Diabetologia (2006) 49:2977–2982
DOI 10.1007/s00125-006-0463-5

ARTICLE

Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients

R. Giannarelli · A. Coppelli · M. S. Sartini · M. del Chiaro · F. Vistoli · G. Rizzo · M. Barsotti · S. Del Prato · F. Mosca · U. Boggi · P. Marchetti

Received: 30 December 2005 / Accepted: 7 July 2006 / Published online: 5 October 2006

Abstract
Aims/hypothesis The effects of successful pancreas transplant alone (PTA) on chronic complications of diabetes, in particular diabetic retinopathy, remain disputed. We prospectively studied the course of diabetic retinopathy in PTA recipients and in non-transplanted (non-PTA) type 1 diabetic patients.
Methods The PTA and non-PTA groups consisted respectively of 33 (follow-up: 30±11 months) and 35 patients (follow-up: 28±10 months). Best corrected visual acuity, slit lamp examination, intraocular pressure measurement, ophthalmoscopy, retinal photographs, and in selected cases angiography were performed. Diabetic retinopathy and its improvement/deterioration were assessed according to criteria proposed by the Eurodiab Study.
Results At baseline, 9% of PTA and 6% of non-PTA patients had no diabetic retinopathy, 24 and 29% had non-proliferative diabetic retinopathy (NPDR), whereas 67 and 66% had laser-treated and/or proliferative diabetic retinopathy (LT/PDR), respectively. No new case of diabetic retinopathy occurred in either group during follow-up. In the NPDR PTA group, 50% of patients improved by one grading, and 50% showed no change. In the LT/PDR PTA, stabilisation was observed in 86% of cases, whereas worsening of retinopathy occurred in 14% of patients. In the NPDR non-PTA group, diabetic retinopathy improved in 20% of patients, remained unchanged in 10%, and worsened in the remaining 70%. In the LT/PDR non-PTA group, retinopathy did not change in 43% and deteriorated in 57% of patients. Overall, the percentage of patients with improved or stabilised diabetic retinopathy was significantly higher in the PTA group. No differences were found between the two groups with regard to cataract lesions and intraocular pressure values.
Conclusions/interpretation Despite a relatively short follow-up, our study shows that successful PTA can positively affect the course of diabetic retinopathy.

Keywords Diabetic retinopathy · Immunosuppression · Pancreas transplantation

Abbreviations

DCCT	Diabetes Control and Complications Trial
ETDRS	Early Treatment of Diabetic Retinopathy Study
LT/PDR	laser-treated/proliferative diabetic retinopathy
NPDR	non-proliferative diabetic retinopathy
PTA	pancreas transplant alone

Introduction

Retinopathy is the most common microvascular complication of diabetes, resulting in blindness for over 10,000 diabetic

R. Giannarelli · A. Coppelli · S. Del Prato · P. Marchetti
Department of Endocrinology and Metabolism,
Metabolic Unit, University of Pisa,
Pisa, Italy

M. S. Sartini
Department of Ophthalmology, University of Pisa,
Pisa, Italy

M. del Chiaro · F. Vistoli · G. Rizzo · M. Barsotti · F. Mosca · U. Boggi
Department of Oncology and Transplant Surgery,
University of Pisa,
Pisa, Italy

P. Marchetti (✉)
Department of Endocrinology and Metabolism,
Metabolic Unit, Cisanello Hospital,
Via Paradisa 2,
56100 Pisa, Italy
e-mail: marchant@immr.med.unipi.it

patients per year [1–3]. After 5 years from diagnosis, 23% of diabetic patients have retinopathy. After 10 years, this prevalence increases to almost 60%, and after 15 years to 80% of patients [1–3]. Several factors affect the development and progression of this complication, with the degree of diabetes control playing a major role [3]. However, intensive diabetes treatment can slow down, but not halt, the incidence of retinopathy. In the Diabetes Control and Complications Trial (DCCT), the cumulative incidence of retinopathy in patients without lesions at baseline was 11.5% in the strict glycaemic control group and 54.1% in the conventionally treated group after 8.5 years of follow-up [4]. In the same study, when retinopathy was present at the beginning of the trial, a worsening of the retinopathy grading was observed in 17.1% of the patients in the intensively treated arm and in 49.2% of patients in the less strictly controlled group [4]. In addition, 8.1% and 15.3% of diabetic patients in the intensive therapy group developed new vessels and macular oedema, respectively [4]. More worryingly, in patients with panretinal photocoagulation, it has been reported that after 2.9 years of follow-up, 35% of eyes developed neovascularisation [5].

