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Original Article

NEW ONSET OF DIABETES MELLITUS IN INDIAN RENAL TRANSPLANT RECIPIENT-A RETROSPECTIVE STUDY

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ABSTRACT

Objective: To identify incidence and determinant of new-onset of diabetes after transplant (NODAT) in Indian renal transplant recipients.

Methods: In this study Indian renal transplant recipients who were not diabetic before transplant and underwent kidney transplantation between July 2004 and June 2011 were enrolled. Various data of all transplant patients including age, gender, body weight, pre transplant Hepatitis C virus (HCV), Hepatitis B virus (HBV) infection status, Human Leukocyte Antigens (HLA) mismatch, maintenance immunosuppressant drug, usage of antibodies, anti rejection treatment, patients and graft survival, post-transplant infection including HCV, HBV, Herpes and Cytomegalo virus (CMV) infection were noted down. In this study patients who had taken anti diabetic medicine beyond 1 month were considered as diabetic.

Results: Total 537 renal transplant recipients were enrolled in the study. Patients age (P<0.0001), body weight (P=0.042) and HLA mismatch (P=0.015) were significantly effected on prevalence of NODAT. Other parameters like sex (P=0.862), type of donor (P=0.191), pre transplant HBV (P=0.285) and pre transplant HCV (P=0.201) were not significantly affecting development of NODAT. NODAT prevalence was not significantly affected by different Calciurine Inhibitors (CNIs) (P=0.079), antibodies (P=0.671) and by anti rejection therapy (P=0.115). Post-transplant infection was significantly higher in NODAT patients (P=0.022) and mainly among them CMV infection was prevalent (P=0.002). Other infections were found similar in patients with or without NODAT. NODAT was not significantly affecting patients survival (P=0.828) and graft survival (P=0.101).

Conclusion: Age more than 45 years, body weight more than 70 kilogram, HLA mismatch, tacrolimus treatment are significantly affecting development of NODAT in Indian transplant recipients. NODAT is strongly associated with development of post-transplant infection and among them CMV infection was prevalent.

Keywords: New-onset of diabetes, Immunosuppressant drug, Kidney transplant, Infection, Calciurine inhibitor.

INTRODUCTION

In renal transplant patients, survival time has gradually increased because of the improved survival rate during the perioperative period and enhancements in treatment with anti rejection drugs [1-3]. So now a day's more attention received on long-term complications and the quality of life of transplant recipients.

New-onset diabetes after transplantation (NODAT) is frequent metabolic complication after renal transplantation and is the major factor leading to dysfunction of the renal graft and patient death and is a risk factor for cardiovascular diseases in these patients [4, 5]. NODAT severely affects the quality of life and long-term survival rate of renal transplant recipients [6-9]. So international consensus guidelines 2003 considered NODAT is one of the risk factor for renal transplant patients [10].

The reported incidence varies by the definition of diabetes and the type of immunosuppressive medications used. The cumulative incidence of NODAT by the end of the first year has generally been found to be 10–30 % in adults receiving cyclosporine (CyA) or tacrolimus plus corticosteroids [11, 12].

Historically, the reported incidence of NODAT in kidney transplant recipients varied widely based on different definitions of the disorder in older studies.

They were summarized and nineteen of these older reports in a Meta-analysis indicated that an incidence of NODAT ranging from 2 % to 50 % in the first post-transplant year [13]. Varying definitions probably also accounted for the fact that some [14, 15], but not all [13] reviews indicate that the incidence of NODAT has increased during the past three decades. So we performed this study to identify the incidence and determinant of new-onset of diabetes after transplant (NODAT) in Indian renal transplant recipients.

