Prevalence and risk factors for Diabetes Mellitus After Renal Transplantation

Professor (Dr.) Monem Makki ALshok C.A.B.M
Consultant physician Babylon university College of Medicine
Assistant professor( Dr) Ahmed Hussein Al-Myali C.A.B.M
Karbala university College of Medicine
Dr.karrar Kadim Mohsin M.B.Ch.B

Abstract
Background : This study reviewed the prevalence of post Renal Transplantation Diabetes Mellitus (PRTDM) and risk factors for its occurrence among renal transplant recipients.
Methods : Records of all kidney recipients with no known diabetes mellitus prior to transplantation and patients with post-transplant period of more than 2 months were included. The following parameters were studied as possible risk factors: age, sex, hypertension, family history of diabetes, immunosuppressive medications , body mass index and donors whether relative or not .
Results: The 97 patients who studied, 20.62% had PRTDM(table I). Family history of diabetes and older age of recipients did not differ significantly between recipients with versus without PRTDM,however, recipients who developed PRTDM had significantly higher body mass index (28.49 versus 25.21) with statistically significant difference (P < 0.05).
Hypertension was prevalent more in recipients with PRTDM (65% versus 53.24%) this difference was statistically significant (P < 0.05),patients with unrelated donors showed higher incidance of PRTDM with significant result.
Conclusion: Diabetes after renal transplantation occurs in significant number of patients. Transplantation from related donors may be associated with lower risk of PRTDM. Diabetes occurs more in recipients with hypertensive & higher body mass index.

Key words: Transplantation, Post Transplant Diabetes Mellitus, Body Mass Index, Hypertension.

Introduction
Renal transplantation has emerged as the treatment of choice for many patients with end stage renal disease. (1) There is increasing concern about the complications that develop after the transplantation of a functioning allograft. One of the more significant adverse complications in this setting is PRTDM, because this often unanticipated by the patients, and has the potential to lead to poor outcome.

Numerous reports in the literature have demonstrated that the development of PRTDM is associated with impaired long – term graft function and survival in transplant recipients.
In one study, 12-year graft survival in kidney transplant recipients who developed diabetes after transplantation was reported as 48 VS. 70% in those with no development of diabetes(3).
In addition to having adverse effects on graft, PRTDM may also reduce the survival of transplant recipients(4-7). Development of the condition may also be detrimental to the long – term survival of transplant recipients, with a reported mean survival of 8.1 years for kidney recipients with PTDM versus 11.0 years for those with no PRTDM(4).
It is well established that patients with diabetes in the general population have an increased risk for cardiovascular mortality. Similarly, the risk of cardiovascular disease (CVD) is considerably higher in PRTDM compared with those who do not developed the condition (8,10). In kidney transplant recipients, diabetes was found to be the most important risk factor for developing both cerebrovascular disease and peripheral vascular disease (9). In a further study, diabetes carried the highest relative risk for ischemic heart disease in kidney transplant recipients > 1 year post transplant, imposing a greater relative risk than hyperlipidemia, hypertension, or smoking(10).
PRTDM not only predisposes transplant recipients to CVD, but also increases the risk of death from cardiovascular complication. Death following ischemic heart disease is 20.8 times higher in transplant patients with diabetes than in the general population(8).

