Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Effects of pancreas–kidney transplantation on diabetic retinopathy

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Keywords
cyclosporine, diabetes, diabetic retinopathy, kidney transplantation, pancreas transplantation.

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Received: 3 December 2003
Revised: 28 July 2004
Accepted: 26 January 2005

doi:10.1111/j.1432-2277.2005.00108.x

Summary

The effects of pancreas transplantation (PTx) on diabetic retinopathy (DR) are still debated. We studied the course of DR in 48 patients (age: 40 ± 7 years; males/females 26/22, body mass index (BMI): 23.0 ± 2.4 kg/m^2, duration of diabetes: 24 ± 8 years) bearing a successful PTx (combined with a kidney). Follow-up ranged 6–60 months (median: 17 months). Before transplantation, according to the Eurodiab Study classification, 12 patients (25%) had nonproliferative retinopathy (NPDR; mild, moderate or severe), and 36 patients (75%) had laser-treated and/or proliferative retinopathy (LT/PDR). During the follow-up, in the NPDR group improvement/deterioration was defined as regression/progression to a lower/higher retinopathy grade; in the LT/PTD group, stabilization was defined as no new neo-vessel formation or development of new lesions requiring laser-treatment. In the NPDR group, five (41.7%) patients improved of one or more lesion grading, three (25%) patients showed no change, and four (33.3%) patients progressed of one grade. In the LT/PDR group, the post-transplant data were: stabilization in 35 (97%) patients, and worsening in one (3%) patient. The number of improved/stabilized patients was significantly higher in the transplanted than in a control group of nontransplanted type 1 diabetic patients. In conclusion, despite a relatively short follow-up period, successful PTx in our cohort of patients was associated with improvement and/or stabilization of DR in the majority of recipients.

Introduction

Diabetic retinopathy (DR) is the most common condition that can cause visual loss in people with diabetes [1]. It involves changes to the retina, which is the nerve and blood vessel tissue in the back of the eye, and its development and severity are associated with the degree of diabetes control [2]. Indeed, studies such as the Diabetes Control and Complication Trial (DCCT) [3] and the United Kingdom for Prevention of Diabetes Study (UKPDS) [4], have demonstrated that lowering glycated hemoglobin (HbA1c) levels can reduce the rate of onset and the progression of DR, thus clearly confirming the role of plasma glucose concentrations in affecting this diabetes microvascular complication. It is therefore conceivable that normalization of glycemia as it can be achieved by pancreas transplantation (PTx) would have a beneficial impact on retinopathy. However, such issue is still debated. Ramsay *et al.* [5] found that PTx and subsequent normalization of blood glucose concentrations neither reversed nor prevented the progression of DR. These findings were then confirmed by other groups [6–8]. On the contrary, Konigsrainer *et al.* [9] reported that the course of retinopathy was positively influenced by

successful PTx, and Chow *et al.* [10] found stabilization of severe proliferative retinopathy (PDR) after PTx and appropriate laser therapy. The beneficial effects of PTx on DR have been confirmed in recent studies [11–13]. One possible explanation of these inconsistent results may be the use of different methods to classify DR. In the present report we studied 48 patients with successful PTx (combined with a kidney) in whom a careful eye examination was performed before and up to 60 months after grafting. DR was classified according to the Eurodiab Study [14]. The results showed that, as compared with a group of nontransplanted, matched type 1 diabetic patients, PTx recipients had a significantly higher rate of stabilization or improvement of DR.

Patients and methods

A group of 48 patients with successful pancreas–kidney transplantation was studied. Their main clinical characteristics were: age, 40 ± 7 years; males/females, 26/22; body mass index (BMI), 23 ± 2 kg/m^2, duration of diabetes, 24 ± 8 years. A group of 43 nontransplanted type 1 diabetic patients was also evaluated (age, 45 ± 8 years; males/females, 23/20; BMI, 24 ± 4 kg/m^2, duration of diabetes, 28 ± 7 years). In the transplanted group, immunosuppression maintenance therapy was based on tacrolimus (given at doses to achieve blood through levels of 10–15 ng/ml during the first month post-transplant, and of 8–12 ng/ml thereafter) or cyclosporine (given at doses to achieve blood through levels of 150–200 ng/ml up to 1 month, and 140–180 ng/ml thereafter), mycophenolate mofetil (1–2 g/day) and steroids (5 mg/day). All the patients (for a total of 89 eyes −7 blind eyes were excluded, in the transplanted group) were examined in a blinded manner with corrected visual acuity (according to the 'Early Treatment of DR Study', ETDRS, suggestions) [15], slit lamp examination, measurement of intraocular pressure, indirect and direct retinoscopy, and two nonstereoscopic 45° retinal photographs for each eye. Follow-up was 6–60 months (median: 17 months) in the transplanted group, and 8–66 months (median 18 months) in the control group. DR was classified according to the Eurodiab Study [14]: grade 0 means absence of lesions; grades 1–3 mean nonproliferative retinopathy (NPDR), respectively mild, moderate or severe; grades 4 and 5 mean proliferative and/or laser treated (LT) retinopathy. In the nonproliferative group, improvement/deterioration was defined as regression/progression to a lower/higher retinopathy grade [14]; in the proliferative and/or laser treated group, stabilization was defined as no new neo-vessel formation or development of other new lesions requiring laser treatment [14]. Statistical analysis was performed by the Student's *t*-test or chi-square test.

