

# Incidence and risk factors of post-transplant diabetes mellitus among transplanted renal allograft recipients

MJ Mojahedi<sup>1</sup>, P Layegh<sup>2</sup>, M Hami<sup>1\*</sup>, F Khosravi<sup>3</sup>

<sup>1</sup>Nephrology Unit, Department of Internal Medicine, <sup>2</sup>Endocrinology Unit, Department of Internal Medicine, <sup>3</sup>Department of Internal Medicine, Mashad University of Medical Sciences, Mashad, Iran

## Abstract

**Background:** Post-transplant diabetes mellitus (PTDM) contributes to the risk for cardiovascular diseases and infection, reducing graft and patient survival. This study was conducted to identify the incidence and risk factors for development of PTDM.

**Methods:** We studied 50 non-diabetic adult dialyzed patients awaiting renal transplantation prospectively. Oral glucose tolerance test (oGTT) was performed pre- and post-transplantation. The relationship between age, weight (BMI), dialysis modality, family history of diabetes, and duration of dialysis and PTDM was assessed.

**Results:** Based on oGTT<sub>1</sub>, 13 patients had unknown diabetes mellitus; however, after transplantation only 9 had similar results. Based on oGTT<sub>2</sub>, 6 (16.22%) patients had actually PTDM. The age of patients with PTDM was significantly higher than that of those with normal test ( $43\pm 17$  vs  $31\pm 11$  years old). There was a significant relationship between duration of dialysis with PTDM, as normal oGTT was seen in 85.2% of patients dialyzed for less than 1 year. There was no significant relationship among dialysis modality and family history of diabetes and BMI with PTDM.

**Conclusion:** Risk factors for diabetes in our study were age and duration of dialysis before transplantation. Therefore, identifying them might allow modification of post-transplant immunosuppressant with non-dibetogenic agents in high risk patients.

**Keywords:** Transplant; Diabetes mellitus; Oral glucose tolerance test; Kidney

## Introduction

New onset diabetes after transplantation contributes to the risk for cardiovascular disease and infection, reducing graft and patient survival.<sup>1</sup> The incidence, risk factors and clinical relevance of post-transplant diabetes mellitus (PTDM) vary among reports from single-center observational studies and clinical trials.<sup>2</sup> PTDM is a manifestation of several complex metabolic abnormalities, including obesity, insulin resistance (with elevated blood insulin levels), and islet cell dysfunction.<sup>3</sup> The prevalence of PTDM will probably increase in parallel with the growing number of overweight and

older renal transplant recipients observed during last decade.<sup>4</sup> Risk factors consistently reported in the literature include aging, higher body weight, family history of diabetes mellitus, presence of abnormal glucose tolerance parameters, and Hepatitis C viral infection.<sup>5</sup> Also, both corticosteroids and calcineurine inhibitors are additional risk factors, which produce peripheral insulin resistance and reduce insulin secretion, respectively.<sup>5</sup> Few studies have implemented oGTTs to diagnose post-transplant intolerance.<sup>4</sup> This study was conducted to identify the incidence and pre-transplant risk factors for development of PTDM, using oGTTs.

## Materials and Methods

All patients, with end-stage renal disease (ESRD) awaiting for renal transplantation from living donors

\*Correspondence: Maryam Hami, MD, Assistant Professor of Nephrology, Department of Internal Medicine, Ghaem Hospital, Mashad University of Medical Sciences, Mashad, Iran. Tel: +98-511-7659556, Mobile: +98-915-3015842, e-mail: [hamim@mums.ac.ir](mailto:hamim@mums.ac.ir)  
Received: November 1, 2007 Accepted: May 26, 2008

were studied either on HD or on PD between September 2004 and October 2005. All the patients were on CsA-based immunosuppression, with a protocol including CsA (started in first day 9 mg/kg and then 5mg/kg/day regulated by assessing of cyclosporine blood levels, with Azathioprine 1-2 mg/kg/day or Mycophenolate Mofetile 2 gr/day) and Prednisolone (in first three days methylprednisolone succinate 10-15 mg/kg, and then oral Prednisolone 1mg/kg with tapering over the time). Exclusion criteria were cadaveric renal transplant recipients, hepatitis B and C viral infection, graft dysfunction after transplantation and patients with diabetes mellitus before transplantation. Patients' details included age, sex, weight, and height, and dialysis modality, family history of diabetes, blood pressure, and duration of renal failure. All assessments were performed when the patients were clinically stable. An oral glucose tolerance test (oGTT) was performed before and 2 months after transplantation. Plasma glucose level was measured immediately before and 1, 2, and 3 hours after a 75 gram oral glucose load (based on WHO recommendation). Based on the results of post-transplant oGTTs, the patients were classified into those with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or overt diabetes (PTDM). Patients with a 2-h plasma glucose value of >140mg/dl on the post-transplant oGTT were categorized as having impairment of glucose tolerance (IGT), and those >200 mg/dl as PTDM. The relationship with pre-transplant glucose tolerance parameters was studied. All the results were expressed as means±SD. The Chi square test and Fisher exact test for proportions and linear trends, and one way ANOVA were used to analyze the differences between groups.

