypoglycemic agents, while insulin was prescribed to 10 patients for the treatment of post-transplant diabetes.

Table 2: Characteristic of patients with or without diabetes

	NODAT (n=23)	**No NODAT (n=54)**	**P value**
Non-Modifiable risk factors			
Age	37.91±7.69	34.24±7.23	0.0245*
Male	14 (60.7)	42(77.8)	0.1643
Positive family history of diabetes	8 (34.8)	6(11.1)	0.0225*
Modifiable risk factors			
BMI at transplant (>25 kg/m^2)	7 (30.4)	5 (9.3)	0.0352*
Pre-Tx HCV positivity	4 (17.4)	1 (1.2)	0.0259*
Mean Pre-Tx cholesterol levels (mg/dl)	204.3±54.55	171.06±45.07	0.0144*
Mean Pre-Tx triglyceride levels (mg/dl)	149.78±77.73	106.9±55.84	0.01485*
Positive CMV infections	3 (13)	4 (7.4)	0.4203
Acute rejection (yes)	5 (21.7)	5 (9.3)	0.1541
Mean Trough Tacrolimus level (ng/ml)	6.55±1.57	6.42±2.37	0.4041

P value finds by fisher exact test or by unpaired t test.; data are expressed as mean values, with Plus–minus values as standard deviation(SD), or as numbers, with percentages in parentheses; *statistically significant; Tx, Transplantation; HCV, hepatitis C virus; CMV, Cytomegalovirus; HCV, Hepatitis C Virus.

Table 2 shows a comparison of potential risk factors for NODAT in patients of both the groups. The occurrence of NODAT was significantly higher in patients with older age (37.91±7.69 y versus 34.24±7.23 y; p<0.05). The Odd ratio (OR) for the development of NODAT by univariate logistic regression analysis was 1.07 (95% CI, 0.9989-1.1486; p<0.05; table 3). Positive family history was important risk factors for NODAT (OR: 3.58; 95% CI: 1.1124-11.5277; p<0.05; table 3). Patients with NODAT displayed greater BMI (21 kg/m^2 versus 18 kg/m^2) and were more frequently overweight (p<0.05) as compared to patients without NODAT. Odd ratio for the development of NODAT was 4.28 (95% CI: 1.1934-15.408) among patients with>25 kg/m^2 BMI. Likewise, risk factors such as pre-transplant HCV infections (OR: 11.15; 95% CI: 1.0051-106.19; p<0.05), pre-transplant serum cholesterol levels (204.3±54.55 mg/dl versus 171.06±45.07 mg/dl; p<0.05) and triglyceride levels (149.78±77.73 mg/dl versus 106.9±55.84 mg/dl; p<0.05) were significantly higher in patients with NODAT.

Table 3: Univariate logistic regression analysis of risk factors for NODAT

	OR	95% CI	P value
Age	1.07	0.9989-1.1486	0.0460
Positive family history of diabetes	3.58	1.1124-11.5277	0.0326
BMI at transplant (>25 kg/m^2)	4.28	1.1934-15.408	0.0257
Pre-Tx HCV positivity	11.15	1.0051-106.19	0.0160
Mean Pre-Tx cholesterol levels (mg/dl)	1.01	1.0049-1.0288	<0.005
Mean Pre-Tx triglyceride levels (mg/dl)	1.0147	1.0051-1.0288	<0.005

CI, Confidence interval; OR, Odd ratio

Mean trough tacrolimus levels and prevalence of CMV infections were higher with NODAT cohort as compared to patients without NODAT, but the differences were not significant. The majority of patients (78.3%) had NODAT within three months after transplantation while very few patients (21.7%) were diagnosed with diabetes within six months of transplantation.

DISCUSSION

NODAT is a serious metabolic complication after solid organ transplantation with an incidence ranging from 2-53 % after one year of transplantation [9]. The incidence of NODAT in the present study was 29.9% after one year. There are mainly two types of risk factors responsible for NODAT: Modifiable and Non-Modifiable risk factors. Modifiable risk factors include overweight recipients, immunosuppressive therapy, HCV infection, CMV infection, pretransplant hypertriglyceridemia and hypercholesterolemia. Non-modifiable risk factors include Ethnicity, older age (>40 y), male recipient, positive family history of diabetes, deceased donor, the presence of polycystic kidney disease, and impaired fasting glucose levels.

