

Insulin Requirement After a Renal Transplant in Patients With Type 2 Diabetes: The Choice of Calcineurin Inhibitors

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Objectives: Hyperglycemia is a common adverse event of immunosuppressive drugs used in organ transplant. Because cyclosporine is less diabetogenic than tacrolimus is, cyclosporine may be preferred in patients with pre-existing diabetes mellitus type 2, to prevent insulin treatment after a transplant.

Materials and Methods: From March 2005 to June 2011, adult renal transplant patients with pre-existing diabetes mellitus type 2, who were not treated with insulin before a transplant, were treated with cyclosporine in combination with mycophenolate mofetil and corticosteroids. For comparison, we used historical controls who were treated with tacrolimus instead of cyclosporine.

Results: Of the 16 patients treated with cyclosporine, only 4 remained free of insulin treatment after a follow-up of least 1 year, compared with 2 of 12 patients who were treated with tacrolimus (25% vs 17%; $P = .67$). Almost all patients required insulin treatment within 2 months of the transplant, and patients required comparable doses of insulin at different times after the transplant in both groups. None of the baseline characteristics could sufficiently predict the need to start insulin treatment.

Conclusions: Cyclosporine cannot be preferred over tacrolimus to minimize either the chance of requiring insulin treatment posttransplant or the

dosage of insulin in patients with pre-existing diabetes mellitus type 2.

Key words: *Insulin, Diabetes mellitus, Calcineurin inhibitor*

Use of immunosuppressive drugs in organ transplant is hampered by a number of adverse events. Several of the commonly used drugs, such as corticosteroids and calcineurin inhibitors, can impair glucose metabolism. The negative effect on glucose metabolism is greater for tacrolimus than it is for cyclosporine, because treatment with tacrolimus is associated with significantly more cases of new onset diabetes mellitus after transplant.¹⁻³ Although much research has focused on new-onset diabetes mellitus after a transplant, little attention has been given to glucose management of patients with pre-existing diabetes mellitus type 2 not treated with insulin at the time of the transplant. Because of the diabetogenic effects of immunosuppressive drugs, these patients are at high risk for requiring insulin treatment after a transplant. Obviously, administering insulin is more cumbersome than using oral antidiabetic drugs, and it requires more intensive control of blood glucose levels. Furthermore, using insulin can add to the frequently occurring weight gain after a transplant.

The selection of a specific calcineurin inhibitor that minimizes the chance of requiring insulin treatment after a transplant could be one of the options to facilitate glucose management in this population. Based on the difference in diabetogenic potential between tacrolimus and cyclosporine, we hypothesized that cyclosporine might be preferred over tacrolimus in patients with pre-existing diabetes mellitus type 2, to prevent the use of insulin treatment after a transplant. We evaluated this hypothesis in a prospective cohort study.

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Acknowledgements: The authors received no financial support for this study. The authors declare they have no conflicts of interest.

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Experimental and Clinical Transplantation (2013) 3: 234-238

Materials and Methods

All adult patients who had received a kidney transplant from a living or deceased donor in Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, between January 2000 and June 2011 were evaluated for eligibility. Inclusion criteria were a current or previous diagnosis of diabetes mellitus type 2, based on a fasting blood glucose concentration ≥ 7.8 mmol/L, a random glucose level of ≥ 11.1 mmol/L, or treatment with oral antidiabetic drugs. Patients were excluded if they had been treated with insulin before the transplant, or if there were any reason to deviate from our standard immunosuppressive protocol, which consisted of a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids.

Between January 2000 and March 2005, patients who met the above-mentioned inclusion criteria were treated with tacrolimus, mycophenolate mofetil, and corticosteroids. In March 2005, the treatment protocol in our hospital was changed, and patients who met the above-mentioned criteria were treated with cyclosporine instead of tacrolimus, based on the difference in diabetogenic potential of these 2 drugs. The rest of the immunosuppressive therapy (mycophenolate mofetil and corticosteroids) remained unchanged.

The initial dosage of cyclosporine was 6 mg/kg/d orally, starting within 24 hours of the transplant. The cyclosporine dosage was adjusted to target a trough level of 125 to 150 ng/mL. The initial dosage of tacrolimus was 0.2 mg/kg/d orally, starting within 24 hours of the transplant. The tacrolimus dosage was adjusted to target a trough level of 15 to 20 mg/L in the first 2 weeks of the transplant, 10 to 15 mg/L during weeks 3 to 6 after the transplant, and 5 to 10 mg/L thereafter. The dosage of mycophenolate mofetil during the first 6 months was 2000 mg/d orally in cyclosporine-treated patients and 1500 mg/d orally in tacrolimus-treated patients, accounting for the influence of cyclosporine on the pharmacokinetics of mycophenolic acid.^{4,5} From 6 months after transplant, the dosage of mycophenolate mofetil was reduced stepwise to zero over 2 months. Steroids were given at a dosage of 100 mg/d intravenously for 3 days after the transplant, followed by 15 to 25 mg/d orally with tapering to 0.1 mg/kg/d orally at 3 months after the transplant. In individual cases, our protocol permitted