## Results

In our centers, 145 patients received graft between September 2004 and October 2005. Graft in 96 patients (66.21%) was from living donors, and in 49 patients (33.79%) from cadaveric donors. From 96 patients, 46 were excluded, consisting of 10 patients (10.42%)

with overt diabetes mellitus before transplantation, 11 cases (11.46%) with severe graft dysfunction after transplantation, 4 cases (4.03%) that returned to hemodialysis (HD), 2 cases (2.08%) who died, and 19 patients (19.8%) not accepting the oGTT condition. Then only 50 patients (52.08%) were registered in the study. According to the results, the patients' mean (SD) age was 36.34±14.69 years. 32 (64%) were male with a mean age of 36.59±14.69 and 18 (36%) cases were female with a mean age of 35.89±14.47. Of the 50 patients, 45 (90%) were on HD and 5 (10%) on PD (CAPD). The mean duration of dialysis was 2.8± 3.62 years. In this study, 42 patients (84%) had no family history of diabetes in the first degree relatives but 8 patients (16%) had such a history.

The mean BMI in all cases was 21.23± 3.42 kg/m<sup>2</sup>.

In the pre-transplant period, based on oGTT1 in 50 patients, 24 patients (48%) had normal test, 13 (26%) impaired test, and 13 (26%) unknown diabetes. Based on oGTT2, in post-transplant situation, 33 patients (66%) had normal test, 2 (4%) impaired test, and 15 (30%) PTDM, but only 6 patients (16.22%) from the last group had normal oGTT1, and the reminder (9 patients) had impaired oGTT1. Then the incidence of PTDM in our study was 16.22%. Table 1 shows relevant various risk factors for IGT/PTDM. Aging was significantly associated with PTDM (P<0.05). There wasn't a significant relationship between sex and PTDM (P>0.05). The mean of BMI was not significantly different in pre-and post-transplant, and also there wasn't a significant relationship between BMI and the development of diabetes in post-transplant period (P>0.05). There was a significant relationship between duration of renal failure and impaired oGTT2 (P<0.05) (Table2). The modality of dialysis had no significant effect on the incidence of PTDM in patients with peritoneal dialysis versus hemodialysis before transplantation (P>0.05) (Table3). Regarding patients with no family history of diabetes mellitus, 32 cases (76.2%) oGTT2 were normal, and 10 cases (23.8%) had PTDM. In patients with family history of diabetes mellitus, 5 (62.5%) had no PTDM but 3 (37.5%) had this problem. In this study, a significant

**Table 1:** relating various factors to IGT/PTDM.

	Non-IGT	IGT	PTDM	P value
Number	24 (48%)	13 (26%)	13 (26%)	
Age (years)	31±11.04	43±17.33	38±14.02	0.025
Male: female	17:7	7:6	8:5	0.576
BMI	21.67±3.63	21.99±3.43	19.64±2.65	0.147

Age is significantly associated with PTDM (P<0.05)

**Table 2:** relating duration of dialysis to IGT/PTDM

Duration of Dialysis	Non-IGT	IGT	P value
Less than 1 year	23 (85.2%)	4 (14.8%)	0.012
More than 1 year	12 (52.2%)	11 (47.8%)	

Longer duration of dialysis is significantly associated with higher incidence of PTDM ( $P < 0.05$ ).

**Table 3:** relating type of dialysis to IGT/PTDM

Type of Dialysis	Non-IGT	IGT	P value
Peritoneal Dialysis	1 (20%)	4 (80%)	0.418
Hemodialysis	23 (51.1%)	22 (48.9%)	

Modality of dialysis does not have significant effect on the incidence of PTDM ( $P > 0.05$ ).

relationship between family history of diabetes mellitus and PTDM was not found ( $P > 0.05$ ). A significantly higher proportion of patients with pre-transplant impairment of glucose tolerance (2-h glucose values of  $> 140$ ) had PTDM ( $P < 0.001$ ) (Table 4).