The etiology of PRTDM is multifactorial, It includes The immunosuppressive regimens (steroid use and calcineurine inhibitors seem to have the most important relevance), The patient's ethnicity, older age, BMI, and increasing HLA mismatches (11,12). On the other hand, factors that reduce the risk for PRTDM include the use of mycophenolate mofetil, azathioprine, younger recipient age, glomerulonephritis as a cause of kidney failure (12).
Corticosteroids may help induce diabetes by a number of mechanisms. The most important of these is the induction of insulin resistance, which occurs by steroids stimulating endogenous glucose production (13) and impairing glucose uptake in muscle and fat(14). Prednisolone is likely to contribute to PRTDM through its effect on lipid and carbohydrate metabolism. Withdrawing or reducing the dose of corticosteroids has been shown to reduce hyperglycemia and may decrease the incidence of PRTDM. However, steroid withdrawal or dose reduction associated with increase risk for acute rejection, (15) and some studies have shown diabetes to persist despite complete steroid removal, (16) .
Both tacrolimus and cyclosporine have been shown to be diabetogenic. Post transplant diabetogenicity is associated with higher levels of both drugs (17). The combination of prednisolone with either of these agents possibly more diabetogenic than either treatment alone. Early studies with tacrolimus and azathioprine demonstrated a 19.9% incidence of PRTDM, primarily in African-American patients. This was significantly higher than that seen when cyclosporine and azathioprine were used. At that time, levels and doses of both tacrolimus and steroids were far higher than they are today. More recent studies seem to show that the combination of tacrolimus and mycophenolate mofetil (MMF) does not lead to a higher incidence of PRTDM than cyclosporine and MMF (19).

The diabetogenic effect of (CSA) has been difficult to show in some studies in which patients did not receive steroids, which raised the hypothesis that there may be an interaction between (PRD) and (CSA) that could result in more adverse effects than with either agents alone. CSA has the potential to inhibit the metabolism of steroids by the P-450 system, thereby increasing the level of steroids and the frequency of such toxicities as PRTDM. (20)

Along with the potential interaction of (CSA) with steroids and increased insulin, the mechanism by which (CSA) leads to PTDM probably involves diminished insulin production, inhibited secretion of insulin, and a reduction in beta cell volume (21-25).

All renal transplant recipients should be screened for diabetes mellitus. As among non-transplant diabetic patients, American Diabetes Association treatment guidelines should be followed. Patients with PRTDM should establish a healthy (weight-reducing, if necessary) diet with a structured exercise program. Depending on the level of hyperglycemia, treatment with oral hypoglycemic agents and insulin may be indicated. Sulfonylurea agents are often used to treat mild to moderate hyperglycemia in transplant recipients. However, most of these agents are excreted renally and should be used with caution in the presence of any renal dysfunction. Prolonged hypoglycemia can occur with long-acting sulfonylurea agents in the presence of renal dysfunction (26). Metformin, which acts by inhibiting hepatic glucose metabolism and is effective only in the presence of insulin, is the preferred treatment for overweight diabetic patients because it does not cause an increase in insulin secretion and may facilitate weight loss. (27).

The dose of metformin may also need to be reduced in patients with compromised allograft function. Careful monitoring of blood glucose and glycosylated hemoglobin concentration is essential. Just as with any patient with diabetes mellitus, instruction regarding ophthalmological evaluation are important preventive measures. Referral to diabetologist may also be of benefit. (26)

Aims of the study

Study the prevalence of diabetes mellitus in renal allograft recipients.
Study the possible risk factors that contributed to or associated with the development of post transplant diabetes mellitus.
Study the association between immunosuppressive medications and development of

**PRTDM**

Patients and methods

This study was conducted on a kidney transplant recipients who presented to the clinic that follow renal transplant recipients in marjan hospital from November 2006 to November 2007.
The medical records of 97 renal transplant recipients were retrospectively reviewed. Recipients with no known diabetes mellitus prior to transplantation and with at least two months post transplant follow-up were selected for this study. 79 patients were male and 18 patients were female, their age ranging from 15 years to 64 years. Blood sugar measurement were done by glucose oxidase method. PTDM was diagnosed according to American diabetes association/WHO criteria or the need to start insulin or an oral hypoglycemic agents(15,28), namely, fasting plasma glucose (FPG) > 7.0 mmol/l on two separate occasions, or casual plasma glucose > 11.1 mmol/l with symptoms of diabetes mellitus, including polyuria, polydypsia, and unexplained weight loss(30).

The following parameter were studied: age, sex, hypertension; family history of diabetes mellitus (grandparents, parents, sibling, brothers, sisters), immunosuppressive medication and their dialy dose, body mass index, donors whether relative or not. Hypertension was defined as: The diastolic blood pressure measurement on at least two occasions was 90 mm Hg or higher, or the systolic blood pressure on two or more occasions was consistently greater than 140 mm Hg, or they were already on antihypertensive drugs(29).