Lately, the effects of combined pancreas–kidney transplantation on diabetic retinopathy have been described, and conflicting results reported [6–14]. Some work showed no significant change or even progression in retinal complications following combined pancreas–kidney transplantation [6–9]. In addition, an increased prevalence of post-transplant cataract has also been observed [15]. Other authors, however, reported more consistent improvements, including slower progression of established retinopathy and less need for laser therapy [10–14]. Little information is available with regard to the effects of pancreas transplant alone (PTA) on diabetic retinopathy. In a preliminary report, we suggested early improvement of retinopathy in nine patients at 6 months after PTA [16]. In the present study, we assessed the course of diabetic retinopathy in 33 patients who had had successful PTA and in whom a careful eye examination was performed before and up to 48 months after grafting. Diabetic retinopathy was classified according to the Eurodiab Study [17] and the results were compared with those obtained in a group of non-transplanted, matched type 1 diabetic patients.

Subjects, materials and methods

Patients' clinical data

A group of 33 consecutive patients with a successful PTA and a follow-up of at least 1 year was prospectively studied, together with 35 non-transplanted, matched type 1 diabetic patients, who had refused consent to the transplantation procedure. The PTA cohort included nine patients whose 6-month post-transplant data have already been briefly reported [16]. The main clinical characteristics of the studied subjects are reported in Table 1. The indication for PTA was established after assessment of benefits and risks for each patient. In line with recommendations from other studies [18–20], in our centre we consider PTA for patients who have two or more overt diabetic complications and/or glucose hyperlability with hypoglycaemic unawareness and impaired quality of life. Contraindications include: age >60 years, active smoking, obesity (BMI >30 kg/m^2), left ventricular ejection fraction <40%, active malignancy or infection, and unstable psychological profile. In the present study, 30 patients (91%) were transplanted because of the presence of diabetic complications and 3 patients (9%) due to glucose hyperlability (Table 1). The number of patients in the non-transplanted group with these conditions was 34 (97%) and 1 (3%), respectively. Follow-up was 30±11 months in the PTA group and 28±10 months in the control group. All subjects gave written, informed consent, as did pancreas donors or their next of kin.

Transplantation procedures and immunosuppression

Pancreas grafting was performed through a midline intraperitoneal approach [21]. All the grafts were transplanted using the portal-enteric drainage technique [22]. Briefly, the portal vein of the pancreas was anastomosed end-to-side to a major tributary of the superior mesenteric vein, while the donor iliac artery bifurcation graft was anastomosed end-to-side to the right common iliac artery. The transplanted duodenum was then anastomosed side-to-side to a diverting Roux-en-Y limb of the recipient jejenum. To prevent tissue rejection, induction therapy consisted of 20 mg basiliximab on the day of transplant and 4 days later, and maintenance therapy was based on tacrolimus (given at doses to achieve fasting blood

Table 1 Main clinical characteristics at baseline of transplanted and non-transplanted type 1 diabetic patients

	Transplanted	Non-transplanted
Number of patients (*n*)	33	35
Male/female	17/16	17/18
Age (years)	38±9	44±7
BMI (kg/m^2)	23.7±3	24.6±6
Indication for transplant		
Nephropathy+PN+DR[a]	5	2
Nephropathy+DR	16	17
PN+DR	9	15
Glucose hyperlability[b]	3	1

No statistically significant difference was shown between the two groups.

[a] Nephropathy: micro- or macroalbuminuria with GFR >50 ml/min

[b] Glucose hyperlability: hypoglycaemic unawareness and impaired quality of life

PN, painful neuropathy; DR, diabetic retinopathy

levels of 10 to 15 ng/ml during the first month post-transplant, and of 8 to 12 ng/ml thereafter), mycophenolate mophetil (1–2 g per day) and steroids (500 mg on the day of transplant, followed by tapering to 5 mg per day after 3 months).

