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Post-transplantation diabetes is better controlled after conversion from prednisone to deflazacort: a prospective trial in renal transplants

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Abstract It is well known that long-term use of steroids plays a decisive role in the development of glucose intolerance and diabetes mellitus (DM). Deflazacort, an oxazoline derivative of prednisolone, has been introduced as a potential substitute for conventional steroids in order to ameliorate glucose intolerance. We initiated a randomized study of conversion from prednisone to deflazacort in kidney transplantation (Tx) recipients presenting with pre-Tx or post-Tx DM to ascertain whether or not the switch to deflazacort would ameliorate the diabetic state. Forty-two recipients in the conversion group were compared with 40 patients on prednisone (the control group) in a prospective manner. The dose reduction of insulin or oral blood glucose-lowering agents, the adequacy of glucose control, and the development of side effects were the criteria for evaluating outcome. In the conversion group, patients were switched to deflazacort at a dose ratio of 6 mg deflazacort to 5 mg prednisone. During the mean follow-up period of 13.2 months, neither graft dysfunction nor acute rejection developed in the conversion group. Improvement in blood glucose control in the conversion group was noted. When the conversion group was stratified into pre- or post-Tx DM, promising effects were clearly evident in the post-Tx DM patients. More than 50 % dose reduction of blood glucose-lowering agents was possible in 42.3 % of post-Tx DM patients. In conclusion, it was readily possible to control blood glucose better in post-Tx DM recipients without seriously affecting the immunosuppressive activity after conversion to deflazacort.

Key words Kidney transplantation, diabetes mellitus, deflazacort · Diabetes mellitus, kidney transplantation, deflazacort · Deflazacort, kidney transplantation, diabetes mellitus

Introduction

Controlling blood glucose in diabetic kidney transplant (Tx) recipients is more difficult than in nondiabetics because long-term use of steroids and cyclosporin (CyA) is inevitable. CyA is partly responsible for post-Tx diabetes mellitus (DM) [14], but steroids are mainly responsible for glucose intolerance after Tx [2, 8]. There have been several studies since the mid-1980s that have attempted steroid withdrawal or steroid-free immunosuppression protocols after kidney Tx, and they have had promising outcomes in terms of adequate control of blood glucose [5, 8, 9]. However, rejection was incurred with steroid-free regimens in 24 %–74 % of patients and, ultimately, 24 %–60 % of them had to go back on oral steroids [9].

Deflazacort (Hoechst Marion Roussel), a 17-oxazoline, 21-acetate ester derivative of prednisolone, has

been introduced in clinical medicine and subsequently administered to Tx recipients as a substitute for conventional steroids to ameliorate glucose intolerance [1, 4, 11, 12] and to counteract growth failure in pediatric recipients [6]. The anti-inflammatory [10] or immunosuppressive activity [3, 4] of deflazacort is said to be equivalent to prednisone and to produce fewer side effects. Better control of blood glucose in diabetic renal Tx patients was reported after using deflazacort instead of 6-methylprednisolone in a small series [4]. We performed this prospective pilot trial to document the benefits and risks of elective conversion to deflazacort from prednisone in recipients who had pre-Tx or post-Tx DM during the maintenance phase of immunosuppression.

Patients and methods

As of January 1995, 154 kidney Tx patients at our hospital were found to have pre-Tx or post-Tx DM. After giving informed consent, 82 out of 154 were enrolled in this study. Seventy-two patients were excluded for the following reasons: short duration (< 6 months) after the onset of post-Tx DM ($n = 19$); switch to deflazacort before initiation of the study ($n = 14$); biopsy-proven chronic rejection and/or graft dysfunction ($n = 10$); age greater than 65 ($n = 5$); restrictive ambulatory state ($n = 13$), and poor compliance ($n = 11$). Various kinds of insulin preparations had been required in 16 pre-Tx, adult-onset, non-insulin-dependent DM patients because of prior difficulty obtaining adequate control of glucose with oral blood glucose-lowering agents. Forty-two of 66 post-Tx DM patients were taking either sulfonylureas ($n = 30$) or biguanides ($n = 12$) whilst the rest were dependent on insulin at the time of entry into the study. Forty-two patients were converted to deflazacort (the conversion group) and 40 remained on conventional prednisone (the control group). In the conversion group, patients were converted to deflazacort at a dose ratio of 6 mg deflazacort to 5 mg prednisone. The actual dose of prednisone was 10 mg/day in 31 conversion and 30 control group patients, while the remainder of each group was on 12.5 mg/day at the time of enrollment. There was no induction or overlapping period for the conversion trial. The dose of CyA or azathioprine was not changed intentionally.