For all patients, history was taken with proper clinical examination weight and height calculated. FBS was done for all patients. Body mass index (BMI) was calculated as

\[ \text{BMI} = \frac{\text{weight (kg)}}{\text{height (square meter)}} \]

BMI was defined as normal ( < 25 kg/m\(^2\) ), overweight ( 25-30 kg/m\(^2\) ), or obese ( > 30 kg/ m\(^2\) ).

The dominant immunosuppressive regimen have been used in our patients following kidney transplantation include three drugs combination regimen: prednisolon (5-15 mg dialy), azathioprine (50-100 mg daily), cyclosporine A (100-400 mg daily).

**Statistical methods:**

Descriptive statistics: Statistical tables, arithmetic mean, standard deviation, and graphic presentation.

Differential statistics: Fisher exact test, Chi-square test and students-t test when appropriate. (P value < 0.05) considered the levels of significance.

**Results**

In this clinical study, the total number of recipients was 97, those with PTDM were 20 patients (20.62%). 79 recipients were male, 18 recipients were female. (table I). The mean age of all recipients was 35.25 ± 8.02 years. The mean age of patients with PTDM was 36.33 ± 10.28 years, while that of recipients with out diabetes was 34.75 ± 6.21 years. (table II).

Table III showed the immunosuppressive drugs used as maintenance treatment. Steroid was used in all patients (diabetics and non-diabetics). Azathioprine was used in 88.65% of all patients. 85% of patients with PTDM were on AZA versus 89.61% of patients without diabetes. Cyclosporine A was used in 97.93% of all patients and used in all patients with PTDM 100% (20 patients), while 97.4% in those with no diabetes. Triple therapy (PRD, AZA, CSA) was used in 86.59% of all patients, 85% in those with PTDM versus 87.01% in those with no diabetes.

All renal allograft were from living donors. The grafts were from related donors in 50.52% of all patients. In patients with PTDM the number of unrelated donors were
13(65%), while in patients with no diabetes the number of unrelated donors were 35(45.45%). This difference was statistically significant (p<0.05), (table IV).

The average dose of PRD was 10 ± 1.42 mg/day. The average dose of CSA was 234±53 mg/day (table V).

Family history of diabetes was presents in 28 patients of all recipients (28.86%). 6 patients with PRTDM showed family history of diabetes (30%), while 22 patients (28.57%) without diabetes showed family history of diabetes (Table VI).

Body mass index of all recipients was 27.59±4.1, It was 28.49±3.52 in diabetes patients and 25.21±4.69 in those without diabetes with statistically significant differance (P value < 0.05). (Table VII).

Table VIII showed the prevalence of hypertension. Patients with PRTDM showed higher prevalence of hypertension 65% compared to those with no PRTDM 53.24% with statistically significant difference (P < 0.05), the prevalence of hypertension in all patients was 55.67%. (figure I).

All diabetics patients were on treatment except 4 patients were on diet control only (20%). Six patients (30%) were on insulin. All other patients 10 (50%) were on oral hypoglycemic agents mostly glibenclamide. (table IX), (figure II)

### Tables and Graphs

**Table I** Distribution of patients according to sex and presence of diabetes

<table>
<thead>
<tr>
<th></th>
<th>PRTDM</th>
<th>NO DM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>61</td>
<td>79</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>20.62%</td>
<td>79.38%</td>
<td>81.44%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>20.78%</td>
<td>18.56%</td>
</tr>
<tr>
<td>P &gt; 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table II** Distribution of patients according to mean age and presence of diabetes

<table>
<thead>
<tr>
<th></th>
<th>PRTDM</th>
<th>NO DM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>36.33±10.28</td>
<td>34.75±6.21</td>
<td>35.25±8.02</td>
</tr>
<tr>
<td>P &gt; 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table III**