Our study demonstrates that using American Diabetes Association (ADA) criteria for the diagnosis of diabetes, the incidence of NODAT is higher than a previously reported study using arbitrary criteria. The present study confirmed previously reported several risk factors but was unable to confirm others. Of all risk factors, only overweight, HCV infection and triglyceride levels are potentially modifiable

The incidence of diabetes after transplantation is greater in older age patients [10]. According to Cosio *et al.*, older recipients with more than 45 y are 2.9 times more likely to develop diabetes [11]. In the present study, thirteen percent of patients over the age of 45 y developed diabetes. Likewise, obese (>30 kg/m^2) or overweight (25-30 kg/m^2) patients have a higher risk of developing NODAT [12, 13]. Thirty-nine percent of patients were weighing more than 60 kg at the time of transplantation while 26% of patients below 50 kg developed NODAT. Seventeen percent of patients in the group over the age of 45 y and weighing more than 65 kg developed NODAT.

Chakkera *et al.* found that pre-transplant elevated serum triglyceride levels as an important risk factor for post-transplant diabetes development (P<0.05, OR: 1.61) [5]. Similarly, the mean triglyceride level was significantly higher in patients with NODAT compared to patients without NODAT (OR: 1.012; CI: 1.0051-1.0288: p<0.005; table 3) in the present study. Additionally, mean serum cholesterol level was also significantly higher in patients with NODAT (OR: 1.02; CI: 1.0049-1.0288: p<0.05; table 3).

Immunosuppressive therapy is responsible for 74% risk of developing NODAT [9]. Steroids are clearly associated with NODAT and are related to cumulative dosages and therapy duration [14]. In accordance, the beneficial effect of steroid-sparing regimen on the incidence of NODAT has been studied in the various studies [15]. As per our hospital protocol, steroid-free immunosuppressive therapy does not practice and effect of cumulative doses of steroids at the time of occurrence of NODAT was not analyzed in the present study. Hence effects of this important factor, on the risk of development of NODAT, could not be studied. The present study could not find a significant difference of trough tacrolimus level between two groups (6.55±1.57 ng/ml versus 6.42±2.37 ng/ml; P>0.05). Therefore, tacrolimus level was not associated with increased risk of development of NODAT in our study cohort. It is consistent with previous studies by Prakash *et al.* [16] and Bora *et al.*[17] In contrast to this, Shah *et al.* found a significant correlation between tacrolimus levels and incidence of NODAT [13].

HCV infection is significant comorbidity in kidney transplant recipients, occurring in 10% to 40% of patients, and it is associated with an increased risk of both graft failure and mortality [18]. There is a strong association between HCV infection and NODAT, particularly in patients receiving tacrolimus-based maintenance immunosuppressant [18]. Likewise, pretransplant HCV positive patients had a higher incidence of NODAT compared to patients without NODAT (OR: 11.15; 95% CI: 1.0051-106.19; p<0.05) in the present study. HCV infection is a potentially modifiable risk factor for NODAT after kidney transplantation. Successful pretransplant treatment of HCV could reduce the incidence of NODAT.

In the present study, the incidence of AR episodes was higher in patients with NODAT (21.7% versus 9.3%; P>0.05). The possible reason might be the more usage of immunosuppressant including pulse therapy of methylprednisolone that results in increased incidences of NODAT. Moreover**,** the presence of NODAT itself can increase the risk of rejections [19]. The lack of significant association between some of the risk factors in the present study may be due to small sample size and follow-up for only 12 mo.

CONCLUSION

In conclusion, NODAT is still common in Indian kidney transplant recipients. The present study confirmed various demographic risk factors for NODAT such as positive family history and older recipients. The prevalence of potentially modifiable risk factors in our study cohort was overweight recipients and pretransplant HCV infection, serum triglycerides, and cholesterol levels.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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