MATERIALS AND METHODS

Subjects

This retrospective study was conducted at Muljibhai Patel Urological Hospital, Nadiad, Gujarat. For conduction of this study; we had taken permission from the dean of Hospital. In this study, we analyzed the records of 632 patients who underwent renal transplant at study center from July 2004 to June 2011. All patients followed till their follow up interval completed on or before June 2012. The reports of patients who were belong to foreign nationality, patients whose data were not available and those patients who suffered from diabetes before transplant was excluded. The remaining 537 non-diabetic patients who underwent a renal transplant were included for analysis.

Collection of data

Basic preoperative data included general data (gender, age, body weight, Human Leukocyte Antigens (HLA) mismatch) preoperative examination, primary renal diseases and source of donor kidney were collected. Data on the condition during the perioperative period included intra operative the patient's immune induction; initial immunosuppressant regimen and acute rejection (AR) treatment were collected. Postoperative follow-up data included patient's survival, graft survival, infections like hepatitis B virus (HBV)/hepatitis C virus (HCV)/cytomegalovirus (CMV) markers, herpes infection, postoperative immunosuppressant maintenance regimen was reported.

All patients received a triple drug regimen comprising of calciurine inhibitor (CNI) (Tacrolimus/cyclosporine), antiproliferative (mycophenolate mofetil/azathioprine) and glucocorticoids as a postoperative immunosuppressant treatment. Dose of these drugs was used as per standard protocol and continued throughout follow up period.

All patients underwent periodic follow-up after surgery as required by the follow-up system at our medical center (frequent outpatient department visits and indoor stay when indicated).

Definition of NODAT

NODAT was defined as a requirement of drugs (oral agents with or without insulin) for at least one month to control blood sugar. Blood sugar was monitored at each visit to the hospital and at home by self monitoring by glucometer.

Statistical analysis

Data was analyzed using SPSS software. Chi square test and Z test were applied. P value below 0.05 was considered as significant.

RESULTS

General preoperative conditions of patients with and without NODAT

Characteristic of renal transplant donors and recipients are shown in table 1.

Table 1: Characteristic of renal transplant donors and recipients

Parameter	Mean±SD or total (percentage) responses
Recipient	
Age	34±11.2
Males	433 (80.6 %)
Female	104 (19.4 %)
Native Kidney Disease	
Undetermined	259 (48.2 %)
CGN	120 (22.3 %)
CTID	43 (8.0 %)
Hypertensive nephropathy	24 (4.5 %)
Nephrolithiasis	18 (3.4 %)
Reflux Nephropathy	24 (4.5 %)
Other	49 (9.1 %)
Viral infection	
Hepatitis B	25 (4.7 %)
Hepatitis C	29 (5.4 %)
Donor	
Donor Age	46.6±10.24
Donor male	193 (35.9 %)
Donor female	344 (64.1 %)
Type of Donor	
Cadaveric Donor	7 (1.3 %)
Living Donor	530 (98.7 %)
HLA mismatch	
0	37 (6.9 %)
1	48 (8.9 %)
2	111 (20.7 %)
3	144 (26.8 %)
4	86 (16.0 %)
5	62 (11.5 %)
6	49 (9.1 %)

Prevalence of NODAT

Out of 537 patients, 182 patients developed NODAT during follow up period. So prevalence rate for NODAT was 33.89 % in our study. The prevalence rate of NODAT is not significantly different between male and female transplant recipients (P=0.862) and incidence rate of NODAT was 33.72 % and 34.62 % respectively.

Effect of age and weight

Among this 537 non diabetic recipients, 99 recipients age was more than or equal to 45 years and incidence rate of NODAT was significantly higher in this age than recipients age below 45 years (P<0.0001). Same higher incidence rate was also observed in patients having weight above 70 kilogram as compare to patients with weight less than or equal to 70 kilogram (P=0.042).

NODAT and type of donor

The proportion of NODAT in recipients with cadaveric donor kidney was not significantly higher than patients with living donor kidney (P=0.191).

In our study, we found that Human Leukocyte Antigens (HLA) mismatch has significantly affected the development of NODAT between recipients who had HLA mismatch with donor (P=0.015).

