



## Favorable Renal Allograft and Patient Outcome after Transplantation in Patients with Diabetes Mellitus: A Five-Year Single Center Experience

Behzad Einollahi<sup>1</sup>, Fatemeh Heidary<sup>1</sup>, Hoda Einollahi<sup>1\*</sup>, Zohreh Rostami<sup>1</sup>

<sup>1</sup> Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran

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### ABSTRACT

**Background:** Diabetic patients are increasing rapidly worldwide and kidney transplantation is generally accepted as a treatment of choice in these patients with end stage kidney disease.

**Objectives:** We made a plan to evaluate the 5-year outcome of kidney transplantation in patients with and without DM.

**Patients and Methods:** Two groups of adult kidney recipients including 117 with history of DM mellitus (DM) and 135 non- DM mellitus between March 2006 and September 2009, were enrolled in this study. The clinical information was retrieved from both paper records and electronic databases and additional details were obtained from phone call.

**Results:** From total of 252 recipients, 182 received kidney from living donors (11% living related and 89% living unrelated) and 70 from deceased donors. Renal function was preserved among the diabetic patients same as the non-diabetic cases (median serum creatinine 1.35 mg/dL versus 1.30 mg/dL,  $P=0.8$ ). Triglyceride ( $P=0.000$ ), cholesterol ( $P=0.000$ ) and uric acid levels ( $P=0.004$ ) were significantly higher in patients with DM. In addition, no significant differences were seen between two groups in terms of graft survivals at univariate and multivariate analyses. There was no significant difference in patient survival between recipients with and without DM (log-rank,  $P=0.2$ ). Multivariate analysis by Cox regression showed that the age and gender of recipient, donor source and DM had no adverse effect on mid-term outcome among our patients.

**Conclusions:** Diabetic and non-diabetic kidney transplant recipients had similar short- and mid-term graft and patient survivals.

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### ► Implication for health policy/practice/research/medical education:

This article focuses on the impact of pre-transplant diabetes mellitus on renal transplant outcomes. Surprisingly, there are not enough published papers in literature on pre-transplant diabetes; on the other hand, there are a lot of studies about the new onset diabetes mellitus.

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## 1. Background

Diabetes mellitus (DM) is a common chronic disease worldwide affecting up to 180 million people (1). In addition, diabetic nephropathy is the leading cause

of end-stage renal disease (ESRD) requiring renal replacement therapy, accounting for up to half of all cases of ESRD in developed countries (2). In the past, however, clinicians tended to exclude the diabetic patients from renal transplantation due to the adverse effects of immunosuppressive drugs and high morbidity and mortality after surgery. Although the outcome of kidney transplantation is inferior for diabetic than for nondiabetic patients (3), the survival of uremic diabetic patients who remained on chronic hemodialysis is

\* Corresponding author at: Hoda Einollahi, Ground Floor of Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Mollasadra Ave., Vanak Squ., P.O. Box: 19395-5487, Tehran, IR Iran. Tel/Fax: +98-2181262073.  
E-mail: einollahi2008@gmail.com

significantly lower than diabetic recipients (4, 5). Nowadays, number of diabetic patients is rapidly rising worldwide and kidney transplantation is generally accepted as a treatment of choice in diabetic patients with ESRD. In addition, it is demonstrated that the one year patient survival rate is similar in diabetic and nondiabetic transplant recipients (6, 7), while other studies show that the 5-year patient survival rate is worse in diabetics compared to nondiabetic recipients (8, 9). However, in another study no significant differences were observed in the 5-year rates for both patient and graft survival between diabetic and nondiabetic individuals (10).

## 2. Objectives

Although Iran has the largest reported experience of kidney transplantation among the Middle East countries (11), there are limited data available on DM in Iranian kidney recipients. Therefore, we evaluated the 5-year outcome of kidney transplantation in patients with and without DM.

