Early Basal Insulin Therapy Decreases New-Onset Diabetes after Renal Transplantation

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ABSTRACT
No effective interventions to reduce risk for new-onset diabetes after transplantation (NODAT), a condition associated with postoperative hyperglycemia and reduced patient and graft survival, have been established. In this 1-year, proof-of-concept clinical trial, we randomly assigned 50 renal transplant recipients to immediate-postoperative isophane insulin for evening blood glucose ≥140 mg/dl (treatment group) or short-acting insulin and/or oral antidiabetic agents for blood glucose 180–250 mg/dl (standard-of-care control group). We included only patients without a history of diabetes who received tacrolimus. By the third postoperative evening, all patients in the treatment group had blood glucose ≤140 mg/dl and were subsequently treated with basal insulin; during the first 3 weeks after transplantation, the mean ± SD daily insulin dosage was 17 ± 11 IU/d. Among controls, 23 (92%) of 25 had blood glucose ≥200 mg/dl and 18 (72%) of 25 received standard-of-care antihyperglycemic treatment. Asymptomatic hypoglycemia occurred five times in the treatment group and once in the control group. Throughout follow-up, the treatment group had 73% lower odds of NODAT (odds ratio, 0.27) than the control group, and hemoglobin A1c was on average 0.38% lower in the treatment group than the control group. Twelve months after transplantation, all patients in the treatment group were insulin-independent, whereas 7 (28%) of 25 controls required antidiabetic agents. The groups did not differ for insulin sensitivity, but the treatment group showed better β-cell function throughout the 1-year follow-up. In conclusion, this study suggests regimens that include basal insulin significantly reduce the odds for NODAT after renal transplantation, presumably via insulin-mediated protection of β cells.


New-onset diabetes after transplantation (NODAT) is associated with a 63% increased risk for graft failure and an 87% increased risk for death, thereby posing a “threat to graft and patient survival”. NODAT is also a costly condition; in 1994–1998, Medicare paid an extra $21,500 per newly diagnosed diabetic patient by 2 years after transplantation. This burden may be explained by the fact that NODAT increases the risk for cardiovascular disease, the most common cause of death with graft function. Strategies to decrease NODAT have thus been suggested to help improve long-term outcomes in the transplant population.

Immunosuppressants, corticosteroids, and calcineurin inhibitors synergistically exert a strong diabetogenic effect, especially when administered at
high doses soon after transplantation to prevent acute rejection. Although post-transplantation hyperglycemia is the strongest predictor of subsequent NODAT development, step-up strategies (from nonpharmacologic to oral therapy and finally to insulin) have been recommended for NODAT treatment. However, transient insulin therapy acts against hyperglycemia and improves β-cell function, as well as long-term glycemic control in patients with newly diagnosed type 2 diabetes; this therapy may effectively provide temporary β-cell protection.

Compared with short-acting and biphasic insulin, basal insulin leads to fewer hypoglycemic events in patients with type 2 diabetes. Therefore, we designed a randomized, controlled study (TIP [Treat-to-target Trial of Basal Insulin in Post-transplant Hyperglycemia]) to test the following hypotheses. We first sought to assess whether basal insulin therapy during the immediate post-transplantation phase might be an efficacious strategy to control postoperative hyperglycemia in previously nondiabetic patients. We chose hemoglobin A1c (HbA1c) at 3 months as the primary endpoint and hypoglycemic events as the secondary endpoint for safety. The second research goal was to determine whether basal insulin reduces the risk for NODAT by offering long-term β-cell protection.

RESULTS

Study Participants
The CONSORT (Consolidated Standards of Reporting Trials) flow chart of the TIP study is provided in Figure 1. Baseline characteristics of the study groups were not significantly different, but there was a trend for higher body weight and body mass index (BMI), higher percentage of first grafts, less glomerular disease, and more basiliximab (induction) therapy in the control group compared with the treatment group (Table 1). Among those receiving basiliximab, all control patients and all but one patient in the treatment group participated in the European Senior Program, but the control group’s older age (by 3.7 years) did not show a strong statistical trend ($P=0.29$; Table 1). The remaining treatment patient with basiliximab therapy received an organ from a non–heart-beating donor. One control patient had no HbA1c data available at 3 months, and one treatment patient had no reliable HbA1c data because of a hemoglobin variant.