Ophthalmological examination

All patients (133 eyes, as 3 blind eyes were excluded) were examined in a masked manner as follows: best corrected visual acuity (according to the Early Treatment of Diabetic Retinopathy Study [ETDRS] suggestions) [23], slit lamp examination, measurement of intraocular pressure, indirect and direct ophthalmoscopy, and two non-stereoscopic 45° retinal photographs for each eye. At baseline, retinal angiography was performed in three patients with grade 3 non-proliferative retinopathy (NPDR, see below) and in 11 subjects with laser-treated and/or proliferative retinopathy (LT/PDR, see below). During the follow-up, criteria for performing retinal angiography were progression to grade 3 (three patients), and development of new vessels or suspected ischaemic areas (nine patients), as assessed by ophthalmoscopy. Retinopathy was classified according to the Eurodiab Study [17]: grade 0 means absence of lesions; grades 1 to 3 mean NPDR (mild, moderate or severe); grades 4 and 5 mean LT/PDR. Panretinal photocoagulation had been performed in 12 PTA and 14 non-transplanted patients; focal treatment had been done in 9 PTA and 8 non-transplanted patients. Based on the Eurodiab Study [17], in grades 0 to 3, improvement/deterioration of diabetic retinopathy was defined as regression/progression to a lower/higher retinopathy grade [17]; in grades 4 and 5, stabilisation was defined as no new neo-vessel formation or development of other new lesions requiring laser treatment and, conversely, deterioration meant new neo-vessel formation and/or development of lesions requiring laser treatment [17]. Macular oedema was assessed according to the ETDRS [23], and cataract lesions were defined according to the Lens Opacities Classification System III [24].

Statistical analysis

Results are expressed as mean±SD. Comparisons were performed by the Student's *t* test or the chi-square test (see Results).

Results

Metabolic effects of PTA

Pancreas transplantation restored sustained normoglycaemia, without exogenous insulin administration (Table 2). In addition, plasma lipid levels and blood pressure values improved significantly after PTA, proteinuria decreased and no significant change of creatinine concentration occurred (Table 2). None of these parameters changed significantly in the control group (Table 2). At baseline, the number of patients treated with ACE-inhibitors was 14 in the PTA group and 18 in the control group, and the number of patients treated with a statin was 6 and 8, respectively. At the end of follow-up, ten and two patients in the PTA group were on ACE-inhibitor or statin therapy respectively (nine and ten respectively in the control group).

Ophthalmological effects of PTA

Mean best corrected visual acuity did not change significantly, either in the transplanted patients (from 8.6±2.0 to 8.0±3.3 lines), or in the non-transplanted patients (from 8.8±1.9 to 7.9±3.3 lines).

Retinopathy data at baseline showed no significant difference between patients who were then transplanted and those in the control group: absence of retinopathy was

Table 2 Some metabolic, blood pressure and kidney function parameters in transplanted and non-transplanted patients

	FPG (mmol/l)	HbA_{1c} (%)	C-peptide (nmol/l)	Total-CH (mmol/l)	LDL-CH (mmol/l)	HDL-CH (mmol/l)	TG (mmol/l)	SBP (mmHg)	DBP (mmHg)	Creatinine (μmol/l)	Proteinuria (g/24 h)
Transplanted											
Baseline	13.9±5.9	8.8±2.2[a]	0.003±0.0	5.2±0.8	3.35±0.87	1.47±0.37	1.16±0.56	130±14	81±10	84.8±23.8	1.2±2.4
Last control	4.9±0.9**	5.2±0.4**	0.90±0.4**	4.5±0.7*	2.66±0.58*	1.45±0.40	1.17±0.40	122±11*	77±8*	88.4±26.5	0.5±0.7*
Non-transplanted											
Baseline	10.7±4.4	7.9±0.8	0.009±0.0	5.2±0.8	3.27±0.72	1.55±0.32	0.87±0.39	133±12	80±8	78.6±17.7	1.0±0.5
Last control	10.6±3.9	7.4±1.5	0.009±0.0	4.9±0.52	3.18±0.5	1.57±0.4	0.86±0.37	136±16	77±8	76.0±10.6	0.9±0.5