Influence of immunosuppressant drug

As per institutional protocol all patients received intravenous methylprednisolone single dose before engraftment followed by oral prednisolone which was tapered gradually. Selected patients (31.8 %) also received Anti thymocyte globulin (ATG) (6.3 %), Basiliximab (12.3 %), or Daclizumab (13.2 %), as an induction agent. Prevalence rate of NODAT in antibody treated patients was 33.3 % while in patients without antibody treated patients it was 34.1 % and it was not statistically significant between these two groups (P=0.671).

If considering NODAT in two different CNIs (Tacrolimus and cyclosporine) treated patients as a maintenance regimen then we did not find either of Tacrolimus or cyclosporine (P=0.079) affect significantly on the prevalence of NODAT after renal transplant patients.

Among these transplant patients few patients were developing rejection during hospitalization or in follow up visits. These patients were treated with a higher dose of steroids or combination of steroids and ATG as an anti rejection therapy. But we were not finding any statistically significant difference between this two groups for the development of NODAT (P=0.115).

Influence of infection on NODAT

Non-significant difference was also observed in our study in recipients who were treated with Hepatitis C virus (HCV) or hepatitis B virus (HBV) infection before transplant than patients without pre transplant HCV or HBV infection history (P= 0.201 and P=0.285 respectively).

Influence of NODAT on infection

Comparing the infection ratio in NODAT patients with recipients without NODAT it shows that the prevalence rate of infection is higher in NODAT patients than patients without NODAT (P=0.022). Prevalence Cytomegalo virus (CMV) infection in NODAT patients was statistically significant than control group (P=0.002). Prevalence of HBV infection (P=0.404), HCV infection (P=0.901) and herpes infection (P=0.063) was not statistically significant in between NODAT group and control group.

DISCUSSION

The prevalence rate of diabetes in patients with kidney transplant is significantly elevated compared with the normal population [16]. A study conducted by Brzezinska B *et al.* on 209 in renal transplant recipients underwent oral glucose tolerance test shows that the prevalence rates of NODAT, impaired glucose tolerance, and impaired fasting glucose were 19 %, 14 %, and 17 %, respectively [17]. While other studies conducted by Chaoyang LV *et al.* on Chinese population shows that prevalence rate of NODAT was 20.32 % in kidney transplant recipients [18]. But in our study we found that 33.89 % renal transplant patients developed NODAT after transplant which is higher than literature. In our study prevalence rate of NODAT is higher it may be due to all recipients were administered steroids as a part of immuno supression protocol and Indian population are more prone to diabetes than other [19].

Older age is the strongest and most consistent risk factor for NODAT in kidney transplantation and is reported in the majority of studies [15, 20, 21]. Study conducted by Cosio *et al.* on 2078 allograft recipients showed that those who were older than 45 years were 2.9 times more likely to develop diabetes [14]. Data from the US Renal Data System (USRDS) showed that first kidney transplant recipients who were between 45 and 59 year had a relative risk (RR) for NODAT of 1.9 (95 % confidence interval (CI) 1.73 to 2.09; *P* <0.0001), whereas patients who were above 60 year had a risk of 2.6

(95 % CI 2.32 to 2.92; *P*<0.0001) [15]. In our study, it was reflected that patients with more than 45 years age having more chances to develop NODAT than patients with age less than 45 years (P<0.0001). One of the reasons for development of NODAT in older age recipients is they required the higher dose of immunosuppressant drug to suppress their immune system for survival of graft as compared to younger recipients.

Body weight is one of the factors for the development of NODAT after transplantation. One study conducted to identify the effect of weight in renal transplant patients shows that individuals whose age was>45 years and weight was>70 kg had an OR of 6.4 (95 % CI 1.2–33.4) for the development of NODAT [22]. In our study, we also found same higher rate of NODAT in patients having weight more than 70 kilogram.