Glucose Measurements, Oral Glucose Tolerance Tests, and Antidiabetic Treatment during Follow-up

Postoperative Hospitalization
Mean ± SD lengths of initial hospitalization in the control and treatment groups were similar (22.6 ± 10.6 days and 22.9 ± 7.7 days, respectively), and respective numbers of glucose measurements were 1913 (3.4 ± 0.5 times per patient per day) and 2158 (3.8 ± 0.3 times per patient per day).

Twenty-three of the 25 control patients (92%) had blood glucose levels ≥200 mg/dl at least once. These levels occurred by postoperative day 7 in 20 control patients (80%). Short-acting insulin was administered intermittently in 18 control patients (72%), in 3 of them intravenously. Two of the latter patients also subsequently received subcutaneous dual-release insulin. Three control patients began receiving and were discharged with the sulfonylurea gliclazide (30–90 mg/dl).

All 25 patients in the treatment group had glucose levels ≥140 mg/dl by the end of postoperative day 2 and received isophane insulin on the following morning. In all these patients, glucose levels ≥140 mg/dl occurred before or after supper alone, or occurred at additional time points. In the control group, average daily glucose levels were significantly higher and average insulin doses were significantly lower than in the treatment group (Figure 2). Of note, the overall average glucose level in the control group was 15 mg/dl higher than that in the treatment group in the morning but 30 mg/dl higher before supper (Figure 2B; $P<0.001$ for all comparisons). Daily glucose profiles consistently showed the glucose concentration to peak before supper by the end of the first postoperative week (Supplemental Figure 1). Hyperglycemic episodes (≥200 mg/dl at least once daily) occurred during 47.6% ± 29.9% of days per patient in the control group versus

**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) flow chart of the study. tx, transplantation.
Table 1. Baseline demographic and patient characteristics

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Unless otherwise noted, values are expressed as number of patients. Continuous variables are reported as means ± SDs. P values determined using two-tailed t test or chi-squared test when appropriate.

CMV, cytomegalovirus; PRA, panel-reactive antibody.

*P values determined using Fisher exact test.

28.4%±23.1% of days per patient in the treatment group (P=0.014).

Study Visits at 3, 6, and 12 Months
By 3, 6, and 12 months, respectively, were receiving antidiabetic medication, whereas 2, 1, and 0 patients in the treatment group, respectively, still required isophane insulin therapy (Figure 3). All patients who did not receive antidiabetic agents underwent an oral glucose tolerance test (OGTT) near these time points; the mean numbers of days ± SD for when the OGTTs were performed in the control versus the treatment group were 91±6 versus 102±12 (P=0.001), 185±13 versus 184±8 (P=0.93), and 373±17 versus 373±16 (P=0.79), respectively. The difference at 3 months was due to prolonged insulin weaning in the treatment group.

The odds ratios for impaired glucose metabolism and diabetes at 3, 6, and 12 months showed a markedly reduced risk for NODAT as well as a reduced risk for overt NODAT plus impaired glucose tolerance in the treatment group (Figure 4; definitions provided in the Concise Methods section). In a sensitivity analysis, we considered a possible effect of observed between-group differences in BMI and age (Table 1), prednisone dose at time of the OGTT, and cumulative steroid dose (Supplemental Table 1, B and D) on the outcomes by adjusting for these factors in logistic regression models. However, the odds ratios for impaired glucose metabolism and diabetes increased only slightly in the treatment group, as shown in Supplemental Table 2A.

HbA1c
At 3, 6, and 12 months, respectively, mean HbA1c ± SD increased from 5.3%±0.4% at baseline to 6.2%±0.7%, 6.3%±0.7%, and 6.0%±0.6% in the control group and from 5.2%±0.5% at baseline to 5.7%±0.6%, 5.8%±0.6%, and 5.8%±0.6% in the treatment group (Figure 5A). Corresponding intrapatient changes in HbA1c from baseline are shown in Figure 5B. The primary endpoint, HbA1c at 3 months, was significantly different between the treatment and control groups (P=0.005, Figure 5A). Estimated group differences and 95% confidence intervals for HbA1c (Figure 5, A and B) were also adjusted for BMI, age, and steroids; however, we observed only slight changes (Supplemental Table 2B).