[a] $p<0.05$ vs non-transplanted
*$p<0.05$ vs baseline
**$p<0.01$ vs baseline and non-transplanted
FPG, fasting plasma glucose; *CH*, cholesterol; *TG*, triglyceride; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

Table 3 Effects of pancreas transplant alone on grades and overall course of diabetic retinopathy

	Transplanted	Non-transplanted
No retinopathy (grade 0)		
Improvement	Not applicable	Not applicable
Stabilisation	3 (9%)	2 (6%)
Deterioration	None	None
Non-proliferative DR		
Grade 1		
Improvement	2 (6%)	None
Stabilisation	1 (3%)	None
Deterioration	None	1 (3%)
Grade 2		
Improvement	2 (6%)	2 (6%)
Stabilisation	2 (6%)	1 (3%)
Deterioration	None	5 (14%)
Grade 3		
Improvement	None	None
Stabilisation	1 (3%)	None
Deterioration	None	1 (3%)
Laser-treated/proliferative DR		
Grade 4		
Stabilisation	17 (52%)	10 (29%)
Deterioration	None	11 (31%)
Grade 5		
Stabilisation	2 (6%)	None
Deterioration	3 (14%)	2 (6%)
Any grade DR		
Improvement/stabilisation	30 (91%)	15 (43%)**
Deterioration	3 (9%)	20 (57%)**

Results are given as *n* and (%).
For details on grades, see text and reference [17]
DR, diabetic retinopathy
**$p<0.01$

found in three (9%) PTA and two (6%) control patients; grades 1 to 3 NPDR were observed in eight (24%) PTA and ten (29%) control patients; grades 4 and 5 retinopathy (LT/PDR) were found in 22 (67%) PTA and 23 (66%) control subjects. Macular oedema (without associated exudates) or cataract were observed in four (12%) and six (18%) patients in the PTA group respectively, and in six (17%) and four (11%) patients in the non-transplanted group. Abnormally high (above 21 mmHg and/or specifically treated) intraocular pressure was not detected in any patient.

At the end of follow-up, none of the patients without retinopathy developed retinal lesions. In the NPDR-PTA group ($n=8$), retinopathy improved in four (50%) patients and remained stable in four (50%) subjects. In the LT/PRD-PTA group ($n=22$), retinopathy remained unchanged in 19 (86%) patients and worsened in three (14%) subjects. In the NPDR non-transplanted group ($n=10$), retinopathy improved, did not change or deteriorated in two (20%), one (10%) and seven (70%) patients, respectively. In the LT/PRD non-transplanted group ($n=23$), retinopathy did not change in ten (43%) patients and worsened in 13 (57%) subjects. Table 3 details the results on diabetic retinopathy according to the grade of lesions and shows that PTA patients had overall a significantly better course of retinopathy. In particular, improvements occurred in the NPDR grade, and stabilisation in the LT/PDR group. An example of pre- and post-PTA retinal fundus is given in Fig. 1, showing marked amelioration at 1 year of follow-up. However, worsening of retinal lesions was observed in three patients with grade 5 diabetic retinopathy even after successful transplantation (Table 3).

In addition to these findings, we found that at the end of the follow-up macular oedema had disappeared in the PTA patients, but not in the control subjects. Corticonuclear cataract developed in three PTA and two non-transplanted patients, and surgical removal was necessary in two PTA patients and one control subject. Ocular tone did not differ between the baseline (14.0±2.0 and 14.2±1.9 mmHg in the PTA and control groups, respectively) and last control (15±2.0 and 14.9±1.9 mmHg) examinations. However, one PTA and one control patient developed neovascular glaucoma.