The clinical data of body weight, daily requirement of insulin or oral blood glucose-lowering agents, CyA dosage, development of acute rejection, and infectious and other complications were monitored monthly. The laboratory data of serum creatinine, fasting blood glucose, whole blood CyA level, and serum cholesterol/triglycerides were tested at each monthly visit. The dose reduction of insulin or oral blood glucose-lowering agents, the adequacy of glucose control reflected in fasting blood glucose and level of glycosylated hemoglobin (HbA1C), and the development of side effects were the criteria for evaluating outcome. Conversion failure was defined as the development of acute or chronic graft dysfunction, biopsy-proven rejection, or severe gastrointestinal problems requiring hospitalization. Patients showing severe side effects or rejection episodes returned to conventional prednisone. The minimum follow-up after entry into the study was 6 months.

Student's *t*-test and Pearson's chi-square test were used to test the significance of the differences between the groups. Results were considered statistically significant when P was below 0.05.

The protocol was reviewed and approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine.

Table 1 Demographic and clinical data of the groups

Characteristics	Conversion group ($n = 42$)	Control group ($n = 40$)	P value
Age at Tx	45.8 ± 8.2[a]	43.5 ± 9.4[a]	0.23
Age at entry into the study	49.7 ± 8.1[a]	47.1 ± 9.4[a]	0.18
Male : female	33 : 9	29 : 11	0.66
Related : unrelated donor	16 : 26	13 : 27	0.27
Double : triple immunosuppression	24 : 18	27 : 13	0.37
Previous acute rejection episode within 1 year (%) after Tx	30.0	40.0	0.35
Interval from Tx to onset of post-Tx DM (months)	22.4 ± 23.0[a]	16.1 ± 16.4[a]	0.22
Interval from Tx to entry into the study[b] (months)	46.4 ± 28.5[a]	43.2 ± 19.5[a]	0.55
Interval from onset of post-Tx DM to entry into the study (months)	34.5 ± 20.6[a]	27.8 ± 15.3[a]	0.15
Pre-Tx : post-Tx DM ratio	13 : 29	3 : 37	0.004

[a] Data are expressed as mean ± standard deviation
[b] Including both pre-Tx and post-Tx diabetic recipients

Results

Demographics and clinical characteristics of the groups (Table 1)

There was no difference in gender or age between the groups. The mean interval from Tx to entry into the study was 46.4 months in the conversion group and 43.2 months in the control group. The mean interval from Tx to the onset of post-Tx DM or from the onset of post-Tx DM to entry into the study was comparable between the groups. More patients in the conversion group had pre-Tx DM than in the control group (31 % vs 7.5 %, $P = 0.004$) because randomization was blind to the presence of either pre-Tx or post-Tx DM. CyA-based immunosuppression protocols (double vs triple) were the same in the two groups. Finally, the percentage of patients experiencing previous acute rejection before entering the study was comparable (30 % vs 40 %) between the groups.

Causes of conversion failure

In the conversion group, nine patients developed mild to severe anorexia, nausea, and/or vomiting. Gastroduodenal endoscopy revealed no significant lesions. In six patients, symptoms were successfully relieved by conservative medical treatment and they continued on deflazacort. However, three patients could not tolerate the severe loss of appetite and anorexia they experienced,

