EFFECT OF SUCCESSFUL COMBINED RENAL AND PANCREATIC TRANSPLANTATION ON DIABETIC RETINOPATHY

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The treatment of diabetic retinopathy (DR) is one of the most challenging problems in ophthalmology. The possibility of modulating DR by successful combined kidney and pancreas transplantation thus holds an attractive promise for the ophthalmologist.
From June 1983 until April 1997, a total of 86 combined kidney and pancreas transplantation procedures were performed at the Prague-based Institute for Clinical and Experimental Medicine.
All recipients are on close follow-up in terms of their ophthalmic status. However, evaluation of the effect of transplantation is problematic because of the advanced status of DR prior to the procedure.
We divided the transplant recipients into two groups according to type of transplantation. In Group I (segmental transplantation), proliferative DR was present in 100% eyes, 70% had undergone vitrectomy, and there were 21% of blind eyes. All eyes had been treated by laser. In this group, long-term stabilization of the finding was observed in three patients. In Group II (whole pancreas transplantation), proliferative and non-proliferative DR was diagnosed in 86% and 14%, respectively. There were 12% of blind eyes, and 70% had been treated by laser prior to transplantation.
After a successful transplantation, stabilization was found in 60%, improvement in 18%, and deterioration in 22% of eyes in this group. The stabilization and improvement can be explained by subsequent normoglycemia (HbAlc 5.6%). By contrast, we were unable to provide a satisfactory explanation for the deterioration and progression of these findings. While the effect of immunosuppression on DR remains unclear, it obviously accelerates the existing cataract.
Conclusion: Successful combined transplantation has a beneficial effect on DR and is worthwhile even for patients at the end stage on account of its beneficial psychosocial effect and prevention of dolorous glaucoma. However, many effects of the procedure on the eye of diabetics remain to be identified in future studies.

PURPOSE

Long-term studies such as the Early Treatment Diabetic Retinopathy study (ETDRS) as part of the U.S. Diabetes 2000 Project have clearly demonstrated a beneficial effect of normoglycemia on DR[1].

Normoglycemia thus becomes the mainstay in the prevention and treatment of DR. Although close diabetes compensation can be achieved by intensified insulin therapy or by insulin pump, this is often not possible at the end stages and with failing kidneys[1–4].

As a result, the possibility of modulating this disease by a successful pancreas transplantation and, consequently, normoglycemia, provides an attractive opportunity to the ophthalmologist[5].

METHODS

After the first-ever successful transplantation performed in 1966 in Minneapolis, USA, the first combined kidney and pancreas transplantation in the Czech Republic was performed in 1983. Up to April 1997, a total of 86 combined transplantations were carried out at the Prague-based Institute for Clinical and Experimental Medicine.

Of this number 38 transplantations performed before 1990 were segmental. Beginning in 1990, 48 whole-pancreas transplantations were carried out (Groups I and II). The mean duration of diabetes to transplantation was 26 years.

In Group I, transplantation was performed in 21 men and 17 women, while the respective figures were 29 men and 19 women in Group II. The mean ages of men on the day of transplantation in Groups I and II were 30 and 42 years. The respective figures for women were 37 and 38 years. 74% of Group I patients died, mortality in Group II was as low as 10.4% (Fig. 1).

All these patients had thorough ophthalmologic examination before transplantation. Photos were also taken of all patients; some had fluoroangiography. The level of DR was assessed and the degree of lens opacification was registered; intraocular pressure was measured. After transplantation, all patients are on regular follow-up.

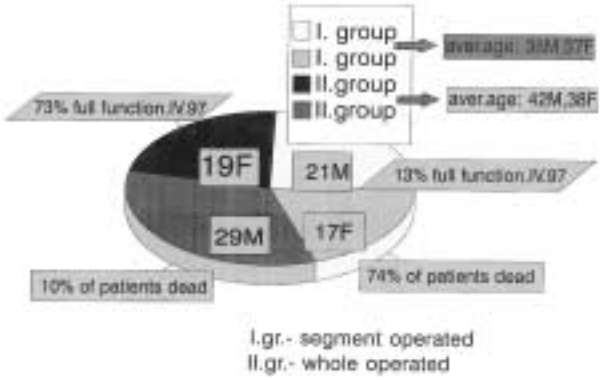


Fig. 1. Combined transplantation of pansreas and kidney – patients cohort

RESULTS

By April 1997, there were 13% and 73% fully functional pancreases in Groups I and II.

The degree of pre-transplant DR: In Group I, pre-transplant proliferative DR (PDR) was present in 100% of eyes, 100% of eyes were after laser therapy, 70% after vitrectomy, and 22% of eyes were blind. The mean visual acuity was 0.2.

In Group II, PDR was found in 86% of eyes, laser therapy had been performed in 70% (90% PRFK, 10% grid) of patients, vitrectomy in 10%, and blindness was diagnosed in 12% of patients. The mean visual acuity was 0.25 (Fig. 2).

In Group I, the findings stabilized in three patients, with the longest follow-up period being 11 years (Fig. 3a, b, c).