Hypoglycemia
Hypoglycemic episodes (41–60 mg/dl), the principal safety outcome measure, occurred once in the control group and five times in the treatment group. No patients noticed the hypoglycemic episode or had more than one episode.

Insulin Sensitivity and β-Cell Function
At 3, 6, and 12 months, mean ± SD insulin sensitivity (the opposite of insulin resistance), as tested by the OGTT-derived oral glucose insulin sensitivity (OGIS) index, was 377±63, 398±39, and 402±43 ml/min per m² in the control group versus 400±45, 395±50, and 385±49 ml/min per m² in the treatment group (Figure 5C). β-cell function (mean ± SD
The insulinogenic index ([IGI]) was 0.026±0.023, 0.035±0.021, and 0.048±0.030 nmol insulin/mmol glucose in the control group versus 0.048±0.027, 0.055±0.045, and 0.067±0.061 nmol insulin/mmol glucose in the treatment group at the same respective time points (Figure 5D).

At 3, 6, and 12 months, 5, 10, and 8 control patients versus 3, 2, and 0 treatment patients, respectively, received antidiabetic agents and did not undergo an OGTT; therefore, we established predictive models for OGIS index and IGI based on age, BMI, and an assumed 2-hour glucose value of 201 mg/dl. We reasoned that patients receiving antidiabetic agents would have a diabetic OGTT result, but we used a conservatively low glucose value. When we included the predicted values, the resulting significance levels for study group differences in OGIS index never went below P=0.20 at 3 months. However, the P values for the group differences in IGI improved from 0.01, 0.13, and 0.26 at 3, 6, and 12 months to 0.003, 0.02, and 0.11, respectively (Figure 5).

Accounting for within-patient repeated measures using generalized estimating equations to test for overall difference, IGI levels were significantly higher in the treatment group over the 1-year follow-up (P=0.009 and P=0.013 for IGI with and without predicted values, respectively). In contrast, corresponding OGIS index values were not significantly different (P=0.65 and P=0.69).

The other insulin sensitivity index we used (the McAuley index) confirmed that the control and treatment groups did not differ in terms of insulin resistance. The OGTT-derived adaptation index, which relates insulin secretion to insulin sensitivity; the disposition index; and the Sharif disposition index.
Serious Adverse Events, Weight Change, and Renal Function

Serious adverse events occurred at similar frequency in the control and treatment groups (Supplemental Table 4). The P value for acute transplant rejections, high-dose steroid treatments, and urinary tract infections is not reported because these events occurred more than once in several patients. However, we observed no significant differences between the groups regarding the number of patients with at least one transplant rejection (five versus eight; P=0.33) and two transplant rejections (four versus none; P=0.11). No patient had three or more acute transplant rejections. Likewise, we observed no significant differences between control and treatment groups regarding the number of patients receiving at least one high-dose steroid treatment (seven versus six; P=0.75) and two high-dose steroid treatments (two versus none; P=0.49). No patient received three or more high-dose steroid treatments.

Three patients in the control group and four in the treatment group underwent a conversion from tacrolimus to cyclosporine A by 6 months (Supplemental Table 1A), as decided by outpatient physicians because of tacrolimus-related side effects (hyperglycemia in one control patient). Weight change was similar in the two groups (Supplemental Figure 2A), and serum creatinine showed a trend to be lower in the treatment group (Figure 6).