## 3. Patients and Methods

### 3.1. Participants

A total of 252 kidney transplant recipients who

underwent kidney transplantation in Baqiyatallah were retrospectively studied. Patients were divided into two groups; 117 patients with history of DM mellitus (DM) and 135 non-DM mellitus (Non-DM) cases. The proposal of this study was approved by the local Ethics Committee of Baqiyatallah University of Medical Sciences.

### 3.2. Inclusion and Exclusion Criteria

We included all patients who had been placed on the renal transplant waiting list between March 2006 and September 2009, as well as those who had received a kidney transplant as their first renal replacement therapy during this same period. Living and deceased kidney transplants were both included. We excluded patients for whom data were missing about date of birth or date of first renal replacement therapy. We also excluded patients who were not between ages 18 and 100 years and those who had undergone renal transplantation before the study's start-date. Finally, we did not include renal transplantations that were part of multiple organ procedures (i.e. kidney-pancreas transplantation).

### 3.3. Clinical and Biochemical Data Collection

The clinical information was retrieved from both paper records and electronic databases and additional details

**Table 1.** Univariate Analysis of Patient Demographics and Transplantation-Related Variables between Patients with and without DM

Variables	Overall, n = 252	Non-DM <sup>a</sup> , n = 135	DM, n = 117	P value
Gender, No.				0.2
Male	166	84	82	
Female	86	51	35	
Donor source, No.				0.8
Living	182	97	85	
Deceased	70	38	32	
Number of hospitalization after transplantation, %				0.7
None	65.5	65.9	65.0	
1	25.4	26.7	23.9	
2	7.1	5.2	9.4	
3	1.2	1.5	0.9	
4	0.8	0.7	0.9	
Follow up mo, median	29	27	31	0.8
Graft loss, No. (%)	12 (4.8)	7 (5.2)	5 (4.3)	0.7
Mortality rate, No. (%)	14 (5.6)	6 (4.4)	8 (6.8)	0.4
Last serum creatinine mg/dL, Mean $\pm$ SD	1.6 $\pm$ 0.9	0.9 $\pm$ 0.2	0.9 $\pm$ 0.3	0.8
Systolic BP, mmHg (Mean $\pm$ SD)	127 $\pm$ 16	126 $\pm$ 15	129 $\pm$ 18	0.1
Diastolic BP, mmHg (Mean $\pm$ SD)	76 $\pm$ 10	78 $\pm$ 9	75 $\pm$ 12	0.04
Triglyceride, mg/dL (Mean $\pm$ SD)	148 $\pm$ 81	135 $\pm$ 76	166 $\pm$ 85	0.004
Cholesterol, mg/dL (Mean $\pm$ SD)	162 $\pm$ 57	149 $\pm$ 50	177 $\pm$ 60	0.000
Uric acid, mg/dL (Mean $\pm$ SD)	5.1 $\pm$ 1.8	4.7 $\pm$ 1.7	5.7 $\pm$ 1.7	0.000
Age of recipient, y (Mean $\pm$ SD)	43 $\pm$ 13 (10-76)	38 $\pm$ 14 (10-76)	49 $\pm$ 10 (23-68)	0.000

<sup>a</sup> Abbreviation: DM, Diabetes Mellitus

were obtained via phone call to patients. Data collected for all patients included age and gender of recipient, donor source (living and deceased), the times of transplantation, hospital admission requirements, renal function, patient outcome, lipid profile, serum uric acid concentration and blood pressure.

### 3.4. Definitions

We defined DM if the fasting blood glucose concentration  $\geq 126$  mg/dL, according to the American DM Association (ADA) criteria (12). For a test result to be positive, it must be confirmed by another test. Graft loss was recognized as need to dialysis for renal replacement therapy.

### 3.5. Immunosuppressive Regimen and Follow Up

The maintenance immunosuppression in all patients was based on cyclosporine plus mycophenolate mofetil or azathioprine and prednisolone. The amount of cyclosporine given to transplant patients was mostly based on blood levels of drug. Cyclosporine monitoring using its trough levels was periodically performed at different times and dose was adjusted as necessary. Target of cyclosporine trough blood level at 3 months was 150-250 ng/mL and then tapered to 100-150 ng/mL by 1 year. Antithymocyte globulin (ATG) was routinely administered in highly sensitized patients. All patients were clinically examined weekly up to 2 months, every 2-4 weeks for months of 2-4, monthly up to one year after transplantation and every 1-2 months thereafter. Blood samples were also taken for measurement of fasting blood sugar (FBS) and other routine laboratory tests. The median follow up was 29 months.

