Posttransplant Metabolic Complications in Living-Related Renal Allograft Recipients of Kashmir Valley

Irfan A. Shera, Qayser Yousuf, Mushtaq A. Mir, Intiyaz A. Wani, M. Saleem Najar

Abstract

Objectives: Renal transplant offers a definitive therapeutic modality for patients with end-stage renal disease; however, 50% to 70% of these patients have graft dysfunction after the transplant. Proactive prevention management of metabolic complications may reduce posttransplant morbidity and mortality in these patients.

Materials and Methods: A retrospective and prospective review of 120 kidney transplant recipients during 5 years’ follow-up was performed to analyze the incidence and status of the various metabolic complications after a renal transplant.

Results: In our study, postrenal transplant diabetes mellitus was seen in 9 of 120 patients (7.5%). The incidence of posttransplant diabetes mellitus was 5% in tacrolimus-treated patients (n=6) compared with 2.5% in cyclosporine-treated patients (n=3). Dyslipidemia, as hypercholesterolemia and hypertriglyceridemia, was seen in 31 recipients (25.83%). Significant posttransplant hyperlipidemia was documented (P < .05). Further, it was noted that 25 patients who developed hyperlipidemia (20.83%) were taking cyclosporine-based therapy, while 6 were treated with tacrolimus-based therapy (5%; P < .05). However, most subjects with hyperlipidemia had renal graft dysfunction. Posttransplant erythrocytosis affected 9 renal transplant recipients (7.5%) with a mean (± SD) hematocrit of 41.3% ± 6.7%. A statistically significant correlation was seen between prerenal and postrenal transplant hematocrit by 12 months. Hyperparathyroidism was observed in 1 renal transplant patient (1.25%).

Conclusions: On the basis of this study, we conclude that posttransplant diabetes mellitus occurred in 7.5% patients, hypercholesteremia and hypertriglyceridemia occurred in 25.83% patients, posttransplant erythrocytosis affected 7.5% patients, and hyperparathyroidism occurred in 1 renal transplant patient (1.25%). Moreover, dyslipidemia contributed to progressive graft dysfunction.

Key words: Posttransplant diabetes mellitus, Dyslipidemia, Erythrocytosis, Hyperparathyroidism, Renal transplant

Introduction

Renal transplant offers a definitive therapeutic modality for patients with end-stage renal disease. However, the potential adverse effects of the immunosuppressive regimens lead to various complications. Proactive management in preventing the metabolic complications may reduce the posttransplant morbidity and mortality in this population.

Posttransplant diabetes mellitus

The development of posttransplant diabetes mellitus (PTDM) is a significant metabolic complication of renal transplant that is associated with cardiovascular morbidity and mortality and contributes to reducing graft and patient survival. However, the incidence and prevalence of PTDM varies among studies depending on the criteria used to diagnose diabetes, the use or kinds of immunosuppressants, the characteristics of the
subject, and the length of follow-up. Posttransplant diabetes mellitus is an adverse effect associated with corticosteroid, cyclosporine, or tacrolimus use. Historically, immunosuppressive regimens consisting of corticosteroids and azathioprine have been associated with an incidence of PTDM as high as 46%. Recently, the incidence of PTDM related to cyclosporine-based and corticosteroid-based regimens has been reported to be as high as 20% among kidney allograft recipients.

According to a report by Roth and associates, graft survival between diabetic and nondiabetic patients after transplant was 71% and 86% the third year after transplant, and 54% and 82% during the fourth year after transplant. Hagen and associates reported that impaired insulin secretion was the dominant mechanism for the development of PTDM. In insulin-secreting cells, calcineurin is involved in stimulating insulin gene transcription by activating the transcription factor, that is, nuclear factor of activated T cells. The association between PTDM and calcineurin inhibitor drugs is well established. Previous in vitro studies on purified islets and insulin-producing β cells have proposed several diabetogenic actions for cyclosporine and tacrolimus. Both drugs impair insulin secretion, decrease insulin content of β cells, and impair insulin transcription, although the primary mechanisms are not yet fully understood.