DISCUSSION

The TIP study showed a significant difference in HbA1c between renal transplant recipients treated with basal insulin during the early postoperative period and standard-of-care control patients at 3 months (primary endpoint). Among the predefined secondary outcome measures, we observed no increase in HbA1c after 3 months over the 1-year follow-up in the treatment group, even without subsequent antidiabetic agent, but we did note improved β-cell function and a 73% reduction in the odds of NODAT at 1 year. These findings indicate a robust benefit of insulin therapy, agree with our secondary hypothesis of β-cell protection (on the basis of previous reports in patients with newly diagnosed type 2 diabetes8–14), and warrant thorough interpretation.
The normoglycemic goal of 110–120 mg/dl was exceeded in the treatment group, as shown by an average glucose value of 139 mg/dl during the postoperative period (Figure 2B). The increase in HbA1c in the treatment group by 3 months also suggests that average glucose levels remained 120 mg/dl for most patients. Hence, for optimized β-cell protection, tighter control to near-normoglycemic treatment goals could be attempted to further reduce the number of patients with impaired glucose tolerance. However, intensive insulin therapy remains controversial, and HbA1c lowering to ≤6% or ≤6.5% in patients with type 2 diabetes was associated with increased cardiovascular complications.

Determining the appropriate blood glucose goal in transplant recipients, as well as the therapeutic means to achieve this goal, will therefore remain an important future challenge.

Figure 5. HbA1c, insulin sensitivity, and β-cell function. (A) Mean HbA1c ± SD in control versus treatment group at baseline and 3, 6, and 12 months. (B) Mean change in HbA1c from baseline ± SD in control versus treatment group at 3, 6, and 12 months. P values were determined using a two-tailed t test (*P<0.05). Generalized estimating equations accounting for within-patient repeated measures. Estimated differences with 95% confidence intervals between study groups were determined using a two-tailed t test and generalized estimating equation. (C and D) Mean insulin sensitivity and β-cell function (by OGIS index in C) and IGI (D) ± SD in control group versus treatment group at 3, 6, and 12 months. P values were determined using a two-tailed t test (for OGIS index, all P≤0.19; for IGI, *P<0.05, *P=0.107, and 2 other P≤0.13). Missing values in all patients requiring antidiabetic agents were conservatively predicted, as explained in the text.

Figure 6. Renal function, as reported with mean ± SD serum creatinine levels at 3, 6, and 12 months. P values were determined using a two-tailed t test.
The mean blood glucose level before supper was 73 mg/dl higher than the fasting level in the control group during post-transplantation days 1–21 (Figure 2). Previously reported self-measurements of blood glucose concentrations in renal transplant recipients similarly showed a substantial number of patients with presuppertime hyperglycemia but only slightly elevated fasting glucose concentrations,26 related to the morning administration of corticosteroids.27 Our data therefore emphasize that evening measurements of blood glucose levels are better suited than fasting measurements to identify renal transplant recipients at high risk of developing NODAT.

The prevalence of NODAT and impaired glucose tolerance at 3 and 6 months in the present study was presumably higher than in the DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C2 Monitoring Versus Tacrolimus) study, where 32.2% of tacrolimus-treated patients had NODAT or impaired fasting glucose at 6 months and half of those required therapy.28 Older age (by approximately 10 years) and more deceased donors in our study (88% versus 68% in DIRECT) are known to increase the risk for NODAT7,29 and might have contributed to these differences.

The high incidence of hyperglycemia observed in the TIP study control group (92%) was also observed in a recently published retrospective analysis.30 In the absence of pretransplantation OGTTs in this study as well as in DIRECT, it might be speculated that some patients in the TIP study (and presumably more patients than in the DIRECT study) had previously undetected diabetes. Particularly in that case, however, the problem of severely impaired glucose metabolism after transplantation has, if anything, been formerly underestimated.

Our study has several limitations. Despite randomization, the control and treatment groups showed some nearly significant differences at baseline, probably related to the relatively small size as a consequence of the study’s design: to test primarily the hypothesis that basal insulin would be efficient and safe against post-transplant hyperglycemia. Of concern was the difference in body weight and BMI and a subsequent trend for higher steroid use in the control group at 6 months. However, adjustment for BMI, steroid dose at OGTT, cumulative steroid dose, and age showed that our findings remained robust (Supplemental Table 2).

Six of 56 enrolled patients (11%) were randomly assigned but had to be replaced by the next eligible patients. Although this percentage is unusually high, it must be clarified that, as shown in Figure 1, only one participant left the study after receiving the allocated intervention (because he was not adhering to the treatment regimen).