Table 2 Change in graft function and CyA dosage during the study period

Parameters		Before the study	End of study	Delta	*P* value
Serum creatinine (mg/dl)	Conversion	1.27 ± 0.38	1.33 ± 0.47	0.06 ± 0.24	
	Control	1.20 ± 0.37	1.19 ± 0.46	−0.01 ± 0.25	0.23
CyA dosage (mg/kg per day)	Conversion	3.74 ± 1.23	3.61 ± 1.34	−0.14 ± 0.89	
	Control	3.66 ± 1.00	3.60 ± 1.07	−0.06 ± 1.13	0.73
CyA whole blood level (ng/ml)	Conversion	163.0 ± 58.6	176.4 ± 43.0	13.4 ± 60.8	
	Control	175.7 ± 49.2	162.8 ± 43.3	−13.0 ± 69.6	0.08

Data are expressed as mean ± standard deviation

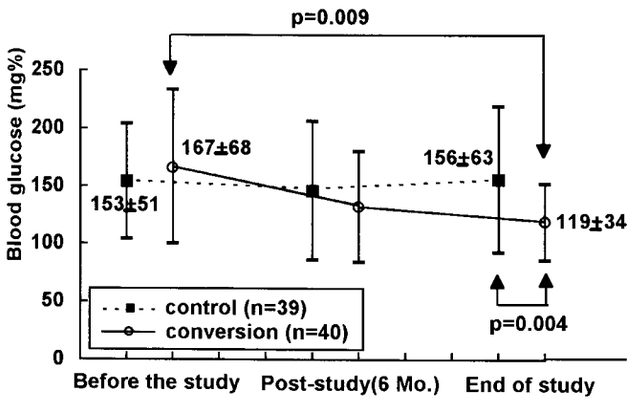

Fig. 1 Serial change in blood glucose levels during the study period. Data represent mean ± SD

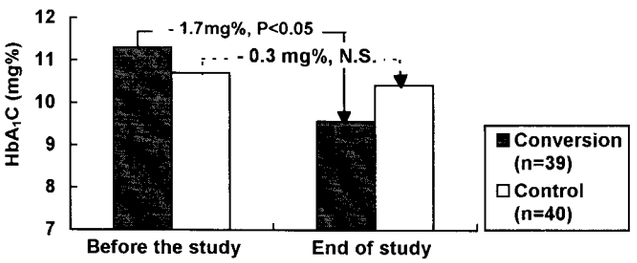

Fig. 2 Change in serum glycosylated hemoglobin A (HbA_1c) level during the study period

which might have been attributable to the rapid withdrawal of prednisone, and so they were ultimately put back on prednisone within 3 months of the conversion trial. Neither significant graft dysfunction nor acute rejection occurred after conversion.

One patient in the conversion group and another one in the control group died of unrelated causes (pre-existing liver dysfunction and recurrent rectal cancer, respectively). The incidence of severe infection requiring hospitalization did not differ (12.8 % in the conversion vs 17.5 % in the control group). No significant change in serum creatinine, CyA dose, or blood levels occurred after conversion (Table 2).

Control of blood glucose

Conversion to deflazacort was successful in 39 patients, and they were followed up for at least 6 months (mean 13.2, range 7–19, months). In 12 patients (30.8 %), more than 50 % dose reduction of required insulin or oral blood glucose-lowering agents was possible; in 4 patients, glucose control was readily possible without any agents or insulin; in another 2 recipients who were dependent on insulin, the switch to oral blood glucose-lowering agents was clinically possible. However, a significant dose reduction of insulin or oral blood glucose-lowering agents was possible in only two patients in the control group (Table 3). Significantly lowered fasting blood glucose and a reduced serum glycosylated hemoglobin level after conversion was evident (Figs. 1, 2). When we stratified the conversion group further into pre-Tx or post-Tx DM, a positive conversion effect was much more evident in patients suffering from post-Tx DM (Table 4). Twelve out of 26 post-Tx DM patients had enjoyed a significant dose reduction of insulin or oral blood glucose-lowering agents, which contrasted with the results in pre-Tx DM patients.

Change in body weight and serum lipoprotein profiles

A significant weight reduction was noted in the conversion group. The average reduction was 1.74 kg, compared to 0.58 kg in the control group. The average reduction in total cholesterol was 23.1 mg/dl in the conversion group, compared to 2.9 mg/dl in the control group, also a statistically significant difference ($P = 0.04$). However, the change in high-density lipoprotein (HDL), low-density lipoprotein, and triglyceride levels was not significantly different between the groups. The ratio of cholesterol to HDL, which had been cited as the most predictable index of myocardial infarction [13], was also not significantly different between the groups.