## Discussion

Kidney transplantation is the most effective modality in replacement therapy after renal failure. Although there are great advances in management and control of immunologic complication after transplantation, unfortunately metabolic complication, especially diabetes mellitus after transplantation remains a great problem. PTDM leads to several morbidities such as cardiovascular disease and reduced graft survival in these patients.<sup>6,7,8</sup> It is important to know in which patients the probability of PTDM is higher. Boudeaux et al. demonstrated that greater age was a risk factor for PTDM. In their study, 34.2% of patients more than 45 years had PTDM, but in patients less than 45, only 5.2% had this problem.<sup>6</sup> Other studies reported that in higher age, PTDM was 2.6 to 2.9 more prevalent than that in lower age.<sup>2,9</sup> This was confirmed in our study.

According to other studies, there is no relationship between sex and PTDM,<sup>5,10</sup> and no significant relationship was found in our study either. Increase in BMI in general population leads to insulin resistance and diabetes mellitus.<sup>2,6,9,11,12</sup> In the USA, 60% of the patients with renal transplantation, based on BMI, are

overweight, tending to have increased weight in the first year after transplantation, causing a high risk of PTDM.<sup>13</sup> But in our study, BMI of the patients was not significantly different before and after transplantation and only 7 patients (14%) were overweight ( $BMI > 25$ ). There was no significant relationship between BMI and the incidence of PTDM. As patients with BMI more than 25 were 7 cases, and in 3 of them oGTT1 was normal, the relationship was not significant, probably due to the low number in each group ( $P > 0.05$ ).

In our study, it was shown that with increase in duration of dialysis, the risk of PTDM increased significantly ( $P < 0.05$ ). We found similar results in other reports. One of them showed that decrease in duration of dialysis before transplantation can cause decrease in diabetes mellitus after transplantation, concluding that increase in risk was about 6% per year in patients in waiting list.<sup>14</sup> We found that modality of dialysis (hemodialysis versus peritoneal dialysis) was not a risk factor for PTDM. This result was reported before.<sup>15</sup> In this study, we did not find a significant relationship between family history of diabetes mellitus and PTDM, but it may be because of the low number of patients in this study. Family history of diabetes mellitus is known as a risk factor for PTDM.<sup>5</sup> The use of HbA1C is not recommended in the first three months after transplantation.<sup>16</sup> Oral glucose tolerance test with 75 gram oral glucose and check of blood sugar 2 hours later showed that oGTT was more sensitive than FBS for the detection of PTDM.<sup>17</sup> We checked oGTT before and 2 months after transplanta-

**Table 4:** relating oGTT1 to oGTT2

oGTT2, oGTT1	Non-IGT	IGT	Total	P value
Non-IGT	31 (83.8%)	6 (16.2%)	37 (100%)	0.001
IGT	4 (30.8%)	9 (69.2%)	13 (100%)	
Total	35 (70%)	15 (30%)	50 (100%)	

A significantly higher proportion of patients with pre-transplant impairment of glucose tolerance have PTDM ( $P < 0.05$ ).

tion. In this study, we found that a significantly higher proportion of patients with pre-transplant impairment of glucose tolerance (2-h glucose values of >140) suffered from PTDM ( $P < 0.05$ ). It must be remembered that other factors such as immunosuppressive drugs (corticosteroids and calcineurine inhibitors) are important as well,<sup>18-22</sup> but in this study the protocol for their use was similar; as a result, their effect is ignored as a risk factor.

The older patients with abnormal oGTT parameters in pre-transplant period are at a higher risk of developing PTDM. This risk may increase if duration of dialy-

sis before transplantation is prolonged. Identifying the risk factors in high risk patients for PTDM might allow modification of post-transplant immunosuppressant with nondibetogenic agents.

### Acknowledgement

The authors would like to thank the Office of Vice Chancellor for Research of Mashad University of Medical Sciences for financial support of this study.