The lack of blinding as well as different glucose measurement practices (all patients in the treatment group versus 11 controls learned to measure glucose) could have influenced patient adherence to diet and exercise. However, weight change after transplantation did not differ between the study groups. Major diabetes studies31,32 were similarly not blinded and had to consider benefits unrelated to insulin. Our data on β-cell function, however, would not be affected by such potential effects.

The use of HbA1c at 3 months as the primary endpoint of this study is debatable because (1) HbA1c may be considered a trivial outcome in patients receiving a more intensive versus a less intensive antidiabetic treatment, at least after transplantation, and (2) HbA1c in renal transplant recipients may not adequately reflect glycemia.33 Therefore, it might be argued that NODAT prevalence would have been a better primary outcome measure. In the absence of prospective data on standardized insulin regimens after transplantation, however, we had to show the feasibility of basal insulin therapy and could not assume that this treatment would decrease NODAT prevalence at all. Choosing HbA1c as the primary endpoint was therefore our only option, given the current state of research.

Regarding HbA1c’s potentially inadequate reflection of glycemia due to post-transplantation caveats (e.g., anemia and various degrees of impaired renal function after transplantation),34 we refer to our HbA1c results at 6 and 12 months, which may be less influenced by such factors.

Although OGTT-derived insulin resistance surrogates have previously been validated and used in renal transplant recipients,34,35 similar validations for insulin secretion are lacking. In the nontransplanted population, IGI is accepted as a common evaluator of β-cell function during an oral test.36 With use of IGI, we showed that our treatment group was characterized by systematically improved β-cell function, whereas insulin resistance (the opposite of insulin sensitivity), as assessed by the OGIS index, was largely unaltered. The adaptation index, the product of OGIS index × dynamic area under the curve (AUC) of insulin (in this study, termed disposition index), and the Sharif disposition index were improved in the treatment group, although none of these changes were statistically significant (Supplemental Table 3). Thus, in this relatively small study, the amelioration of β-cell function was not sufficient to improve the dynamic glucose disposal rate and consequently glucose tolerance under postprandial conditions.

Basal insulin treatment may nevertheless have considerably relieved the pancreatic islets from post-transplantation stress. Our second study hypothesis of β-cell protection is supported by the 6- and 12-month findings of lower diabetes prevalence and no increase in HbA1c in the treatment group, despite discontinuation of insulin treatment. The difference in HbA1c between the two study groups was significant at 6 months but not at 12 months; this is most likely due to the constant use of antidiabetic agents in seven or more control patients over at least the last 9 months of the 1-year follow-up, as shown in Figure 3.

Withdrawal of antidiabetic agents was encouraged in both groups. The observed inability to withdraw these agents in the control group suggests that the need to initiate prolonged antidiabetic therapy due to severe hyperglycemia or markedly abnormal 2-hour glucose levels on OGTT (up to 430 mg/dl) reflects pancreatic decompensation that could not be rescued by conventional antidiabetic treatment. Future research should determine whether insulin alone rather than sulfonylureas might be the preferred treatment option for such patients.
Despite the described limitations, our study may ignite a change in clinical practice toward early insulin therapy after transplantation, if our results can be reproduced by other centers, and with non–tacrolimus-based immunosuppression protocols. Of note, a prospective NODAT-prevention trial should be extended to >12 months to ensure that the proposed insulin regimen may prove beneficial, despite the possibility that some patients with postoperative hyperglycemia may revert to normoglycemia without intervention.

A future study should also ask treatment patients to keep logs of their glucose measurements and insulin dosage in order to better account for hypoglycemic events in the outpatient setting. Such an approach might in fact be necessary to confirm the safety of basal insulin therapy, although we observed that hypoglycemic events were very rare and were not of clinical concern during the postoperative period; in addition, none of the serious adverse events during the remaining follow-up of our study were related to hypoglycemia. Last, the effect of insulin treatment on the metabolic syndrome should be examined; this common complication after renal transplantation is associated with cardiovascular risk profiles.37,38

In summary, our study shows that evening hyperglycemia (glucose level ≥200 mg/dl) is the rule, not the exception, after renal transplantation and that early basal insulin is effective in reducing HbA1c and decreasing NODAT over the long term (presumably by improving B-cell function). This promising evidence in favor of early basal insulin therapy after transplantation needs to be addressed in larger clinical trials. More-intensive insulin regimens after transplantation should also be studied further.

