Glucose Metabolism in Renal Transplant Recipients on Tacrolimus: The Effect of Steroid Withdrawal and Tacrolimus Trough Level Reduction

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Abstract. The relative role of steroids and tacrolimus in the development of glucose metabolic disorders and hyperlipidemia after renal transplantation has not yet been clearly established. Therefore, glucose metabolism was prospectively evaluated by intravenous glucose tolerance test, as was lipid profile, in fifteen white nondiabetic renal transplant recipients three times: before and after steroid withdrawal and after tacrolimus trough level reduction. After withdrawal of 10 mg of prednisolone, insulin resistance decreased (fasting C-peptide, 0.99 to 0.77 nmol/L [P < 0.0009]; fasting insulin, 9.5 to 8.1 mU/L [P = 0.09]; insulin/glucose ratio, 1.85 to 1.45 mU/mmol [P = 0.10]) and lipid levels decreased (total cholesterol, 5.1 to 4.2 mmol/L [P = 0.006]; HDL cholesterol, 1.4 to 1.1 mmol/L [P = 0.01]; LDL cholesterol, 3.0 to 2.5 mmol/L [P = 0.15]; triglycerides, 1.52 to 0.91 mmol/L [P = 0.02]). After tacrolimus trough level reduction from 9.5 to 6.4 ng/ml, pancreatic β-cell secretion capacity improved (C-peptide secretion increased from 49.0 to 66.6 nmol × min/L [P = 0.04] and insulin secretion increased from 1134 to 1403 mU × min/L [P = 0.06]). HbA1c improved also, from 5.9 to 5.3% (P = 0.002). Lipids did not change. In conclusion, steroid withdrawal resulted in a decrease in insulin resistance and a reduction in lipids, and tacrolimus trough level reduction resulted in an improved pancreatic β-cell secretion capacity. Therefore, these therapeutic measurements may contribute to the reduction of the cardiovascular morbidity and mortality in renal transplant recipients.

Both posttransplant diabetes mellitus (PTDM) and hyperlipidemia contribute to cardiovascular mortality and graft failure after transplantation (1–4). PTDM occurs in up to 36% of transplant patients (4–9). PTDM develops because of impairment of insulin secretion and/or increase of insulin resistance. Patients with an impaired β-cell function before transplantation are mainly at risk for developing PTDM during use of calcineurin inhibitors (10–11). In dialysis patients, we were able to demonstrate that tacrolimus caused impaired insulin secretion but had no influence on insulin resistance. However, insulin resistance has been suggested as an additional mechanism responsible for the development of PTDM during maintenance therapy with tacrolimus in renal transplant recipients (5). The coadministration of steroids might well have been the cause of this increased insulin resistance (10,12).

Hyperlipidemia occurs in many patients after solid organ transplantation (13). The type of calcineurin inhibitor plays a role in the hyperlipidemia; lipid profiles in renal transplant recipients treated with tacrolimus were better than those in patients treated with cyclosporine (14–15).

Aside from causing other side effects (16), steroids play a role in the development of both PTDM and posttransplant hyperlipidemia (17–18). Several investigators have shown that steroid withdrawal is safe in a large proportion of transplant recipients (15,19). Since then, improvement in lipid profile after steroid withdrawal on both cyclosporine and tacrolimus-based immunosuppression has been described in liver transplant recipients (20). In renal transplant recipients, lipid profile improvement after steroid withdrawal has been reported only in patients on cyclosporine (21–22) but not in patients on tacrolimus. In renal transplant recipients on tacrolimus, it is unknown what the effects are of steroid withdrawal on glucose metabolism. Not only the use of steroids, but also tacrolimus exposure, are important factors that influence glucose metabolism, because it is a well known observation that PTDM disappears in a high proportion of the patients after tacrolimus dose reduction (23). The relative role of steroids and tacrolimus levels in the development of glucose metabolic disorders and hyperlipidemia is unknown. Therefore, we prospectively evaluated glucose metabolism and lipid profile in renal transplant recipients on tacrolimus-based immunosuppression three times: before and after steroid withdrawal, and subsequently, after tacrolimus trough level reduction.

*Both authors contributed equally to this study.

