

INCIDENCE AND RISK FACTORS OF NEW ONSET DIABETES MELLITUS AMONG TRANSPLANTED RENAL ALLOGRAFT RECIPIENTS

Mohammad Javad Mojahedi⁽¹⁾, Parvin Layegh⁽²⁾, Maryam Hami⁽³⁾, Fariba Khosravi⁽⁴⁾

Abstract

INTRODUCTION: Post-transplant diabetes mellitus (PTDM) contributes to the risk for cardiovascular disease and infection, reducing graft and patient survival. This study was conducted to identify 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 () was performed pre- and post-transplantation. The relation of age, weight (BMI), dialysis modality, family history of diabetes, duration of dialysis was assessed with occurring PTDM.

RESULTS: Based on 1, 13 patients had unknown Diabetes Mellitus; however after transplantation only 9 of them had same results. Based on 2 6(16.22%) patients had actually PTDM. Age of patients with PTDM were significantly higher than those with normal test (43 ± 17 versus 31 ± 11 year old) ($P < 0.05$). There was significant relation between duration of dialysis with PTDM ($P < 0.05$), as normal was seen in 85.2% patients that dialyzed less than 1 year. There was no significant relation among dialysis modality and family history of diabetes and BMI with PTDM ($P > 0.05$).

CONCLUSION: Risk factors for diabetes in our study were age and duration of dialysis before transplantation. Then identifying them might allow modification of post transplant immuno-suppressant with nondibetogenic agents in high risk patients.

Keywords: post-transplant diabetes mellitus, oral glucose tolerance test, renal transplantation.

ARYA Atherosclerosis Journal 2008, 3(4): 233-236

Date of submission: 10 Oct 2007, *Date of acceptance:* 21 Feb 2008

Introduction

New onset Diabetes after transplantation contributes to the risk for cardiovascular disease and infection, reducing graft and patient survival.¹

The incidence, risk factors and clinical relevance of post-transplant diabetes mellitus (PTDM) vary among reports from single-center observational studies and clinical trials.²

PTDM is a manifestation of several complex metabolic abnormalities, including obesity, insulin resistance (with elevated blood insulin levels), and islet cell dysfunction.³

The prevalence of PTDM will probably increase in

accompany with the growing number of overweight and older renal transplant recipients observed during last decade.⁴

Risk factors consistently reported in the literature include greater age, higher body weight, family history of diabetes mellitus, presence of abnormal glucose tolerance parameters, and Hepatitis C viral infection.⁵

Few studies have implemented s to diagnose post transplant intolerance⁴.

This study was conducted to identify the incidence and pre-transplant risk factors by s for development of PTDM.

1) MD. Nephrology Unit, Department of Internal Medicine, Mashad University of Medical Sciences, Mashad, Iran.

2) MD. Endocrinology unit, Department of Internal Medicine, Mashad University of Medical Sciences, Mashad, Iran.

3) MD. Assistant Professor of Nephrology, Ghaem Hospital, Mashad University of Medical Sciences, Mashad, Iran.

E-mail: hamim@mums.ac.ir

4) MD. Internal Medicine Dept. Mashad University of Medical Sciences, Mashad, Iran.

Corresponding author: Maryam Hami

Methods and Materials

All patients, with end-stage renal disease (ESRD) waiting for renal transplantation from lived donors, between September 2004 and October 2005, either on HD or on PD were studied. All patients were on CsA-based immunosuppression therapy, with protocol that included CsA (started in first day 9mg/kg and then 5mg/kg/day that 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 10-15mg/kg, and then oral Prednisolone 1mg/kg with tapering over the time).

Exclusion criteria were defined as cadaveric renal transplant recipients, hepatitis B and C, viral infection, graft dysfunction after transplantation and patients with diabetes mellitus before transplantation.

Patients' data that collected were 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 () was performed pretransplant and 2 months after transplantation. Plasma glucose level was measured immediately before and at 1, 2, and 3 hour after a 75 gram oral glucose load (based on WHO recommendation).

Based on the results of post-transplant, 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 $>140\text{mg/dl}$ on the post-transplant were categorized as having impairment of glucose tolerance (IGT), and $>200\text{ mg/dl}$ as PTDM. The relationship to pre-transplant glucose tolerance parameters was studied.

All results were expressed as means \pm SD. The Chi square test and Fisher exact test were used for proportions comparing and linear trends, and the one way ANOVA was used to test the mean 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 live donors, and in 49 patients (33.79%) was from cadaveric donors. From 96 patients, 46 patients were omitted, that consist of 10 patients (10.42%) who had overt diabetes mellitus before transplantation and 11 cases (11.46%) who had severe graft dysfunction after transplantation and 4 cases (4.03%) that returned to hemodialysis (HD) and 2 cases (2.08%) who died, also 19 patients (19.8%)

didn't accept the condition. Then only 50 patients (52.08%) entered to study.