Immunosuppressive drugs
**Table IV**  
Relation between donors and recipients

<table>
<thead>
<tr>
<th></th>
<th>PRTDM 20</th>
<th>NO DM 77</th>
<th>Total 97</th>
<th>Related Donors</th>
<th>Unrelated Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Donors</td>
<td>7</td>
<td>42</td>
<td>49</td>
<td>35 %</td>
<td>65 %</td>
</tr>
<tr>
<td>Unrelated Donors</td>
<td>13</td>
<td>35</td>
<td>48</td>
<td>54.54 %</td>
<td>45.45 %</td>
</tr>
</tbody>
</table>

**Table V**  
Average dose of immunosuppressive Drugs

<table>
<thead>
<tr>
<th></th>
<th>PRTDM (mg / day)</th>
<th>NO DM (mg / day)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRD</td>
<td>10</td>
<td>10</td>
<td>10 ± 1.42</td>
</tr>
<tr>
<td>CSA</td>
<td>237 ± 52</td>
<td>232 ± 53</td>
<td>233 ± 53</td>
</tr>
</tbody>
</table>

**Table VI**
Family history of diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>PRTDM 20</th>
<th>NO DM 77</th>
<th>Total 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of diabetes</td>
<td>6 30%</td>
<td>22 28.57%</td>
<td>28 28.86%</td>
</tr>
<tr>
<td></td>
<td>0.05&gt;P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table VII
Body mass index

<table>
<thead>
<tr>
<th></th>
<th>PRTDM</th>
<th>NO DM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>28.49 ± 3.52</td>
<td>25.21 ± 4.69</td>
<td>27.59 ± 4.1</td>
</tr>
</tbody>
</table>

P . value < 0.05 significant

Table VIII
Prevalence of hypertension

<table>
<thead>
<tr>
<th></th>
<th>hypertension</th>
<th>No hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRTDM 20</td>
<td>13 65%</td>
<td>7 35%</td>
</tr>
<tr>
<td>NO DM 77</td>
<td>41 53.24%</td>
<td>36 46.75%</td>
</tr>
<tr>
<td>Total 97</td>
<td>54 55.67%</td>
<td>43 44.32%</td>
</tr>
<tr>
<td></td>
<td>0.05 &lt;P</td>
<td></td>
</tr>
</tbody>
</table>

Table IX
Management of diabetic recipients

<table>
<thead>
<tr>
<th>Diet control</th>
<th>insulin</th>
<th>Oral hypoglycemic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 20%</td>
<td>6 30%</td>
<td>10 50%</td>
</tr>
</tbody>
</table>
Discussion
PRTDM developed in 20.62% of the patients in our study (table I) , which was within the 2% to 53% range of published reports.(30)
There has been significant variability in the reported incidence of PRTDM, most likely due to the criterion used to diagnose PRTDM are variable among studies and to the immunosuppressive drugs used (31 , 32 ). In our study, PRTDM was diagnosed according to the American Diabetes Association / WHO criteria or the need to start insulin or an oral hypoglycemic agent.
Male who developed PRTDM were 90% of all Male recipients , while Females who developed PRTDM were 10% of all Female recipients In general , Female recipients were 18.56% of all recipients (table I) few studies show male gender is risk factor for PRTDM however in our study this difference was not significant.
Several studies showed that transplant recipient who develop PRTDM are consistently older than patients without this complication (37). In our study the mean age of all
recipients was 35.25 ± 8.02 years, the mean age of patients with PRTDM was 36.33 ± 10.28 years, while that of patients without PRTDM was 34.75 ± 6.21 years (table II). This difference was statistically not significant (P > 0.05).

In our patients the treatment initially was triple therapy consisting of (PRD, AZA, CSA) in 86.59% of all recipients, (table III) so the incidence of DM after renal transplantation is double than general population because of using immunosuppressive drugs: in our study we cannot blame which drug is more diabetogenic because all recipients receive the same immunosuppressive regimen.

Other studies showed that regimens containing CSA had higher incidence for PRTDM in our patients although 100% of PRTDM were take CSA but need to compare with those who take other regimens to confirm the diabetogenicity of CSA.

In our study, all transplants were from living donors, 50.52% were from related donors, other were from unrelated donors (table IV).