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Materials and Methods

Patients
Renal transplant recipients on tacrolimus and prednisolone were eligible to participate in the study if they were \( \geq 16 \) yr of age and scheduled for steroid withdrawal between 3 and 12 mo posttransplantation after obtaining a normal ACTH stimulation test. Additional use of mycophenolate mofetil (MMF) was allowed. Exclusion criteria were as follows: contraindications for steroid withdrawal (defined as severe acute rejection [grade 2 or more in the Banff classification] or steroid-resistant rejection), use of steroids for comorbidity, pre-existing diabetes mellitus or development of PTDM before the first test (defined as a need for oral blood glucose–lowering medication or insulin), and underlying disease known to interfere with the hypothalamic-pituitary-adrenal axis or glucose metabolism. Written informed consent was obtained from all patients. The medical ethical committee of our hospital approved the protocol of steroid withdrawal.

Fifteen white patients (13 men, 2 women) participated in the study. Their median age was 58 yr (range, 16 to 75 yr), and their median body mass index (BMI) was 23.8 kg/m\(^2\) (range, 20.4 to 27.5 kg/m\(^2\)). There were 13 first transplantations and 2 retransplantations; 12 patients had a cadaveric donor, 2 a living unrelated donor, and 1 a living related donor.

Immunosuppression
All patients started tacrolimus (0.1 mg/kg orally twice daily) within 12 h before transplantation. Further dosage adjustments were made according to whole blood 12-h trough levels (Imx, Abbott, Hoofddorp, The Netherlands). The target range was 15 to 20 ng/ml in weeks 1 and 2 posttransplantation and 10 to 15 ng/ml in weeks 3 and 4. Thereafter, the dose was gradually tapered to target levels below 10 ng/ml. Immediately after transplantation, 14 patients were also treated with MMF (1000 mg/d). At the time of the first and second intravenous glucose tolerance tests (IVGTT), nine patients were still using MMF. At the time of the third tests, four patients were still using MMF. The prednisolone dose was 20 mg in weeks 1 and 2 and 15 mg in weeks 3 and 4 after transplantation. Thereafter, the dose was 10 mg until withdrawal. Withdrawal was started at a median of 185 d (range, 81 to 358 d) after transplantation. The prednisolone dosage was reduced to 5 mg/d for 1 wk and 2.5 mg/d for a second week; thereafter it was stopped. For each patient, we aimed for the same individual tacrolimus trough level before and after steroid withdrawal. After the second test, tacrolimus dosages were adjusted gradually to reach target trough levels of 5 to 7 ng/ml.

Glucose Metabolism
The tests were performed in the morning, after a 12-h overnight fast. Tacrolimus was ingested after completion of the tests. The other medication was ingested at the usual time of day. In case of a stressful event (e.g., surgery or infection), the test was postponed for at least 3 wk.

Glucose 50% (0.5 g/kg body wt) was administered intravenously for 2 to 3 min. Blood samples for measurement of whole blood glucose, C-peptide, and insulin were taken from the opposite arm at \( t = -15, 0, 5, 10, 15, 20, 30, 40, 50, \) and 60 min. Insulin sensitivity index (glucose disappearance rate \( = \Delta G \)) was calculated by linear regression from the log-transformed glucose values of \( t = 10 \) to 30 min. A \( \Delta G \) value >1.2 mmol/L per min was considered normal (24–25). C-peptide and insulin secretion (increment), i.e., the secretion response to a glucose load, were calculated as area under the curve using a linear trapezoidal technique from the serum value at each time point after subtraction of the \( t = 0 \) value. Insulin resistance was calculated by using the fasting insulin/glucose ratio and the homeostasis model assessment (HOMA-R: fasting glucose [mmol/L] \times \) fasting insulin [mU/L]/22.5) (26–27). Mean BP, renal function (Cockcroft-Gault formula), hemoglobin, and HbA1c were measured at the time of the IVGTT. The use of drugs that might interfere with glucose metabolism (antihypertensive drugs [especially beta-blockers and diuretics], oral contraceptives, phenytoin, and pentamidine) and lipids were monitored.

During each visit to the outpatient clinic, urine was examined for glucosuria (by dipstick). When glucosuria was detected, whole blood glucose was examined. When no glucosuria was detected, whole blood glucose was evaluated at least every 3 mo. PTDM was diagnosed when glucose values were abnormal (>6.1 mmol/L in the fasting state or >7.8 mmol/L in the nonfasting state) for two or more different samples without any other explanation, such as additional high-dose steroids, infection, or operative stress.