### 3.6. Statistical Analysis

Statistical analyses were performed using the SPSS version 17.0 for Windows. All quantitative data have been expressed as mean  $\pm$  SD and the qualitative variables have been shown by percentage. The Kolmogorov-Smirnov test showed that FBS in our patients were normally distributed ( $P = 0.19$ ), thus parametric tests were used. Comparisons between the categorical variables were performed using the Chi square test or the Fisher exact test, while continuous data were compared by student's t-test. Overall patient and graft survival rates were calculated using the Kaplan-Meier method, and the log-rank test was used to determine statistical differences in survival rates between two groups. Multivariate analysis was done by the Cox proportional hazard model to see whether age and gender of recipient, donor source and DM influenced the patient and graft outcomes. Statistical significance was considered as a  $P$  value less than 0.05.

## 4. Results

### 4.1. Patient Demographics

A total of 252 kidneys have been transplanted within the period of study, of which 182 were from living donors (11% living related and 89% living unrelated) and 70 from deceased donors. DM was seen in 46% of recipients. The majority of patients had first kidney transplantation ( $n = 239$ , 94.8%), while second transplantation was done in 11 (4.4%) of cases and third kidney transplantation was only performed in 2 (0.8%) of patients. First and re-transplantation were not significantly different between both groups ( $P = 0.09$ ). Patients who had DM were significantly older at the time of transplantation compared to non-diabetic recipients (Table 1).

### 4.2. Univariate Analysis

Univariate analysis of patient demographics (including age and sex of recipients, transplant kidney source, and number of admission) and transplantation-related parameters among the two groups are presented in table 1. No significant differences were found between the two groups in gender, number of hospital admission and blood pressure ( $P < 0.05$ ). Renal function was preserved among the diabetic patients same as the non-diabetic cases (median serum creatinine 1.35 mg/dL versus 1.30

**Table 2.** Patient and Graft Survival Rates in Patients with and Without DM

	Non-DM <sup>a</sup>	DM	P value <sup>b</sup>
Patients survival, %			0.2
1 year	97.0	96.2	
3 year	94.7	89.9	
Graft survival, %			0.9
1 year	98.5	98.1	
3 year	94.6	93.4	

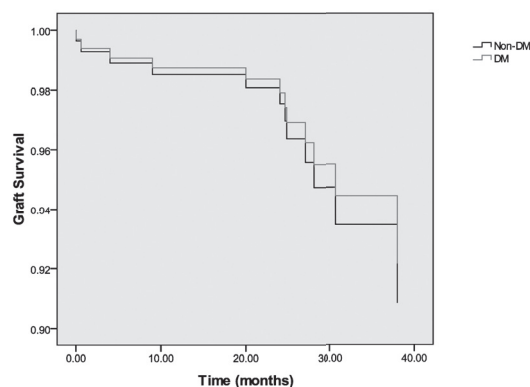
<sup>a</sup> Abbreviation: DM, Diabetes Mellitus

<sup>b</sup> Log rank

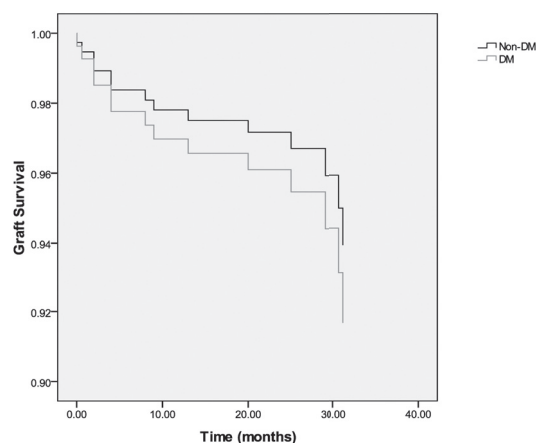
**Table 3.** Cox Regression Analysis for Assessment of Sex, Age of Patients, Donor Source and DM for Patient and Graft Survival