termination of steroids, so long as the patient received double immunosuppressive therapy (a calcineurin inhibitor and an antimetabolite). Induction therapy was not used in either group. Primary antirejection therapy consisted of methylprednisolone 500 to 1000 mg (depending on body weight) intravenously for 3 consecutive days. In case of a steroid-resistant rejection, anti-T-cell therapy was given.

All data were extracted from the medical files. At baseline, data were collected about sex, age, body mass index (BMI), time since diagnosis of diabetes mellitus, treatment of diabetes mellitus, pretransplant Hb A1c level, and hepatitis C serology.

After transplant, patients with impaired glycemic control were treated primarily with sulfonylurea drugs. Other antidiabetic drugs like metformin and thiazolidinediones were avoided. Insulin treatment was started when blood glucose levels were repeatedly > 15 mmol/L and/or Hb A1c was above 8.0% despite the maximum dosage of oral antidiabetic drugs. After a minimum follow-up of 1 year, data were collected about the need to start insulin treatment, interval between transplant and start of insulin treatment, insulin dosage and dosages of concomitant immunosuppressive drugs, including cumulative steroid dosage, weight gain, laboratory results, and treatment for rejection.

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 18.0.2, IBM Corporation, Armonk, NY, USA). For categorical (dichotomous) variables we used the Fisher exact test. For continuous variables, we used an independent-sample *t* test for normally distributed data or the Mann-Whitney *U* test when there was a nonnormal distribution of the data. To determine statistical significance, we used an alpha of .05. Because this study was observational instead of interventional (eg, the standard treatment protocol in our hospital was changed, see above), ethics committee approval and patient consent were not required according to Dutch legislation. However, all protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Results

Between January 2000 and June 2011, one thousand one hundred eleven adults underwent a renal transplant. We identified 28 patients (2.5%) with pre-existing diabetes mellitus type 2, who were not using insulin before the transplant. Sixteen of these patients

(11 men and 5 women) underwent a transplant after March 2005 and received cyclosporine as a calcineurin inhibitor. One patient accidentally started with tacrolimus, but this error was corrected on the second day after transplant. The control group consisted of 12 patients (8 men and 4 women) who received tacrolimus as calcineurin inhibitor. The characteristics of the patients of each group are shown in Table 1. All patients were hepatitis C seronegative. There were no differences in any of the patient characteristics.

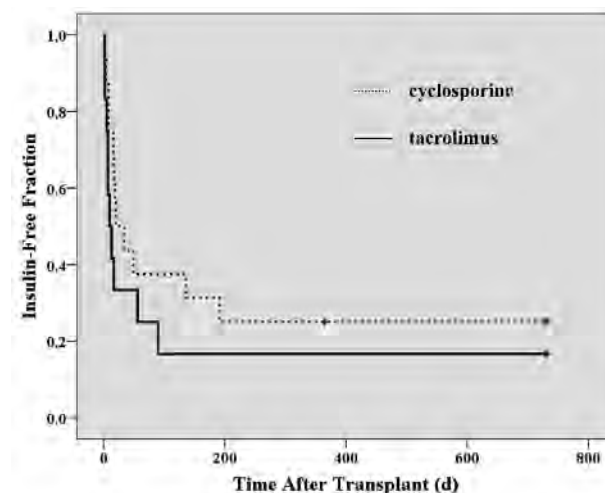
Table 1. Patients Characteristics in Each Treatment Group at the Time of Transplant

Variable	Cyclosporine n=16	Tacrolimus n=12
Sex, m/f	11/5	8/4
Age, y $\pm$ SD	61.7 $\pm$ 7.0	60.1 $\pm$ 8.0
BMI, kg/m ² $\pm$ SD	26.6 $\pm$ 3.8	28.3 $\pm$ 3.9
Time since diagnosing diabetes mellitus, y $\pm$ SD	12 $\pm$ 7	10 $\pm$ 8
Treatment of diabetes mellitus, none/oral antidiabetic drugs	7/9	4/8
Hb A1c pretransplant, % $\pm$ SD	6.4 $\pm$ 0.6	6.6 $\pm$ 1.3

Abbreviations: BMI, body mass index

*There were no statistically significant differences between the groups

Figure 1. Insulin-Free Survival During the First 2 Years Posttransplant in Patients With Pre-Existing Diabetes Mellitus Type 2, Who Were Treated With Cyclosporine or Tacrolimus



During follow-up, only 4 of 16 patients treated with cyclosporine remained free of insulin treatment, compared to 2 of 12 patients who were treated with tacrolimus (25% vs 17%; $P = .67$). In both groups, almost all of the patients required insulin treatment within 2 months of the transplant and the required dosages of insulin were comparable at different time intervals after the transplant (Figure 1 and Table 2).