For the measurement of glucose in whole blood, the CX7 (Beckman, Mijdrecht, The Netherlands) was used. For C-peptide and insulin, IRMA (Autodelfia; Wallac, Turku, Finland) was used. For HbA1c, HPLC (Variant 2; Biorad, Hercules, CA). Normal reference values from our laboratory were 3.1 to 6.1 mmol/L for fasting glucose, 1.0 to 25.0 mmol/L for fasting insulin, 0.12 to 1.20 mmol/L for fasting C-peptide levels, and 4.4 to 6.2% for HbA1c.

Lipid Profiles
Fasting blood samples for lipid measurements were taken at the time of the IVGTT. The LX (Beckman) was used to determine lipid levels: total cholesterol (Roche Diagnostics, Almere, The Netherlands), HDL cholesterol (Roche Diagnostics), LDL cholesterol (LDL precipitating reagent; Merck, Amsterdam, The Netherlands), and triglycerides (Synchron; Beckman). Normal reference values from our laboratory were 4.1 to 6.4 mmol/L for total cholesterol, 0.6 to 1.9 mmol/L for HDL cholesterol, 3.0 to 4.5 mmol/L for LDL cholesterol, and 0.80 to 1.94 mmol/L for triglycerides.

Throughout the study, no changes in lipid-lowering drugs were allowed.

Statistical Analyses
For statistical analysis, SPSS version 10.0 for Windows (SPSS Inc., Chicago, IL) was used. To compare glucose metabolism before and after steroid withdrawal, as well as before and after tacrolimus trough level reduction, the Wilcoxon matched-pairs signed rank sum test was performed. For correlations between the different parameters, the Spearman rho rank correlation coefficient was used. Statistical significance was defined as \( P < 0.05 \). Unless indicated otherwise, data are described as median (range).

Results
Table 1 shows median levels of BMI, mean BP, renal function, hemoglobin levels, tacrolimus trough levels, parameters of glucose metabolism, and lipid profiles before and after steroid withdrawal and after tacrolimus trough level reduction.