Mean (SD) age in patients was 36.34 ± 14.69 years (32 male with 36.59 ± 14.69 and 18 female with 35.89 ± 14.47 years old). Of the 50 patients, 45 (90%) were on HD and 5 (10%) were on PD (CAPD). The mean of duration of dialysis was 2.8 ± 3.62 years. In this study, 42 patients (84%) hadn't family history of diabetes in first degree relatives and 8 patients (16%) had such history.

The mean BMI in all cases was $21.23 \pm 3.42\text{ kg/m}^2$.

In pre-transplant period, based on 1 in 50 patients, 24 patients (48%) had normal test, 13 patients (26%) had impaired test, and 13 patients (26%) had unknown diabetes. Based on 2, in post-transplant situation, 33 patients (66%) had normal test, 2 patients (4%) had impaired test, and 15 patients (30%) had PTDM, but only 6 patients (16.22%) from last group had normal 1, and reminder (9 patients) had impaired 1, then the incidence of PTDM in our study was 16.22%.

Table 1 shows analyses relating various factors to IGT/PTDM. Greater age was significantly associated with PTDM ($P < 0.05$).

There wasn't significant relation between sex and PTDM ($P > 0.05$).

The mean of BMI did not show any significant different in pre-and post-transplant, and also there wasn't significant relation between BMI and developing of diabetes in post transplant period ($P > 0.05$).

There was a significant relation between duration of renal failure and impaired 2 ($P < 0.05$) (Table 3).

The modality of dialysis hadn't significant effect on the incidence of PTDM in patients that had peritoneal dialysis versus hemodialysis before transplantation ($P > 0.05$).

It was reported that in patients without family history of diabetes mellitus, 32 cases (76.2%) 2 was normal, and 10 cases (23.8%) had PTDM. In patients with family history of diabetes mellitus, 5 cases (62.5%) hadn't PTDM and 3 patients (37.5%) had this problem. In this study, there wasn't significant relation between family history of diabetes mellitus with PTDM ($P > 0.05$).

Discussion

Kidney transplantation is the most effective modality in replacement therapy after renal failure. Although there are great progressions in management and control of immunologic complication after transplantation, but unfortunately metabolic complication specially Diabetes mellitus after transplantation is remained as a great problem.

Table 1. Relationships between New Onset of Diabetes Mellitus and Study Group Characteristics.

Factor		Not-IGT	IGT
Age		31±11.04	43±17.33
Male: female		17:7	7:6
BMI		21.67±3.63	21.99±3.43
Duration of Dialysis	Less than 1 year	23(85.2%)	4(14.8%)
	More than 1 year	12(52.2%)	11(47.8%)
Type of Dialysis	Peritoneal Dialysis	1(20%)	4(80%)
	Hemodialysis	23(51.1%)	22(48.9%)

IGT: Impaired Glucose Tolerance

PTDM lead to several morbidities like cardiovascular disease and reduced graft survival in this patients.^{6,7,8}

It is important to know that in which patients probability of PTDM is higher. Boudeaux and et al demonstrated that greater age is as a risk factor for PTDM. In their study 34.2% patients with age more than 45 year old had PTDM, but in patients less than 45 year old, only 5.2% had this problem⁶. In other studies were reported that in higher age, PTDM was 2.6 until 2.9 more prevalent than lower age^{2,9}. In our study this effect is accepted.

According to other studies, there isn't any relation between sex and PTDM,^{5,10} and also we didn't find significant relationship between them.

Increase in BMI in general population leads to insulin resistance and diabetes mellitus.^{2,6,9,11,12} In USA, 60% patients with renal transplantation, based on BMI, are overweight, that tend to have increase in weight in first year after transplantation that cause increase risk of PTDM¹³, but in our study BMI of patients wasn't significantly different before and after transplantation and only 7patients(14%) were overweight (BMI>25). There wasn't any significant relationship between BMI and incidence of PTDM. Patients with BMI more than 25 were 7cases, and in 3 of them 1 was normal, but relation wasn't significant, that may be because low number in each group and needs a new study with more patients (P>0.05).

In our study it was showed that with increase in duration of dialysis, risk of PTDM was increased significantly (P<0.05). We found similar results in other reports, like in one of them, they showed that decrease in duration of dialysis before transplantation can cause decrease in diabetes mellitus after transplantation, they found that increase in risk was about 6% per every year in patients in waiting list.¹⁴

We found that modality of dialysis (hemodialysis versus peritoneal dialysis) wasn't as a risk factor for PTDM. This result was reported before.¹⁵

In this study, we didn't find significant relation between family history of diabetes mellitus and PTDM, but it may be because of low number of pa-

tients in this study. Family history of diabetes mellitus is known as a risk factor for PTDM.⁵

Use of HbA1C is not recommended in first three months after transplantation.¹⁶ Oral glucose tolerance tests with 75 gram oral glucose and check of blood sugar 2 hour later showed that is more sensitive than FBS for detection of PTDM.¹⁷

Then we check before transplantation and 2 months after that. In this study we found that the significantly higher proportion of patients with pre-transplant impairment of glucose tolerance (2-h glucose values of >140) had PTDM (P<0.05).