Diabetes has been reported to be more common in patients with hepatitis C than in other types of liver disease in the general population [23, 24]. The mechanism of diabetes caused after virus infection is not clear, but it has been assumed that insulin resistance and defects in islet cell secretion are both involved. In patient having HCV-positive at the time of transplantation, one year incidence of NODAT was 25.6 % compared with HCV-negative patients (15.4 %; *P*<0.0001) [15]. A meta-analysis of clinical studies that involved 2502 kidney recipients concluded that the adjusted odds ratio for NODAT was 3.97 (95 % CI 1.83 to 8.61) [25]. In renal transplant recipients, NODAT associated with a positive hepatitis C virus (HCV) serology ranges from 1.3 to 1.4 [26]. But in our study we are not finding any significant difference between recipients who were treated for HCV infection before transplant than patients with no history of HCV infection. If considering pre transplant HBV positive effect on transplant recipients than our results shows that there is no any significant observation found between two groups.

Type of donor means living or cadaver also effect on incidence of NODAT after renal transplant. Two different studies conducted by Kuo HT *et al.* and Chaoyang LV *et al.* shows that recipients of cadaveric donor kidneys are at higher risk for NODAT [27, 18]. But in our results we have not found any significant difference between renal transplant recipients who receive kidney from cadaver donor and who receive from Living donor.

HLA mismatch is also one of the risk factors for the NODAT after kidney transplant. Study conducted by Kasiske BL *et al.* using united stated renal system of year 1996 to 2000 shows that recipients having 6 HLA mismatch donor had a relative risk (RR) for NODAT of 1.33 (95 % confidence interval [CI] 1.07 to 1.58; *P*<0.0001) as compare to recipients having 0 HLA mismatch donor [15]. In our study, we also found significant difference in HLA mismatch patients. Incidence rate of NODAT is in higher recipients having higher HLA mismatch because they require higher dose of immunosuppressant drug at the time of transplant and after transplant for the survival of graft and patients as compare to less HLA mismatch patients.

Effect of immunosuppressant drug on NODAT

Glucocorticoids

Glucocorticoids induce a state of insulin resistance, and also lead to increasing hepatic gluconeogenesis which leads to increase the chances of diabetes [28]. In our study, we found all patients were administered the higher dose of glucocorticoids on the day of transplant as an inducing agent and this may be one of the reasons for the higher prevalence rate of NODAT in our study. Because of this reason in many centers steroid avoidance protocol is implemented but same steroid avoidance protocol is not found in our study. Postoperative withdrawal of corticosteroid therapy is controversial in clinical studies of a renal transplant but it is commonly recognized that postoperative short-term pulsed therapy and low-dose maintenance therapy are not only safe but also reduce the risk of NODAT [29]. Study conducted by Ghisdal L *et al.* and Maes BD et at shows that pulse glucocorticoid therapy given in the context of acute rejection treatment remains an independent risk factor of NODAT [30, 31]. But in our study we are not able find whether the anti rejection treatment is an independent risk factor for NODAT or not.

Calcineurin inhibitor

CNIs are diabetogenic by inducing a defect in insulin secretion by interfering with the nuclear factor of activated T-cell signaling in β-cells of pancreas. This pathway triggers the expression of genes critical for β-cell function, including at least six genes mutated in hereditary forms of monogenic diabetes [32]. Registry analyses, meta-analyses, and the prospective study conducted by Vincenti *et al.* showed that the risk of NODAT was significantly higher in patients on tacrolimus versus cyclosporine [15, 26, 33-35]. Tacrolimus induces a reversible suppression of insulin secretion at the level of insulin messenger RNA transcription, mediated by the binding of the drug to FK506 binding protein-12 and a subsequent inhibition of calcineurin in the β-cell [36]. The high level of FK506 binding protein-12 present in pancreatic β-cells might explain why tacrolimus more profoundly inhibits insulin secretion than cyclosporine and this is the reason for the higher prevalence rate of NODAT in tacrolimus treated recipients. But in our study we have not found a significant difference for NODAT between patients treated with tacrolimus or cyclosporine and reason for that is not identified.