Table 2. Posttransplant Outcomes*

Variable	Cyclosporine n=16	Tacrolimus n=12
Need for insulin treatment, yes/no	12/4	10/2
Time between transplant and start of insulin treatment, d $\pm$ SD	42 $\pm$ 60	21 $\pm$ 29
Insulin dosage at different time points posttransplant		
At 3 months, units/d (range)	37 (4-118)	57 (12-86)
At 6 months, units/d (range)	37 (8-110)	69 (36-114)
At 1 year, units/d (range)	47 (8-132)	73 (44-140)
Hb A1c at start of insulin treatment, % $\pm$ SD	7.8 $\pm$ 1.8	8.1 $\pm$ 1.4
Hb A1c at 1 year posttransplant, % $\pm$ SD	7.6 $\pm$ 1.1	6.7 $\pm$ 0.88
Actual steroid dose at different time intervals		
At 3 months, mg/d $\pm$ SD	10.2 $\pm$ 1.4	11.0 $\pm$ 1.3
At 6 months, mg/d $\pm$ SD	10.2 $\pm$ 2.9	10.4 $\pm$ 3.5
At 1 year, mg/d $\pm$ SD	7.8 $\pm$ 3.4	9.5 $\pm$ 3.7
Cumulative steroid dose at 1 year posttransplant		
Excluding antirejection steroids, mg (range)	4177 (3109-5280)	4441 (3199-5793)
Including antirejection steroids, mg (range)	6599 (3109-10590)	5524 (3199-10765)
Actual CNI levels achieved at different time intervals (as percentage of median level of target range)		
At 3 months, % (range)	108 (40-199)	113 (53-173)
At 6 months, % (range)	98 (73-135)	109 (66-293)
At 1 year, % (range)	88 (39-120)	111 (53-160)
Weight change posttransplant, kg $\pm$ SD	6.0 $\pm$ 8.4	13.4 $\pm$ 11.9
Treatment for acute rejection, yes/no	8/8	2/10

Abbreviations: CNI, calcineurin inhibitors

*There were no statistically significant differences

In none of the patients was it necessary to start insulin treatment after the first posttransplant year. All patients in whom insulin treatment was started were still using insulin at the end of the follow-up.

Three of the 16 patients (19%) treated with cyclosporine were not treated with the maximum dosage of oral antidiabetic drugs at the start of insulin treatment, because increasing the dosage was thought to be insufficient to achieve proper control of blood glucose levels. The same applied to 3 of 12 patients (25%) who were treated with tacrolimus and started with insulin. Hb A1c levels at the start of insulin treatment were comparable between patients treated with cyclosporine versus patients treated with tacrolimus ($7.8\% \pm 1.8\%$ vs $8.1\% \pm 1.4\%$; $P = .70$).

Table 3. Baseline Characteristics of Patients Requiring Insulin Treatment Posttransplant Versus Patients Not Requiring Insulin Treatment*

Variable	Patients Requiring Insulin Posttransplant n=22	Patients Not Requiring Insulin Posttransplant n=6
Sex, m/f	15/7	4/2
Age, y $\pm$ SD	61.2 $\pm$ 7.0	60.2 $\pm$ 9.4
BMI pretransplant, kg/m ² $\pm$ SD	27.0 $\pm$ 3.8	28.7 $\pm$ 4.0
Time since diagnosis of diabetes mellitus, years $\pm$ SD	12.3 $\pm$ 8.1	6.3 $\pm$ 3.4
Treatment of diabetes mellitus, none/oral antidiabetic drugs	7/15	4/2
Hb A1c pretransplant, % $\pm$ SD	6.6 $\pm$ 0.9	6.0 $\pm$ 0.4
Primary immunosuppression, tacrolimus/cyclosporine	10/12	2/4

Abbreviations: BMI, body mass index

*There were no statistically significant differences

Patients treated with cyclosporine tended to have a lower BMI at 6 months after the transplant, compared with patients treated with tacrolimus (28.0 ± 4.3 kg/m² vs 31.4 ± 4.4 kg/m²; $P = .052$). Otherwise, there were no significant differences in other posttransplant outcome parameters in patients treated with cyclosporine, compared with patients treated with tacrolimus. The dosages of steroids and the levels of calcineurin inhibitors (relative to the target range) did not differ between the 2 groups at various times after the transplant (Table 2).