Posttransplant diabetes mellitus complicates the course of treatment in 5% to 10% of patients on cyclosporine-based immunosuppressive therapy. It is more common in black patients and in those with a family history of glucose intolerance. In one multicentric trial, PTDM occurred with greater frequency in patients treated with tacrolimus.

Posttransplant dyslipidemia
In posttransplant dyslipidemia (PTD), approximately two-thirds (66.7%) of transplant recipients have low-density lipoprotein or total cholesterol levels signifying increased cardiac risk; 29% have elevated triglyceride levels 2 years after transplant. Not only is hyperlipidemia a clear risk factor for coronary disease, but it also may contribute to the progressive graft dysfunction associated with chronic rejection. Dyslipidemia is a frequent finding after transplant, and immunosuppressive medications play a central role in its pathogenesis. Historically, the prevalence of hyperlipidemia in renal transplant recipients has been reported as being higher than 80%; however, recent data that reflect the use of more-modern immunosuppressive regimens report that approximately 44% of renal transplant recipients have low-density lipoprotein concentrations greater than 5.6 mmol/L (100 mg/dL) 6 months after the transplant. In a long-term study by Kimak and associates, transplant patients showed that they had a disturbed lipoprotein composition and its consequence was hyperlipidemia, perhaps partly because of the increased use of immunosuppressants and steroids.

Corticosteroids have multiple potential deleterious effects on cholesterol metabolism, including an increase in the activity of acetyl-coenzyme A carboxylase and free fatty acid synthetase, down-regulation of low-density lipoprotein receptor activity, increase in the activity of HMG-CoA reductase and inhibition of lipoprotein lipase.

Posttransplant erythrocytosis
Posttransplant erythrocytosis (a hematocrit of >52%) affects 5% to 10% of renal transplant recipients, most commonly males with excellent allograft function. Posttransplant erythrocytosis occurs primarily during the first year after the transplant, and is characterized by inappropriate elevation of erythropoietin. Predictors for posttransplant erythrocytosis include male sex, diabetes mellitus, pretransplant hematocrit greater than 30%, an absence of rejection, and excellent renal allograft function. The pathogenesis of erythrocytosis remains unknown; it may be multifactorial. Although phlebotomy previously has been advocated to treat some drugs (eg, angiotensin-converting enzyme inhibitors), angiotensin-II receptor antagonists and adenosine receptor antagonists have been used to manage this complication.

Posttransplant hyperparathyroidism
The effects of renal transplant on secondary hyperparathyroidism have been well documented. It is well-recognized that patients with end-stage renal disease have altered bone mineral metabolism and hyperplastic parathyroid glands. Age, duration of dialysis before the transplant, parathyroid gland size, and development of nodular or monoclonal hyperplasia of the parathyroid glands are the main factors responsible for persistent hyperparathyroidism. Hypercalcemia after
transplant may indicate failure of hyperplastic parathyroid glands to regress. Persistent hyperparathyroid activity may require subtotal parathyroidectomy.34

Materials and Methods

A retrospective and prospective study was conducted in the Department of Nephrology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) from July 2007, for 5 years, to analyze the incidence and status of renal transplant recipients with posttransplant diabetes mellitus, posttransplant dyslipidemia, posttransplant erythrocytosis, posttransplant hyperparathyroidism, and other posttransplant complications. One hundred twenty renal transplant recipients attending our outpatient nephrology services who had undergone either a transplant at SKIMS, or outside the Kashmir valley, were regularly followed-up. After receiving approval from the hospital ethical committee, patients with renal transplants in the outpatient department were considered. Upon initial contact, subjects were told about the protocol, and written informed consent was obtained. All protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. All subjects gave a detailed history and had a general physical examination and systemic examination. Data were collected from the charts of the patients being followed-up by the renal transplant unit of SKIMS hospital. Patient demographics such as age at transplant, sex, and type of transplant were recorded.