	Graft survival			Patient survival		
	Exp (B)	95.0 % CI <sup>a</sup>	P value	Exp (B)	95.0 % CI	P value
Gender	0.75	0.24-2.36	0.6	0.69	0.24-2.00	0.5
Age	1.009	0.96-1.06	0.7	1.02	0.98-1.07	0.3
Donor source	3.33	0.92-12.13	0.06	3.08	0.95-9.98	0.06
DM <sup>a</sup>	1.18	0.34-4.05	0.8	0.72	0.24-2.21	0.6

<sup>a</sup> Abbreviation: CI, conservation international; DM, Diabetes Mellitus



**Figure 1.** Graft Survival in Patients with and without DM



**Figure 2.** Patient Survival in Patients with and without DM

mg/ dL,  $P = 0.8$ ). Triglyceride, cholesterol and uric acid levels were significantly higher in patients with DM when compared with non-diabetic individuals (Table 1).

### 4.3. Outcome

#### 4.3.1. Graft Survival

Graft loss rate was not different between groups (Table 1). In addition, no significant differences were seen between two groups in terms of graft survivals at univariate and multivariate analyses (Tables 2 and 3) (Figure 1).

#### 4.3.2. Patient Survival

The overall mortality rate was not significantly different between the two groups (Table 1). There was no significant difference in patient survival between recipients with and without DM (log-rank,  $P = 0.2$ ) (Figure 2). Multivariate analysis by Cox regression showed that age and gender of recipient, donor source and DM had no adverse effect on short term outcome among our patients (Table 3).

## 5. Discussion

The result of this study shows that there is no difference of short- and mid-term patient and graft survival in diabetic and non-diabetic recipients, which matches with two studies (10, 13). Boucek et al reported a similar outcome in terms of 5-year patient and graft survival in diabetic subjects and non-diabetic recipients (13). Converse to prior reports we did not find a significant inferior patient survival in diabetic patients than non-diabetic individuals (7, 14-16). In the current study, the rate of mortality in diabetic recipients was higher than non-diabetic patients (6.8% vs. 4.4%). Arend et al showed that DM had no significant effect on the first year mortality; however, it was associated with a higher risk of mortality for more than 1 year after kidney transplantation (17). Also Cosio et al reported a poorer patient survival in diabetic recipients than in non-diabetic patients (16). According to previous studies not only diabetes but also the duration of DM increases both all-cause and cardiovascular mortality (18-20). Israni et al showed that long-term history of pretransplant DM can compromise patient survival; it may be related to the risk of cardiovascular disease being more frequent in pretransplant diabetic patients versus post-transplant DM (PTDM) individuals (18). Furthermore, Jeong et al reported that the risk of cardiovascular disease was 2 times more in presence of pretransplantation DM versus PTDM (19).

In our study, mean serum creatinine was not different between both the groups. Shaffer *et al* showed no significant difference in mean serum creatinine levels at 5 years between diabetic and nondiabetic recipients (10). Several studies showed that PTDM has a negative impact on graft survival (18, 19, 21, 22). Parallel to several preceding studies (16, 21, 23) hypercholesterolemia and hypertriglyceridemia were also more frequently observed in recipients with DM when compared to non-diabetic patients. As we know, Dyslipidemia is common metabolic disorder in renal transplant recipients, disturbing up to 74% of patients; it may lead to development of atherosclerosis as well as graft loss (24). In this study, we showed that diabetic and non-diabetic kidney transplant recipients had similar short- and mid-term graft and patient survival. Thus, diabetic patients with ESRD are not contraindicated for kidney transplantation. The main limitations of the present study are its retrospective nature and relatively small sample size.

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## Conflict of interest

None declared.

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