CONCISE METHODS

The TIP study was approved by the local ethics committee (EK#541/2008) and registered with ClinicalTrials.gov (NCT00830297). Patients were included from February 2009 through February 2010 and followed until February 2011. Renal transplant recipients older than 18 years of age, lacking a history of diabetes (per medical records and verbal information from the patients directly), and receiving tacrolimus as primary postoperative immunosuppressant were eligible. Fifty-six patients were enrolled and randomly assigned in a 1:1 ratio, without stratification, to the basal insulin (treatment) or standard-of-care (control) group. Randomization took place on the dialysis ward before transplantation through use of sealed envelopes. The randomization code was developed using an Internet-based randomization tool and was not revealed to participants or investigators.

Immunosuppression

Per center protocol, all study patients received triple immunosuppression with tacrolimus, mycophenolate mofetil or mycophenolic acid, and steroids. Tacrolimus trough levels were targeted at 8–12 ng/ml during the first 90 postoperative days and at 6–12 ng/ml thereafter.

All patients received 40 mg of dexamethasone intraoperatively, and doses were tapered to 32, 24, 16, 8, and 4 mg on postoperative days 1, 2, 3, 4, and 5, respectively. From postoperative day 6 onward, patients were maintained on 20 mg of prednisone daily. Tapering to 5 mg of prednisone or less was performed stepwise, in close analogy to the ELITE (Efficacy Limiting Toxicity Elimination) Symphony study, by the attending physicians on the ward or subsequently in the outpatient clinic.

Conversions of the primary immunosuppressant and of the antimetabolite, based on clinical considerations, were likewise at the discretion of the previously mentioned physicians. Basiliximab (induction) therapy was performed immediately before transplantation and on postoperative day 4 in patients participating in the European Senior Program, as well as in patients receiving an organ from a non–heart-beating donor. Antithymocyte globulin therapy and extracorporeal immunoadsorption were performed before transplantation and after transplantation in patients positive for donor-specific antibodies.

Antidiabetic Treatment

**Basal Insulin Group**

Basal insulin treatment was initiated with a morning dose of 6, 8, or 10 IU of isophane insulin (Insulatard, Novo Nordisk) if the blood glucose on the previous evening was >140, 180, or 240 mg/dl, respectively. The normoglycemic goal was 110–120 mg/dl. Rapid downward titration of the isophane insulin dose was prespecified (e.g., decrease by 2 IU with a measured presupper glucose level of 80–100 mg/dl). Upward titration was also prespecified; further corrections of hyperglycemia with short-acting insulin during the postoperative care on the ward were encouraged and followed by subsequent increases in isophane insulin.

**Control Group**

Conventional antidiabetic and antihyperglycemic treatment in the control group was managed by the attending physicians on the ward or subsequently in the outpatient clinic, and followed international consensus guidelines.7 Treatment was not encouraged at nonfasting blood glucose levels <180 mg/dl, the renal threshold for glucose.41 However, severe hyperglycemia (blood glucose levels ≥250 mg/dl) had to be at least intermittently corrected with short-acting insulin, per our study’s protocol. The sulfonylurea glimepiride (Diamicron, Servier Pharma, Vienna, Austria) was suggested as the pharmacologic oral agent of choice.