Discussion

Diabetic retinopathy is a very common and potentially devastating microvascular complication of diabetes [1–5]. Here we demonstrate that successful PTA has a significant-

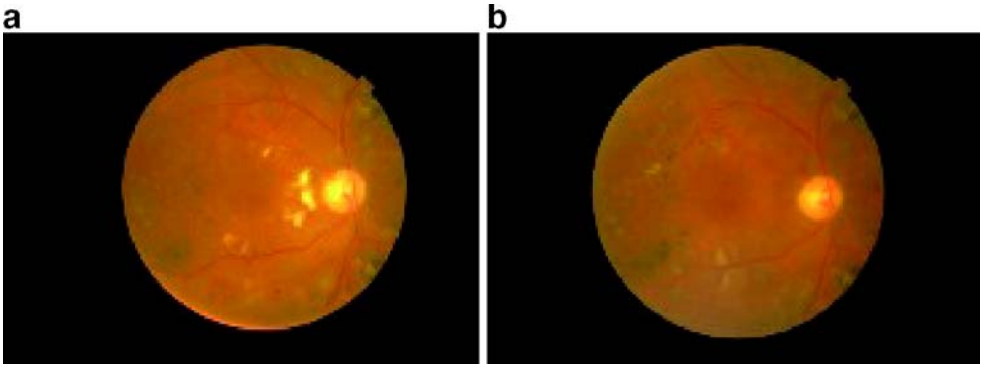

Fig. 1 Photographs of the retina of patient CB, showing laser-treated retinopathy. **a** Before transplantation; **b** 13 months after transplantation. The most apparent improvement was reduction/disappearance of exudates

ly positive effect on the course of diabetic retinopathy in type 1 diabetic patients.

The most plausible explanation for this finding is the achievement of sustained normalisation of blood glucose levels. In fact, normoglycaemia was rapidly obtained after transplantation, and steadily maintained afterwards. It is well established that intensive diabetes therapy can lower HbA_{1c} concentrations and reduce the progression rate of diabetic retinopathy [4]. However, many patients still progress to more severe lesions despite improvements in glucose control [4]. After blood glucose normalisation subsequent to simultaneous pancreas–kidney transplantation, a few groups (but not all) observed amelioration of diabetes ocular complications [6–14], but it cannot be ruled out that the attendant cure of uraemia might have played an important role [25]. Therefore, studying normoglycaemic pancreas-alone recipients is possibly a better way to assess the effects of normoglycaemia on diabetes complications.

Restoration of endogenous insulin secretion and normalisation of glucose concentrations could also have affected the improvement of lipid and blood pressure levels, although the mechanisms are still unclear [26, 27]. Notably, ACE-inhibition and statin therapies, which can favourably influence the course of microangiopathy [28–30], were not substantially different before and after PTA in our patients. In turn, lowered cholesterol and blood pressure levels might have contributed to the rescue of ocular structures. In fact, in patients from the DCCT cohort it was shown that higher serum lipids were associated with macular oedema and retinal hard exudates [31]. On the other hand, reducing blood pressure values can help regulate blood perfusion in the retinal vessels, thus decreasing shear stress and the consequent damage of the endothelial lining of the small vessels of the retina [1, 32].

Finally, it cannot be excluded that immunosuppressive therapy might have a direct, positive effect on the microvasculature. Indeed, chronic low-grade inflammation can lead to endothelial dysfunction and these two conditions are associated with diabetic retinopathy [33]. Since the immunosuppressants used in our anti-rejection protocols (including tacrolimus and mycophenolate mofetil) reduce inflammation through several mechanisms [33, 34], these agents could contribute to an improvement of the endothelial microenvironment.

However, it should be noted that in a proportion of our patients (14%) with proliferative retinopathy the lesions worsened after PTA, despite normalisation/improvement of many parameters. Once more, this supports the concept that in the event of very advanced vessel damage any treatment may arrive too late [1].

In conclusion, the present report describes for the first time the beneficial effects of PTA on diabetic retinopathy. Of course longer follow-ups and larger cohorts of patients will be needed to fully establish the role of this procedure on diabetic complications. Each type 1 diabetic patient who is potentially eligible for PTA will need careful examination to accurately weigh both the benefits and risks. Whereas clear and well defined indications for this procedure are still a matter of debate, our observations of significant improvements in diabetic retinopathy after successful PTA may contribute to the decision-making process.

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

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