65% of patients with PRTDM were transplanted from unrelated donors while 45.45% in those without PRTDM so the prevalence of unrelated donors in diabetic patients was more than that in non diabetic patients with statistically significant (P < 0.05). This may be explained by increase number of HLA mismatches in those from unrelated donors. Other studies showed increase PRTDM with increase numbers of mismatches.

The average dose of PRD was 10 ± 1.42 mg, there was no difference between those patients who developed PRTDM and those who did not. The average dose of CSA was 234± 53 mg/day the average dose in patients with PRTDM was 237 ± 52 mg / day, and that of patients with no PRTDM was 232 ±53 mg/day, the difference was statistically not significant (P > 0.05) (table V) however some studies proved that recipients with acute rejection and high doses of steroid giving after transplantation more liable for PRTDM in our study all patients were on same dose of steroid and may give the negative results.

Family history of diabetes mellitus may increase the risk for developing PRTDM (16).

In this study family history of diabetes was present in only 28 patients (28.86%) of all recipients, Only 6 patients with PRTDM had history of diabetes (table VI), In comparison to 22 patients with no PRTDM (30% Vs 28.57%).

Other factor linked with the development of PRTDM is increasing BMI (39, 40). Obesity after transplantation, like obesity in the general population, has been highly associated with diabetes and hypertension (39, 41) in this study, BMI of recipients with PRTDM was 28.49 ± 3.52 while that of recipients with no PRTDM was 25.21 ± 4.69 (table VII).

Both groups of patients are in the over weight index, the BMI of diabetic patients is higher than that of non diabetic patients, this difference was statistically significant (P < 0.05). It is clear that over weight was obvious in diabetic patients. This also may explain the high prevalence of hypertension among this population (table VIII).

Depending on the level of hyperglycemia, treatment with oral hypoglycemia agents and insulin may be indicated. Around 40% of patients with PRTDM require insulin (38). Sulfonylurea agents are often used to treat mild to moderate hyperglycemia in transplant recipients. However, most of oral hypoglycemic agents are excreted renally and should be used with caution in the presence of any renal dysfunction or the potential for renal dysfunction (26). In this study 50% of patients were on oral hypoglycemic agents and 30% were on insulin while 20% were on diet control only (table IX).

Although hypertension occurred in 40 – 50% of transplant recipients in the pre CSA era, now nearly 75% of all transplant recipients will have hypertension (42). Between 80% and 90% of patients with end stage renal disease by time will be hypertensive. Once on dialysis, the percentage of patients who remain hypertensive still remain high.
with 50 – 60% of patients on hemodialysis and approximately 30% of those on peritoneal dialysis being hypertensive (43). In our study, patients with PRTDM showed higher prevalence of hypertension in post transplant period when compared to those without PRTDM (65% versus 53.24%) with statistically significant difference (P < 0.05).

Conclusion and Recommendations

The prevalence of PRTDM is still high among this precious population. Higher BMI and hypertension may associate with the development of PRTDM. Related donors may show lower association with diabetes than unrelated donors. Achievement of optimum body weight is advisable as obesity contributes to hyperglycemia and hypertension. Further prospective studies are needed that take groups of recipients with different immunosuppressive regimens and compare between them.

References


UK. Prospective Diabetes Study (UKPDS) Group


30. V.M. Montoni, J.A. Velosa and A. Basu et al., posttransplantation diabetes a systemic review of the literature, Diabetes Care 25 (2005), P 583.


33. J. Hjelmesaeth, A. Hartmann and J. Kofstad et al., Glucose intolerance after renal transplantation depends up on prednisolone dose and recipient age, transplantation 64(1997), P.979.


42. William E Braun: The medical management of the renal transplant recipients Comprehensive Clinical Nephrology Harcourt publishers limited, Spain, first ed. 2000; Sec7: ch 44.1.

43. Robert C Davidson, Suhail Ahmad: Hypertension Comprehensive Clinical Nephrology Harcourt publishers limited, Spain, first ed. 2000, Sec7: ch 44.1.