Eight patients treated with cyclosporine were treated with methylprednisolone or anti-T-cell therapy for acute rejection, compared with 2 patients treated with tacrolimus (50% vs 17%; $P = .076$).

None of the baseline characteristics could sufficiently predict the need for insulin treatment after the transplant (Table 3). The need to start with insulin treatment tended to be associated with a larger weight gain during the first year after the transplant; 10.7 kg (-10 to 39.6 kg) in patients requiring insulin, compared with 3.5 kg (-1.7 to 10.6 kg) in patients not requiring insulin, $P = .13$.

Discussion

In this study, we examined whether the posttransplant need for insulin in renal transplant patients with pre-existing diabetes mellitus type 2, can be avoided by choosing cyclosporine as calcineurin inhibitor. This goal was not achieved, since only 4 of the 16 patients treated with cyclosporine (25%) remained free of insulin. This proportion did not differ from that observed in patients treated with tacrolimus (2/12; 17%). Moreover, neither the time interval between transplant and the start of insulin treatment, nor the required dosage of insulin, was related to the type of calcineurin inhibitor used in these patients.

Although cyclosporine has been shown to be less diabetogenic than tacrolimus, other factors apparently were more important in determining the posttransplant requirement for insulin in our patients with pre-existing diabetes mellitus type 2 in whom glycemic control before the transplant was achieved with oral antidiabetic drugs or even without pharmacological treatment.

The concomitant use of steroids either as part of the standard immunosuppressive treatment, or as antirejection therapy, is likely to contribute to the high proportion of patients requiring insulin treatment. Patients in both groups received comparable amounts (3 to 6 grams) of steroids within the first year after transplant, and we noticed that some patients required insulin treatment within a few weeks after receiving high-dose steroids as antirejection therapy. Previous studies have shown a dose-dependent diabetogenic effect of corticosteroids after a renal transplant, and high-dose steroids might increase the diabetogenic effect of calcineurin inhibitors.^{6,7}

Another factor determining the posttransplant need for insulin could be the resolution of the uremic condition of the patients. It is known that in several diabetic patients, the progression of renal failure is associated with (apparent) improvement of glycemic

control. Potential contributors to this so-called "burnt-out diabetes" include decreased renal and hepatic insulin clearance, a decline in renal gluconeogenesis, diminished food intake, loss of weight and body fat, and the hypoglycemic effect of hemodialysis treatment.⁸ After transplant, the reversal or disappearance of these conditions will impair glycemic control. Notably, there was a substantial weight gain (>10 kg) in 10 of our 28 patients.

To date, no other studies have been published that specifically address the issue of avoiding insulin treatment in renal transplant patients with pre-existing diabetes mellitus type 2. We therefore tried to identify baseline characteristics that could predict the need for insulin after a transplant. Patients who required insulin treatment after a transplant tended to have diabetes for a longer period and use oral antidiabetic drugs more frequently compared with patients who did not require insulin treatment, but these differences were not significant, possibly related to our limited sample size.

The most important limitations of this study are its nonrandomized design and the use of a nonconcurrent control group. This could have introduced several biases, although key characteristics (for example calcineurin inhibitor level relative to target range, cumulative steroid dose, and Hb A1c level before start of insulin) were comparable between both groups. Ideally, a larger, multicenter, randomized controlled trial should be performed to answer our main question more definitively. However, we expected a priori that only a few patients would meet the entry criteria, which would significantly impede execution of such a trial. Our data indeed confirmed the small percentage of eligible patients (2.5%). Therefore, our results currently provide the best evidence available concerning the choice of calcineurin inhibitor in this particular patient population.

In randomized clinical trials, immunosuppressive regimens based on cyclosporine instead of tacrolimus have been shown to be less effective in preventing both acute rejection and graft loss.^{2,9} In our study we did not observe a significant difference in rejection or graft loss, but our study was not designed and powered for this purpose. Nonetheless, the reduced efficacy of cyclosporine in preventing rejection could necessitate the increased use of high dosages of

steroids for antirejection treatment, resulting in even worse glucose control.

Finally, we like to emphasize that for long-term patient and graft survival, not only is glycemic control important, but also blood pressure control and the control of the lipid spectrum. Tacrolimus has been associated with less hypertension and dyslipidemia than cyclosporine, although a recent trial suggested that during the first 6 months of tacrolimus treatment, a modest derangement in liver enzymes occurs, suggesting lipid accumulation in the liver.¹⁰

In conclusion, based on the results of our study and the above-mentioned considerations, cyclosporine cannot be preferred over tacrolimus to minimize either the chance of requiring insulin treatment after a transplant, the required dosage of insulin, or the time to start insulin treatment after a transplant in patients with pre-existing diabetes mellitus type 2.

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