### References

- Rodrigo E, Fernandez- Fresnedo G, Valero R, Ruiz JC, Pinera C, Palomar R, Gonzales J, Gomes-Alamillo C, Arias M. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 2006;**17**(12 Suppl 3):S291-5. [17130277]
- Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003;**3**:178-185. [12603213]
- Gaston RS, Chandrakantan A. Diabetes mellitus after kidney transplantation. *Am J Transplant* 2003;**3**:512-513. [12752305]
- Hjelmsæth J, Asberg A, Müller F, Hartmann A, Jenssen T. New-onset posttransplantation Diabetes mellitus: Insulin resistance or insulinopenia? Impact of Immunosuppressive drugs, cytomegalovirus and hepatitis C virus infection. *Curr Diabetes Rev* 2005;**1**:1-10. [18220577]
- Gabriel M. Danovitch. Handbook of Kidney Transplantation. 4<sup>th</sup> ed. Lippincott Williams & Wilkins; 2005.
- Boudreaux JP, McHugh L, Canafax DM, Ascher N, Sutherland DE, Payne W, Simmons RL, Najarian JS, Fryd DS. The impact of cyclosporine and combination immunosuppression on the incidence of post transplant diabetes in renal allograft recipients. *Transplantation* 1987;**44**:376-381. [3307061]
- Steinmüller TH, Stockmann M, Bechstein WO, Settmacher U, Jonas S, Neuhaus P. Liver transplantation and diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2000;**108**:401-405. [11026753]
- Manske CL. Hyperglycemia and intensive glycemic control in diabetic patients with chronic renal disease. *Am J Kidney Dis* 1998;**32**(Suppl5): S157-171. [9820473]
- Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. *Kidney Int* 2002;**62**:1440-46. [12234317]
- Mathew JT, Rao M, Job V, Ratnaswamy S, Jacob CK. Post-transplant hyperglycemia: a study of risk factors. *Nephrol Dial Transplant* 2003;**18**:164-171. [12480976]
- Vesco L, Busson M, Bedrossian J, Bitker MO, Hiesse C, Lang P. Diabetes mellitus after renal transplantation: characteristics, outcome, and risk factors. *Transplantation* 1996;**61**:1475-78. [8633374]
- Pesavento TE, Henry ML, Falkenhain ME, Ferguson RM. Post-transplant diabetes mellitus: Evidence for glucose intolerance and insulin resistance existing pre-transplant. *Am J Transplant* 2003;**3**:239-240.
- Fiedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients a time of kidney transplantation. *Am J Kidney disease* 2003;**41**:480-487. [12552513]
- Woodward RS, Schnitzler MA, Baty J, Lowell JA, Lopez-Rocafor L, Haider S, Woodworth TG, Brennan DC. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant* 2003;**3**:590-9598. [12752315]
- Rodrigo E, Fernandez- Fresnedo G, Valero R, Ruiz JC, Piñera C, Palomar R, González-Cotorruelo J, Gómez-Alamillo C, Arias M. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 2006;**17**(12 Suppl 3):S291-5. [17130277]
- Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, Jardine A, Levitt N, Marchetti P, Markell M, Naicker S, O'Connell P, Schnitzler M, Standl E, Torregosa JV, Uchida K, Valentine H, Villamil F, Vincenti F, Wissing M. Guide line for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005;**3**:291-98. [15877787]
- Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H. New -onset diabetes after transplantation. *Transplantation* 2003;**75**(Suppl10):S3-S24.
- Gunnarsson R, Arner P, Lundgren G, Magnusson G, Ostman J, Groth CG. Diabetes mellitus—a more-common-than-believed complication of renal transplantation. *Transplant Proc.* 1979;**11**:1280-1281. [382510]
- Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J. Post-transplant hyperglycemia: Increased incidence in cyclosporine-treated renal allograft recipients. *Transplantation* 1989;**47**:279-281. [2645712]
- Powers A. Diabetes mellitus. In: Kasper D, Braunwald, Fauci, Hauser, Longo, Jameson, editors. Harrison's principles of internal medicine. 16th ed. New York Mc Graw Hill. 2005; p. 2152-2180.
- Hricik DE, Anton HA, Knauss TC, Rodriguez V, Seaman D, Siegel C, Valente J, Schulak JA. Outcomes of African American kidney transplant recipients treated with sirolimus, tacrolimus, and corticosteroids. *Transplantation* 2002;**74**:189-193. [12151730]
- Maes BD, Kuypers D, Messiaen T, Evenepoel P, Mathieu C, Coosemans W, Pirenne J, Vanrenterghem YF. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: Analysis of incidence and risk factors. *Transplantation.* 2001;**72**:1655-1661. [11726827]