Results

Appropriate graft function in the transplanted patients during the study period was demonstrated by the presence of solid insulin independence (Table 1). Retinopathy data at baseline showed no significant difference between patients who were then transplanted and those in the control group: absence of retinopathy was found in no eye; mild, moderate or severe NPDR was observed in two (4%), five (10%) and five (10%) patients in the study group and in three (7%), six (14%) and three (7%) in the control group respectively; LT/PDR was diagnosed in 36 (75%) transplanted patients and in 31 (72%) nontransplanted patients. Macular lesions, cataract and abnormally high (above 21 mmHg and/or specifically treated) intraocular tone were respectively observed in 15 (31.2%), eight (27%) and four (8.3%) of patients who then received a pancreas–kidney graft, and in 16 (37%), six (14%), two (5%) of the nontransplanted subjects.

The results obtained at the end of follow-up are reported in Table 2 and Fig. 1. Higher rates of improvement/stabilization were observed in the transplanted patients, as compared with the control group, with the differences being particularly apparent in the case of LT/PDR. In addition, at the end of the follow-up macular lesions decreased in transplanted patients (from 31.2 to 10%, $P < 0.05$), but not in the control group (from 37 to 30%, ns). No change in cataract lesions or intraocular tone occurred from baseline to end of the study both in the transplanted and in the nontransplanted groups.

Table 1. Main metabolic parameters before and after transplantation (Tx).

	FPG (mg/dl)	HbA1c (%)	C-peptide
Before Tx	203 ± 76	8.7 ± 1.9	0.6 ± 0.1
Post Tx	84 ± 12*	5.0 ± 0.9*	3.9 ± 1.3*

FPG, fasting plasma glucose; *$P < 0.01$ versus pretransplant value.

Table 2. Evolution of diabetic retinopathy in transplanted and nontrasplanted patients. Results are given as number of patient (percentage).

	Transplanted		Nontransplanted	
	NPDR	LT/PDR	NPDR	LT/PDR
Improved	5 (10)	0 (0)	2 (5)	0 (0)
Unchanged	3 (6)	35 (73)	4 (9)	16 (37)*
Worsened	4 (8)	1 (2)	6 (14)	15 (35)*

*$P < 0.05$ versus LT/PDR transplanted.

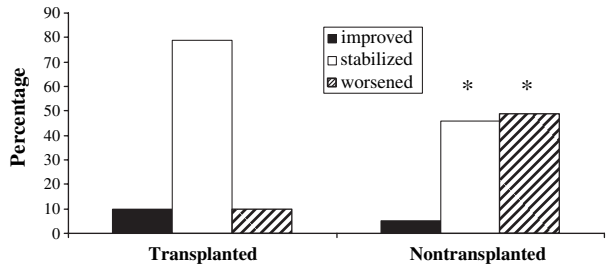

Figure 1 Percentage of patients with improved, stabilized or worsened diabetic retinopathy in the transplanted and nontransplanted groups. *$P < 0.01$ versus Transplanted.

Discussion

Diabetic retinopathy is a very common microvascular complication of type 1 diabetes [1,2]. In fact, after 5 years from diagnosis, 23% of patients have retinopathy. After 10 years, this prevalence increases to almost 60%, and after 15 years, 80% have retinopathy. Several factors affect the development and progression of this complication, and a major role is played by the degree of diabetes control [3]. However, intensive diabetes treatment can slow down, but not halt, the incidence of retinopathy. In the DCCT, the cumulative incidence of retinopathy in patients without lesions at baseline was 11.5% in the strict glycemic control group and 54.1% in the conventionally treated group after 8.5 years of follow-up [3]. In the same study, when retinopathy was present at the beginning of the trial, worsening of the retinopathy grading was observed in 17.1% of the patients in the intensively treated arm and 49.2% of the patients in the less strictly controlled group [3]. In addition, 8.1% and 15.3% of diabetic patients in the intensive therapy group developed new vessels and macular edema, respectively [16]. More scaringly, in patients with panretinal photocoagulation, it has been reported that after 2.9 years of follow-up 35% of eyes developed neovascularization [17]. In the present report we demonstrate that a condition of insulin independence and normoglycemia as achieved by PTxs in type 1 diabetic patients is associated with improvement and/or stabilization of DR in more than 90% of patients. These results were achieved by using a standardized classification of DR [14], which allowed for a more accurate assessment of the course of retinal lesions. Even when the degree of this complication was advanced, we observed that no further progression occurred during the follow-up period. However, a more prolonged period of observation will be needed to fully confirm these results. In any case, our findings clearly support the view that PTx has beneficial effects on DR [11–13]. In this regard, the restored kidney function as achieved with the combined kidney graft may also play a positive role [18]. It should be noted, however, than some patients in the NPDR group showed a worsening of the retinal lesions after transplantation, suggesting that additional strategies are needed to further improve the results.

Acknowledgements

This study was supported by a grant from the Italian Ministry of Education (MIUR 2002–2003).

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