Table 3 Changes in dosage of insulin or oral blood glucose-lowering agents in both groups

	Number (%)		*P* value
	Conversion	Control	
No change	22 (56.4)	35 (87.5)	
Daily dose reduction < 50 %	5 (12.8)	3 (7.5)	
Daily dose reduction ≥ 50 %	6 (15.4)	1 (2.5)	0.0228
Insulin-free but still on oral blood glucose-lowering agents	2 (5.1)	1 (2.5)	
Free of both insulin/oral blood glucose-lowering agents	4 (10.3)	0 (0.0)	
Total	39 (100)	40 (100)	

Discussion

Glucocorticoids are still widely used in conjunction with CyA for various kinds of solid organ Tx worldwide. However, long-term use of steroids causes significant side effects such as diabetes, musculoskeletal complications, and growth retardation in pediatric patients. The development of DM or glucose intolerance after Tx has been a major concern [5, 8, 9].While CyA may contribute to glucose intolerance [7, 14], many clinicians agree that steroids are mainly responsible for the development of DM after Tx. Since 1994, deflazacort, a hexacyclic oxazoline derivative of prednisolone, has been available in Korea. We decided to initiate a prospective, randomized conversion trial from prednisone to deflazacort in 42 stable kidney Tx recipients suffering from pre-Tx (n = 13) or post-Tx (n = 29) DM. After the switch to deflazacort, the positive effects, reflected in a significant dose reduction of required insulin or oral blood glucose-lowering agents and lowered blood glucose, were evident in 42.3 % of the post-Tx DM patients without seriously affecting the immunosuppressive activity of conventional steroids. No increased incidence of rejection, graft dysfunction, or severe infection requiring hospitalization was noted. However, in the pre-Tx DM recipients, a lowered blood glucose level was not evident.

During the study period, daily doses of CyA and its blood levels did not change significantly. We were able to ascertain positive effects of deflazacort, such as significant weight reduction and better glucose tolerance with a reduced dose of insulin or oral blood glucose-lowering agents, which were in accordance with previous papers [4, 1, 12]. Severe side effects, such as refractory anorexia, nausea and/or vomiting, possibly from the acute withdrawal of conventional steroids, was noted in only three patients (7.1 %). Loss of appetite and the subsequent reduction in glucose loading might be among the mechanisms that explain the positive impact of deflazacort in controlling blood glucose.

In conclusion, an elective switch to deflazacort in stable, post-Tx DM renal allograft recipients during the maintenance phase of immunosuppression may represent a solution to the problem of glucose intolerance without interrupting the immunosuppressive action of conventional steroids. We suggest that deflazacort be indicated as a potential substitute for prednisone in recipients suffering from post-Tx DM. However, as this pilot trial was neither single nor double blinded, and since the patient cohort was a mixture of pre-Tx and post-Tx DM recipients, further studies with larger numbers of post-Tx DM patients will be necessary to confirm the benefits of deflazacort for diabetic renal transplant recipients.

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Table 4 Changes in dosage of insulin or oral blood glucose-lowering agents according to the types of diabetes

Change in daily requirement	Number (%)			
	Post-Tx DM		Pre-Tx DM	
	Conversion	Control	Conversion	Control
No change	12 (46.2)	33 (89.1)	10 (76.9)	2 (66.7)
Daily dose reduction < 50 %	3 (11.5)	2 (5.4)	2 (15.4)	1 (33.3)
Daily dose reduction ≥ 50 %	5 (19.2)	1 (2.7)	1 (7.7)	0
Insulin-free but still on oral blood glucose-lowering agents	2 (7.7)	1 (2.7)	0	0
Free of both insulin/oral blood glucose-lowering agents	4 (15.4)	0	0	0
Total	26 (100.0)	37 (100.0)	13 (100.0)	3 (100.0)
P value	0.0037		NS	

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