Definition and Evaluation of Outcome Measures

The primary outcome measure was the difference in HbA1c between the 2 study groups at the 3-month study visit. Predefined secondary outcome measures included differences in HbA1c at the 6- and 12-month study visits; prevalence of NODAT and impaired glucose tolerance at the 3-, 6-, and 12-month study visits; capillary blood glucose profiles and amount of insulin used on postoperative days 1–21; and number of patients, as well as overall number of days with hyperglycemia ≥200 mg/dl and hypoglycemia ≤60 mg/dl. NODAT was defined as need for antidiabetic treatment at the study visit or 2-hour glucose level ≥200 mg/dl during an OGTT. Impaired glucose tolerance was defined as 2-hour glucose level of 140–199 mg/dl.42
After transplantation, capillary blood glucose was measured using Contour TS (Bayer Health Care) or Accu-Chek Go (Roche Diagnostics) glucometers and test strips. All study participants were informed about symptoms of hypoglycemia and were asked to report such symptoms, as well as to obtain immediate capillary blood glucose levels. Advice on diet and exercise was given by the TIP investigators to both groups according to American Diabetes Association guidelines.43

At the study visits, routine blood tests included clinical chemistry and HbA1c by high-performance liquid chromatographic separation of hemoglobin fractions.44 OGTTs were performed with 75 g of glucose dissolved in 250 ml of water, using Glucoral 75 citron (Germania Pharmazeutika, Vienna, Austria) after an overnight fast in patients not receiving antidiabetics. Venous blood was collected from a peripheral venous catheter at 0, 10, 20, 30, 60, 90, and 120 minutes for measurements of glucose, insulin, and C-peptide.

Insulin sensitivity was evaluated through the OGIS index, which describes glucose clearance per unit change of insulin concentration.45 β-cell function was assessed by IGI using the ratio of suprabasal (dynamic) insulin AUC (calculated with the trapezoidal rule for the entire OGTT) to the corresponding suprabasal glucose AUC.36 The ability of the β cell to adapt insulin secretion to the prevailing insulin resistance was determined by the product of OGIS × dynamic AUC of C-peptide (termed the adaptation index), and the posthepatic compensation was calculated as OGIS index × dynamic AUC of insulin (in this study, termed the disposition index). The McAuley index and the Sharif disposition index were calculated as described elsewhere.17,18

Sample Size Calculation
On the basis of an expected 10% SD of HbA1c in transplant recipients without previously known diabetes (Table 2 in the study by Midtvedt et al.46), an α value of 0.05 (two-sided), and a β value of 0.2, a sample size of 25 patients per group was determined to detect a minimum difference of 0.5 percentage point in HbA1c levels between groups.

Statistical Analyses
Data were analyzed per protocol, and, on the basis of the small size of the study, a descriptive analysis was performed. The primary outcome measure was compared between treatment and control groups using the unpaired, two-tailed t test. Continuous baseline characteristics and secondary outcome variables were analyzed using the unpaired, two-tailed t test and ANOVA for repeated measures. Dichotomous baseline characteristics and secondary outcome variables were analyzed using the unadjusted chi-squared test or Fisher exact test when appropriate.

We accounted for within-patient repeated measures by using a generalized estimating equation, both for dichotomous and for continuous outcome variables.47 To allow adjustments for age, BMI, and steroid dosage, we used linear regression models for continuous outcome variables and logistic regression models for dichotomous outcome variables. Odds ratios were calculated with corresponding 95% confidence intervals. Predictive linear regression models for OGIS index, IGI, and the McAuley index, based on age, BMI, and 2-hour glucose value, were established in each study group at 3, 6, and 12 months. All calculations were performed using MS Excel 2003 (Microsoft Corp.) and SAS 9.2 for Windows (SAS Institute, Inc.).

ACKNOWLEDGMENTS
We thank the nursing personnel for outstanding motivation and Drs. Günther, Harm, Hofstetter, Freundl, Auinger, Lang, Stockenhuber, and Wieser for communicating patient data.

For the present analysis, the Department of Nephrology at the Medical University of Vienna received a research grant from Astellas Pharma (Austria) without restrictions on publications.

Parts of the present results have been presented in abstract forms and oral presentations at the World Congress of Nephrology (Vancouver, Canada, April 2011), the American Diabetes Association Scientific Sessions (San Diego, California, June 2011), the European Renal Association—European Dialysis and Transplant Association meeting (Prague, Czech Republic, June 2011), and the European Society of Organ Transplantation Conference (Glasgow, Scotland, September 2011).

DISCLOSURES
None.

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This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2011080835/-/DCSupplemental.