In the end we must to say that other factors like immunosuppressive drugs (corticosteroids and calcineurine inhibitors) are important too,¹⁸⁻²² but in this study protocol for their use was similar, then their effect are omitted as a risk factor.

Conclusion

The older patients with abnormal parameters in pre-transplant period are at higher risk of developing PTDM. This risk may be increased if duration of Dialysis before transplantation was prolonged. Identifying the risk factors in patients that are high risk 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

1. Rodrigo E, Fernandez- Fresnedo G, Valero R, Ruiz JC, Pinera C, Palomar R, and et al. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol*. 2006; 17Suppl3:291-5.
2. Bertram L, Kasiske, Jon J. Snyder, David Gilbertson, Arthur J. Matas. Diabetes Mellitus after kidney transplantation in the united state. *American Journal of Transplantation*. 2003; 3: 178-185.
3. Robert S. Gaston, Arun Chandrakantan. Diabetes Mellitus after kidney transplantation. *American Journal of Transplantation*. 2003; 3: 512-513.

4. Joran Hjlmesaeth, Anders Asberg, Fredrik Muller, Anders Hartmann, Trond Jenssen. New-onset posttransplantation Diabetes mellitus: Insulin resistance or insulinopenia? Impact of Immunosuppressive drugs, cytomegalovirus and hepatitis C virus infection. *Current Diabetes Reviews*. 2005; 1: 1-10
5. Gabriel M. Danovitch. *Handbook of Kidney Transplantation*. 4th ed. Lippincott Williams & Wilkins; 2005
6. Boudreaux JP, Mc Hige L, Canafax D.M., Asher N., Sutherland D.E.R., Payne W., and et al. The impact of cyclosporine and combination immunosuppression on the incidence of post-transplant diabetes in renal allograft recipients. *Transplantation*. 1987; 44: 376-381.
7. Steinmuller T, Stockmann M, Bechstein WO, Settmacher U, Jonas S, Neuhaus P. Liver transplantation and diabetes mellitus. *Exp Clin Endocrinol Diabetes*. 2000; 108: 401-405
8. Manske CL. Hyperglycemia and intensive glycemic control in diabetic patients with chronic renal disease. *Am J Kidney Dis*. 1998; 32 Suppl5: S157-171
9. 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
10. Jayant T. Mathew, Madhumatya Rao, Victoria Job, Selvakumar Ratnaswamy, Chakko K. Jacob. Post-transplant hyperglycemia: a study of risk factors. *Nephrol Dial Transplant*. 2003; 18: 164-171
11. 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
12. 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: 237-239
13. 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
14. Woodward RS, Robert S. A., Schnitzer MA, Baty Jack C, Lowell Jeffrey F., and et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant*. 2003;3: 590-598
15. Rodrigo E, Fernandez- Fresnedo G, Valero R, Ruiz JC, Pinera C, Paomar R. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol*. 2006 ;17(12 Suppl 3):S291-5
16. Wilkinson A, Davidson J, Dotta F, Hom P.D., Keown P., Kiberd B. Guide line for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant*. 2005; 3: 291-98
17. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H. New – onset diabetes after transplantation. 2003; 75(Suppl10):S3-S24
18. Gunnarsson R, Arner P, Lundgren G, Magnusson G, Ostman J, Groth C-G. 2003 International consensus Guidelines. Diabetes mellitus- A more common than believed complication of renal transplantation. *Transplantation proceeding*. 1979; 11: 1280-1281
19. Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J. Posttransplant hyperglycemia: Increased incidence in cyclosporine-treated renal allograft recipients. *Transplantation*. 1989; 47: 279-281
20. Powers A. Diabetes mellitus. In: Kasper D, Braunwald, Fauci, Hauser, Longo, Jameson, editors. *Harrison's principles of internal medicine*. 16th ed. New York Mc Grow Hill. 2005; 2152-2180
21. Hricik DE, Anton HA, Knauss TC, Rodrigues V, Seaman D, Siegel C. Outcome of African American Kidney transplant recipients treated with Sirolimus, Tacrolimus, and Corticosteroids. *Transplantation*. 2002; 74: 189-193
22. Maes BD, Kuypers D, Messiaen T, Evenepoel P, Mathieu C, Coosemans W. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: Analysis of incidence and risk factors. *Transplantation*. 2001; 72: 1655-1661