Statistical analyses

A descriptive analysis of results was undertaken and expressed in percentages. For discrete variables, comparisons between different groups was done with a chi-square test, and for continuous variables we used a t test. A P value < .05 was taken to be statistically significant. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 11.5, IBM Corporation, Armonk, NY, USA).

Results

Table 1 shows the age and sex distribution of our study population. The mean age (± SD) was 36.44 ± 15.79 years. Men outnumbered women (10.83%). The mean age of the donors was 37.80 ± 10.9 years. All the studied subjects were live-related donor renal allograft recipients.

Table 2 shows the posttransplant complications in the renal transplant recipients. The majority of patients (n=41; 34.16%) were anemic after receiving their renal transplant. Besides anemia, other hematologic complications seen were neutropenia in 7 renal transplant recipients (6.25%) and posttransplant erythrocytosis in 9 recipients (7.5%). Among infections, urinary tract infection was the most commonly seen in 35 patients (29.16%), sepsis develop in 13 patients (11.25%), cytomegalovirus infection developed in 4 patients (3.75%), and hepatitis B virus infection was seen in 3 renal transplant recipients (2.5%). In our study, acute graft rejection occurred in 27 patients (22.5%), and chronic graft rejection occurred in 19 of renal transplant recipients (16.25%). Dyslipidemia was found in 31 patients (25.83%), PTDM occurred in 9 patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>41</td>
<td>34.16</td>
</tr>
<tr>
<td>UTI</td>
<td>35</td>
<td>29.16</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>31</td>
<td>26.25</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>27</td>
<td>22.5</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>19</td>
<td>16.25</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13</td>
<td>11.25</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Posttransplant erythrocytosis</td>
<td>9</td>
<td>7.5</td>
</tr>
<tr>
<td>Posttransplant diabetes mellitus</td>
<td>9</td>
<td>7.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>6.25</td>
</tr>
<tr>
<td>CMV</td>
<td>4</td>
<td>3.75</td>
</tr>
<tr>
<td>HBV</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Iliac vessel thrombosis</td>
<td>4</td>
<td>3.75</td>
</tr>
<tr>
<td>Posttransplant hyperparathyroidism</td>
<td>1</td>
<td>1.25</td>
</tr>
<tr>
<td>CNI nephrotoxicity</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Acne</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Gum hypertrophy</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Drug-induced toxicity</td>
<td>1</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; CNI, calcineurin inhibitor; HBV, hepatitis B virus; UTI, urinary tract infection
(7.5%), and hyperparathyroidism occurred in 1 of renal transplant patients (1.25%).

Lymphocele was the most common complication seen in 12 renal transplant recipients (10%), and iliac vessel thrombosis was seen in 4 of our patients (3.75%). In our study, drug-induced toxicity, like acne, was seen in 3 patients (2.5%), gum hypertrophy in 3 patients (2.5%), and neurotoxicity was seen in 1 renal transplant recipient (1.25%). Calcineurin inhibitor-induced nephrotoxicity was seen in 3 renal transplant recipients (2.5%).

In our study, PTDM was seen in 9 of 120 subjects (7.5%); the incidence of PTDM was in 6 tacrolimus-treated patients (5%), compared with 3 in the cyclosporine-treated patients (2.5%; Table 3). Dyslipidemia, in the form of hypercholesterolemia and hypertriglyceridemia was observed in 31 of the renal allograft recipients (25.83%). Statistically significant posttransplant hyperlipidemia was documented \((P < .05)\). Further, 25 patients who developed hyperlipidemia were being treated with cyclosporine-based therapy (20.83%), while 6 were being treated with tacrolimus-based therapy (5%; \(P < .05\); Table 3). Most subjects with hyperlipidemia had renal graft dysfunction.

Figure 1 shows the pretransplant and posttransplant hematocrit of the subjects as mean ± SD (41.3% ± 6.7%). A statistically significant correlation between prerenal and postrenal transplant was seen for 12 months.