Patients and Immunosuppression
All patients completed the study. No person was treated for rejection. BMI and mean BP did not change significantly. Many patients were treated with antihypertensive drugs: beta-blockers \( (n = 11) \), diuretics \( (n = 2) \), calcium-antagonists \( (n = 9 \) to 12, at various time points), angiotensin-converting enzyme–inhibitors \( (n = 3 \) to 5 \), and vasodilators \( (n = 3 \) to 4 \). There were no significant changes in the use of the various antihypertensive drugs. Nobody used other drugs that might
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Steroid Withdrawal</th>
<th>After Steroid Withdrawal</th>
<th>After Trough Level Reduction</th>
<th>Steroid Withdrawal</th>
<th>Trough Level Reduction</th>
</tr>
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<tr>
<td>Patients and immunosuppression</td>
<td></td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 (20.4 to 27.5)</td>
<td>24.0 (19.6 to 27.7)</td>
<td>23.7 (21.0 to 29.1)</td>
<td>0.76</td>
<td>0.07</td>
</tr>
<tr>
<td>mean BP (mmHg)</td>
<td>103 (95 to 123)</td>
<td>102 (88 to 113)</td>
<td>102 (83 to 123)</td>
<td>0.27</td>
<td>0.97</td>
</tr>
<tr>
<td>creatinine clearance (ml/min)</td>
<td>61.3 (32.4 to 83.3)</td>
<td>56.6 (35.5 to 95.8)</td>
<td>65.5 (42.3 to 96.6)</td>
<td>0.61</td>
<td>0.002</td>
</tr>
<tr>
<td>hemoglobin level (mmol/L)</td>
<td>8.7 (7.3 to 10.4)</td>
<td>8.3 (6.8 to 9.7)</td>
<td>8.7 (7.2 to 9.8)</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>tacrolimus trough level (ng/ml)</td>
<td>8.2 (5.9 to 17.3)</td>
<td>9.5 (6.7 to 18.4)</td>
<td>6.4 (5.0 to 10.5)</td>
<td>0.78</td>
<td>0.004</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>fasting glucose (mmol/L)</td>
<td>5.3 (4.2 to 6.5)</td>
<td>5.4 (4.2 to 6.7)</td>
<td>5.2 (4.3 to 6.6)</td>
<td>0.39</td>
<td>0.23</td>
</tr>
<tr>
<td>fasting C-peptide (nmol/L)</td>
<td>0.99 (0.67 to 1.95)</td>
<td>0.77 (0.46 to 1.25)</td>
<td>0.76 (0.38 to 1.10)</td>
<td>0.0009</td>
<td>0.75</td>
</tr>
<tr>
<td>fasting insulin (mU/L)</td>
<td>9.5 (1.6 to 50.0)</td>
<td>8.1 (4.2 to 37.0)</td>
<td>7.6 (3.0 to 13.0)</td>
<td>0.09</td>
<td>0.87</td>
</tr>
<tr>
<td>HOMA-R (mmol/L × mU/L)</td>
<td>2.20 (0.38 to 11.56)</td>
<td>1.88 (1.03 to 8.72)</td>
<td>1.83 (0.69 to 3.06)</td>
<td>0.17</td>
<td>0.87</td>
</tr>
<tr>
<td>insulin/glucose ratio (mU/mmol)</td>
<td>1.85 (0.30 to 9.62)</td>
<td>1.45 (0.75 to 6.98)</td>
<td>1.52 (0.58 to 2.45)</td>
<td>0.10</td>
<td>1.00</td>
</tr>
<tr>
<td>K_G (nmol/L × min)</td>
<td>1.33 (0.93 to 2.53)</td>
<td>1.63 (0.58 to 3.95)</td>
<td>1.57 (0.54 to 5.92)</td>
<td>0.65</td>
<td>0.14</td>
</tr>
<tr>
<td>C-peptide secretion (nmol × min/L)</td>
<td>57.2 (39.0 to 150.1)</td>
<td>49.0 (33.4 to 132.7)</td>
<td>66.6 (37.7 to 176.0)</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>insulin secretion (mU × min/L)</td>
<td>1141 (597 to 4534)</td>
<td>1134 (473 to 4105)</td>
<td>1403 (823 to 5865)</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.0 (5.3 to 7.2)</td>
<td>5.9 (4.8 to 6.5)</td>
<td>5.3 (4.8 to 6.1)</td>
<td>0.17</td>
<td>0.002</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total cholesterol (mmol/L)</td>
<td>5.1 (3.8 to 6.7)</td>
<td>4.2 (3.4 to 6.0)</td>
<td>4.1 (3.5 to 6.0)</td>
<td>0.006</td>
<td>0.62</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.4 (1.0 to 2.1)</td>
<td>1.1 (0.9 to 1.7)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.0 (1.9 to 3.9)</td>
<td>2.5 (1.9 to 3.7)</td>
<td>2.6 (1.8 to 3.9)</td>
<td>0.15</td>
<td>0.44</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>1.9 (1.5 to 2.8)</td>
<td>2.1 (1.8 to 3.0)</td>
<td>2.4 (1.3 to 3.4)</td>
<td>0.16</td>
<td>0.45</td>
</tr>
<tr>
<td>triglycerides (mmol/L)</td>
<td>1.52 (1.21 to 2.07)</td>
<td>0.91 (0.57 to 1.96)</td>
<td>0.91 (0.57 to 1.96)</td>
<td>0.02</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*a Median (and ranges) for all 15 patients.

b The results before and after steroid withdrawal were compared.

c The results after steroid withdrawal and the results after tacrolimus trough level reduction were compared.
have interfered with glucose metabolism. Hemoglobin decreased by 5% \( (P = 0.04) \) after steroid withdrawal and did not change after tacrolimus trough level reduction. Creatinine clearance did not change significantly after steroid withdrawal, but increased by 16% \( (P = 0.002) \) after tacrolimus trough level reduction. After steroid withdrawal, tacrolimus dose was reduced in 11 patients and remained unchanged in the other four patients. Despite the dose reduction, there was a statistically nonsignificant rise in tacrolimus trough level (Figure 1). Between the second and third tests, trough level decreased by 33% \( (P = 0.004) \) as intended (Figure 1).

**Glucose Metabolism**

Glucose metabolism was assessed by IVGTT at a median of 20 d (range, 13 to 35 d) before steroid withdrawal, 68 d (39 to 96 d) after complete cessation of steroids, and 307 d (163 to 345 d) thereafter (after tacrolimus trough level reduction). None of the patients developed hyperglycemia.

Figures 1, 2, and 3 show the median levels of the various parameters of glucose metabolism before and after steroid withdrawal and after tacrolimus trough level reduction. Figure 1 shows fasting glucose and HbA1c. Figure 2 shows fasting parameters associated with insulin resistance, and Figure 3 shows \( K_G \) and stimulated parameters associated with pancreatic \( \beta \)-cell secretion capacity.