In our study, all patients were administered steroids and calciurine inhibitor so it is difficult to identify whether NODAT is due to steroid, calciurine inhibitor or both. It may be possible to reduce the overall risk of NODAT by avoiding or reducing the doses of immunosuppressive medications that are particularly likely to cause NODAT in patients with higher risk factors. But, the risk of acute rejection must also be included in the selection of immunosuppressive medications.

Graft survival and patient's survival

The development of NODAT has also been shown to be associated with an adverse impact on patient survival and an increased risk of graft rejection and graft loss and also increased the incidence rate of infectious complications. A study conducted on 173 renal transplant recipients, one year patient survival rate in patients with NODAT versus those without NODAT were 83 % versus 98 %, respectively (*P*<0.01) [22]. Data from the United Renal Data System, consisting of over 11,000 Medicare beneficiaries who received primary kidney transplants between 1996 and 2000 demonstrated that compared to "no diabetes", NODAT was associated with a 63 % increased risk of graft failure (*P*<0.0001), a 46 % increased risk of death-censored graft failure (*P*<0.0001) and an 87 % increased risk of mortality (*P*<0.0001) [15] while in contrast to this reports, a retrospective analysis of the UNOS/OPTN database (involving patients transplanted between 2004–2007) failed to demonstrate the negative impact of NODAT on transplant survival or CV mortality during a median follow-up of 548 days [37]. In our study, we found same result means we did not found any significant effect of NODAT on patients and graft survival.

Antibody induction

A study conducted by Fu. L. Luan *et al.* shows that in induction medication, recipient who given ATG has higher rate of NODAT then alemtuzumab, Anti IL-2 receptor antibody and other and this incidence of NODAT in ATG treated Patients was 17 % while 10 % and 15.5 % for alemtuzumab, Anti IL-2 receptor antibody respectively [38] while our results were contraindicating to this results. Our results shows that patients who were given basiliximab as an induction agent along with glucocorticoids having a high incidence rate of NODAT than patients treated with declizumab and ATG with glucocorticoids (37.88 % with basiliximab Vs 35.29 % in ATG Vs 28.17 % in Declizumab). But in our results it is not clearly found that any of these antibodies may have significantly affected on the prevalence rate of NODAT.

Infection

In our investigation, the frequency and days of hospitalization due to infections in patients with NODAT are higher than those of patients without NODAT. Use of immunosuppressants after an organ transplant reduces the resistance of the body to exogenous infections and recipients having concomitant NODAT are more vulnerable to infections. This may be due to the lower chemotaxis,

migration and phagocytic function of neutrophil granulocytes in diabetic patients compared with healthy people [39]. In our study, we found that patients with NODAT having a higher incidence rate of infection as compared to patients without NODAT. Among other infection incidence rate of CMV infection is significantly higher in NODAT patients than patients without NODAT. But for other infections like HCV, Herpes and HBV, we have not found statistically significant difference in patients with NODAT then without NODAT. Infection after NODAT may affect the survival rate of the patients so it is required preventing infection after transplantation.

CONCLUSION

Our results show that the prevalence rate of NODAT is higher in Indian patients than other recipients. In our study, we are not finding any significant effect of pre transplant HCV and HBV infection on NODAT. Our result shows a significant effect of recipient's age, body weight and HLA mismatch on the NODAT. Type of donor had no effect on NODAT. In our results, we are not finding a significant effect of different CNI agent, use of antibody and anti rejection therapy on NODAT. In our results, we found that infection is significantly higher in NODAT patients and mainly CMV infection but in other infections like HBV, HCV and Herpes infection we are not able find any significant different.

CONFLICT OF INTERESTS

Declared None

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