Figure 2 shows the prerenal and postrenal transplant lipid profiles of the subjects. Mean serum cholesterol was 4.98 ± 0.82 mmol/L (192.8 ± 31.9 mg/dL). The mean difference found was 0.8 mmol/L (31.2 mg/dL). Similarly, the mean serum triglyceride level was 5.68 ± 1.82 mmol/L (219.7 ± 70.5 mg/dL). The main difference was 1.28 mmol/L (49.7 mg/dL). The results of our study show statistically significant correlations between prerenal and postrenal transplant lipid parameters.

### Table 3. Comparison of Posttransplant Disease Incidence With Immunosuppressive Regimens

<table>
<thead>
<tr>
<th>Incidence of Disease</th>
<th>Tacrolimus-Treated Patients</th>
<th>Cyclosporine-Treated Patients</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>6</td>
<td>3</td>
<td>.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

This study aimed to examine the status and analyze the incidence of posttransplant metabolic complications like PTDM, dyslipidemia, erythrocytosis, and hyperparathyroidism in the live-related donor renal transplant recipients. The incidence of PTDM was 5% in tacrolimus-treated patients \((n=6)\) compared with 2.5% in cyclosporine-treated patients \((n=3); P < .05\). This result is consistent with other studies.

A recent retrospective study by First and associates showed that the incidence of posttransplant diabetes mellitus was 4.9% in tacrolimus-treated patients compared to 3.3% in cyclosporine-treated patients \((P = .453)\). In another study using data from the US renal data system, Kasiske and associates showed that the 11 659 medicare beneficiaries who received their first kidney transplant between 1996 and 2000 showed the cumulative incidence of PTDM to be 9.1%, 16.5%, and 24%, at 3, 12, and 36 months after the transplant.

In our study, posttransplant dyslipidemia as hypercholesterolemia and hypertriglyceridemia was...
observed in 31 renal allograft recipients (25.83%). Significant \((P < .05)\) posttransplant hyperlipidemia was documented. Further, 25 patients who developed hyperlipidemia were taking cyclosporine-based therapy (20.83%), while the rest were treated with tacrolimus-based therapy \((n=6; 5\%)\). It also was observed that most subjects with hyperlipidemia had renal graft dysfunction. Kasiske and associates showed the prevalence of posttransplant hyperlipidemia ranged from 16% to 78%. The incidence of posttransplant hyperlipidemia primarily has been studied in patients managed on cyclosporine-based immunosuppressive regimen. A study by Kimak and associates showed that transplant patients in a long-term study had disturbed lipoprotein composition, and its consequence was hyperlipidemia, perhaps partly because of the increased use of immunosuppressants and steroids.

We also saw that posttransplant erythrocytosis occurred in 9 renal transplant recipients \((7.5\%)\), all were men with good renal function. Although the erythrocytosis resolved spontaneously in 2 patients, the rest required serial phlebotomy and small dosages of angiotensin II receptor antagonist. This result agrees with the study of Gaston and associates, who found posttransplant erythrocytosis \((a \text{ hematocrit} > 52\%)\) affects 5% to 10% of renal transplant recipients, most commonly men, with excellent allograft function. It usually occurs during the first year after transplant.

We also saw that posttransplant hyperparathyroidism occurred in 1 renal transplant patient \((1.3\%)\). The patient presented with asymptomatic hypercalcemia in the third month after the transplant. In most patients, a decrease in parathyroid hormone occurs by approximately 1 year after the renal transplant. However, some renal transplant recipients continue to have elevated level of parathyroid hormone.

In conclusion, after analyzing 120 kidney transplant recipients for 5 years, we found the following:

- **Posttransplant diabetes mellitus** occurs in 7.5% patients of kidney transplant recipients, and the incidence was high in tacrolimus-treated patients.
- **Hypercholesteremia** and **hypertriglyceridemia** occur in 25.83% patients of renal allograft recipients. Most of them \((20.83\%)\) were treated with cyclosporine-based therapy, and dyslipidemia was a contributing factor for progressive graft dysfunction.
- **Posttransplant erythrocytosis** affected 7.5% of all renal transplant recipients, all were men with excellent allograft function.
- **Postrenal transplant hyperparathyroidism** was seen in 1.25% of renal transplant recipients.

### References