After steroid withdrawal, fasting C-peptide levels decreased significantly by 22% \( (P = 0.0009) \), fasting insulin levels and insulin/glucose ratio decreased as well \( (P = 0.09 \text{ and } 0.10, \text{ respectively}) \). C-peptide secretion decreased by 14% \( (P = 0.06) \). There was no significant change in any other parameter of glucose metabolism after steroid withdrawal.

After tacrolimus trough level reduction, C-peptide secretion increased significantly by 36% \( (P = 0.04) \). A similar increase was observed for insulin secretion \( (P = 0.06) \). HbA1c decreased significantly by 10% \( (P = 0.002) \). Insulin resistance parameters did not change.

**Lipid Profile**

Before and after steroid withdrawal, two patients were treated with 10 mg of simvastatin. After tacrolimus trough level reduction, the dosage of simvastatin in one of these patients was increased. Moreover, three additional patients were treated with lipid-lowering drugs. These four patients were therefore excluded from analysis.

After steroid withdrawal, there was a decrease in total cholesterol by 11% \( (P = 0.006) \), HDL cholesterol by 21% \( (P = 0.01) \), and triglycerides by 25% \( (P = 0.02) \), a decrease of LDL cholesterol by 9% \( (P = 0.15) \), and an increase of LDL/HDL ratio by 12% \( (P = 0.16) \). After tacrolimus dose reduction, there were no significant changes in lipids.

**Correlations between Tacrolimus Trough Level and Parameters of Glucose Metabolism**

Tacrolimus trough level correlated significantly with \( K_G \) \( (\rho = -0.362; P = 0.015) \) and with C-peptide secretion \( (\rho = -0.311; P = 0.037) \) but not with any of the other parameters of glucose metabolism.

**Discussion**

In this prospective study in white renal transplant recipients, the relative roles of steroids and tacrolimus on glucose metabolism and lipid profiles were evaluated.

After steroid withdrawal, fasting C-peptide decreased significantly. C-peptide is almost completely cleared by the kidney (28). Renal function did not change significantly. Therefore, improvement in renal function could not have been responsible for the

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![Figure 1](https://example.com/figure1.png)

**Figure 1.** Median tacrolimus trough level, fasting glucose, and HbA1c levels before and after steroid withdrawal and after tacrolimus trough level reduction. Tacrolimus trough level (ng/ml), HbA1c (%), fasting glucose (mmol/L).
From this observation, one can conclude that use of steroids causes an increase in insulin resistance in patients on tacrolimus, confirming the data in cyclosporine patients (12).

After steroid withdrawal, C-peptide secretion also decreased ($P = 0.06$). It is very unlikely that this decrease is due to a direct effect of steroid withdrawal on $\beta$-cell production. In our opinion, this is due to an indirect effect of increased tacrolimus trough levels. We have observed that tacrolimus trough levels (with unchanged dose) increase after steroid withdrawal (manuscript in preparation). This increase of trough levels does not occur in all patients, but in 40 to 60% of the patients. Due to the reduction in

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**Figure 2.** Median fasting parameters of glucose metabolism associated with insulin resistance before and after steroid withdrawal and after tacrolimus trough level reduction. Right y-axis: fasting insulin (mU/L). Left y-axis: fasting C-peptide (nmol/L), homeostasis model assessment (HOMA-R) (mmol/L*mU/L), and insulin glucose ratio (mU/mmol).

**Figure 3.** Median fasting $K_G$ and parameters of glucose metabolism associated with pancreatic $\beta$-cell secretion capacity before and after steroid withdrawal and after tacrolimus trough level reduction. Right y-axis: $K_G$ (mmol/L per min). Left y-axis: C-peptide secretion (nmol × min/L) and insulin secretion (mU × min/L ÷ 10).
tacrolimus dose in 73% of the patients, the increase of tacrolimus trough level in this study was not statistically significant. But despite dose reductions, tacrolimus trough levels increased by more then 20% in 4 patients (range, 43 to 65%). In 3 of the latter patients, C-peptide secretion decreased by 25 to 46%.

In the second part of the study, tacrolimus trough level was reduced, resulting in a significant increase in stimulated C-peptide secretion. Insulin resistance did not change. Thus, pancreatic β-cell secretion capacity increases when tacrolimus trough levels are lowered, confirming the reversibility of β-cell dysfunction caused by tacrolimus (10,23). This occurs even within the normal range for maintenance therapy with tacrolimus; a 33% reduction in the tacrolimus trough level resulted in a 36% increase in median β-cell secretion capacity. The period between the IVGTT before and after trough level reduction was approximately 10 mo because patients were generally seen only once every 2 to 3 mo and a gradual decrease in tacrolimus trough levels to 5 ng/ml was desired. BMI, BP, and the use of antihypertensive drugs did not change in this period. We cannot completely rule out a spontaneous improvement of pancreatic β-cell secretion capacity in this period. However, given the correlation found between tacrolimus trough level and pancreatic β-cell function in both this study and our previous studies (10, 29) and observations of improved glucose metabolism after tacrolimus dose reduction (29), it is more likely that the reduced tacrolimus trough levels explain at least part of the improvement.

Before and after steroid withdrawal, concomitant use of MMF was the same, but before and after tacrolimus trough level reduction, five patients discontinued MMF. Although there are no descriptions of alterations in glucose metabolism or lipid profile due to the use of MMF, we compared changes in parameters of glucose metabolism after steroid withdrawal and after trough level reduction separately for patients using MMF and those not using MMF. The changes in both groups were similar to changes for all patients.

After tacrolimus trough level reduction, HbA1c decreased significantly. This is an important finding, because an association between HbA1c levels and risk of cardiovascular morbidity and mortality has been described in nondiabetic patients (30). In our study, hemoglobin levels did not change significantly after trough level reduction. Therefore, it seems unlikely that the decrease in HbA1c in our study can be explained by an increase in hemoglobin levels (31). HbA1c levels in patients with renal insufficiency and patients after kidney transplantation correlate well with mean capillary blood glucose levels; therefore, the improvement in renal function in our patients does not seem to explain the decrease in HbA1c either (32). Furthermore, fasting glucose levels did not change in our study; therefore, reduced postprandial glucose levels must have caused the decrease in HbA1c. In the DECODE study (33), abnormal blood glucose 2 h after an oral glucose tolerance test was associated with an increased mortality risk by a factor 2.0 for men and 2.8 for women. An increased risk of cardiovascular disease has also been shown in studies comparing normal and increased postprandial blood glucose levels (34). Consequently, tacrolimus trough level reduction, which results in lower postprandial glucose and HbA1c levels might reduce cardiovascular morbidity and mortality, not only in patients with PTDM but also in nondiabetic patients.

Due to a violation of protocol, lipid-lowering drugs were changed in four patients. However, between the first and second test, where relevant changes in lipids occurred, lipid-lowering drugs were unchanged. To exclude bias due to the exclusion of patients, we also compared lipid profiles before and after steroid withdrawal for all 15 patients. The results of this analysis were the same. The changes in lipids after steroid withdrawal, i.e., a decrease in all lipids, are very similar to the changes described after steroid withdrawal in nondiabetic renal transplant recipients on cyclosporine-based immunosuppression (22). The reductions in total cholesterol, LDL cholesterol, and triglycerides are obviously beneficial. The extent to which these beneficial changes are counterbalanced by the concomitant decrease in HDL is unclear. We found no indications that decreasing tacrolimus trough levels influenced lipid profiles, indicating that tacrolimus does not influence lipids. However, a decrease in tacrolimus trough level by 33% did result in a significant improvement in renal function of approximately 16%. This could be of importance, because studies in cyclosporine patients have shown that renal function in the first year after transplantation has a large impact on long-term graft survival (35).

Our findings support our current policy for patients who develop PTDM on tacrolimus-based immunosuppression: at first, steroid withdrawal, while maintaining therapeutic tacrolimus trough levels of approximately 10 to 15 ng/ml for 4 to 6 wk after transplantation to avoid acute rejection. After this period, tacrolimus trough levels are reduced to 5 to 7 ng/ml. This often results in a reduction in, or the cessation of, insulin therapy or even in the disappearance of PTDM (15).

In summary, steroid withdrawal in white renal transplant recipients on tacrolimus-based immunosuppression leads to a general improvement in glucose metabolism due to a decrease in insulin resistance as well as to a reduction in lipids, and tacrolimus trough level reduction improves glucose metabolism by increasing pancreatic β-cell secretion capacity.

Acknowledgment
We would like to thank Monique Mullens for her assistance with the practical aspects of organizing and performing all the tests after tacrolimus trough level reduction.

References

Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/