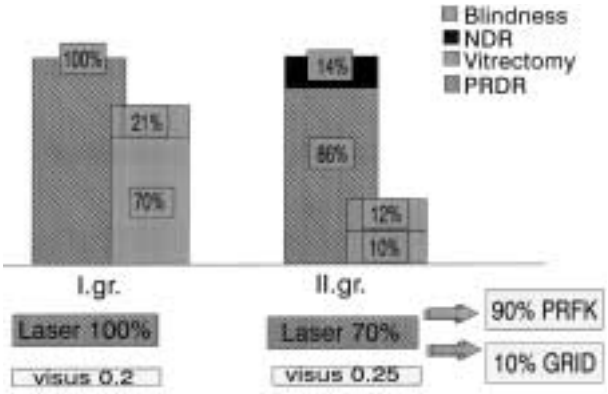


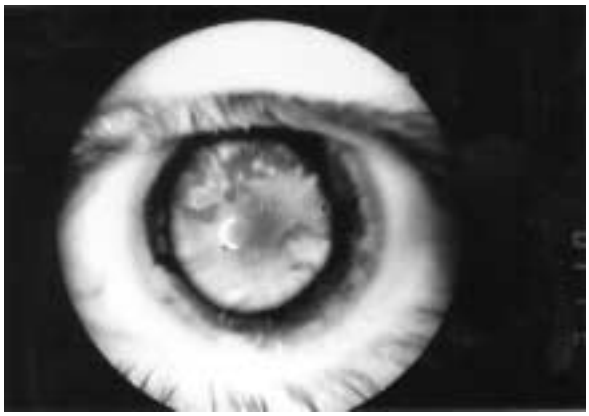
Fig. 2. Level of diabetic retinopathy before transplantation

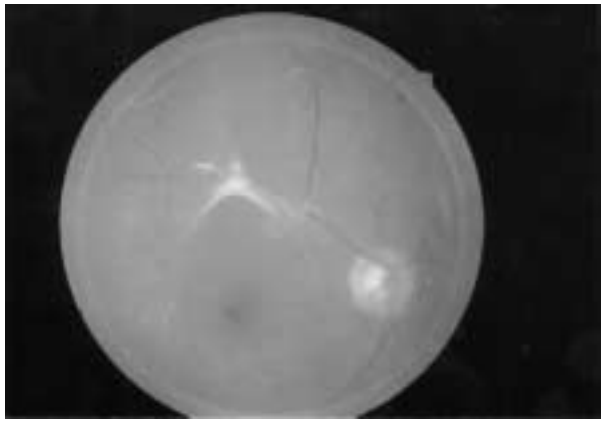
In Group II, the findings stabilized in 60% of patients, improved in 18% of eyes, and worsened in 22%. The longest follow-up period in this group was 28 months (Tab.1).

Table 1. Evolution of diabetic retinopathy after combined tranplantation.

I. group	–	stabilization	8 %
	–	the longest follow-up period	= 132 months
II. group	–	stabilization	60 %
	–	improvement	18 %
	–	deterioration	22 %
	–	the longest follow-up period	= 28 months

Because of cataract acceleration, phacoemulsification combined with IOL implantation was performed in four eyes of three patients.





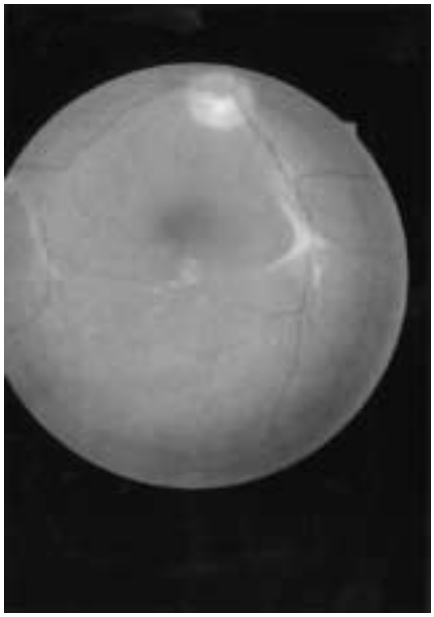


Fig. 3. Female patient, D. M. 1960, I-type DM. Finding prior to combined renal and pancreatic transplantation in 1983.
a) Left eye, final stage of DR, amaurosis,
b) Right eye, fundus, high-risk proliferative DR with large sheet of fibrous tissue extending across the posterior pole.
c) 11 years after successful combined renal and pancreatic transplantation. Finding on fundus fully stabilized

DISCUSSION

Apart from ubiquitous senile macular degeneration, diabetic retinopathy is the most formidable challenge to ophthalmologists. As its pathogenesis is not yet completely understood and because of the multitude of risk and protective factors involved, treatment of DR poses a difficult problem. DR is the most frequent cause of blindness in the industrialized nations[2,3]. In the Czech Republic, about 20% of diabetic patients suffer from DR in various stages. The prevention and, most importantly, the treatment of this disease, whose course is often unpredictable, is very complicated and the outcome is often disappointing.

The reason for this is the variety of risk factors involved, many of which are still not fully understood. Several aspects of the pathogenesis, onset and development of DR also remain unclear. While glycated hemoglobin over 10% and glycemia over 10 mmol/L make a well defined limit of sorbitol overload and, consequently, osmotic destruction, particularly of pericytes, in the capillary endothelium, the role of direct action of insulins on the diabetic retina is still being hotly discussed.

The most controversial issue is the stimulation or inhibition of oedema and proliferation by insulin. The hemorheologic effects on a fibrinolytically and antithrombotically altered capillary endothelium are not completely clear either[6,7]. Another important factor is hypertension and administration of ACE-type antihypertensive agents (angiotensin-converting enzymes). 30–50% of diabetics in Europe suffer from hypertension.

With clinically significant macular oedema, the parameters that have to be monitored include cholesterol levels, triglyceride levels along with the total cholesterol/HDL ratio. ILGF levels also influence DR. An indisputable role is also played by hematologic, hemodynamic, hemorheologic changes and genetic factors.

Our explanation for the improvement and stabilization is subsequent normoglycemia, BP compensation and grade of DR[8–11]. By contrast, we were unable to explain totally the deterioration and progression of DR in cases of completely compensated DM and BP associated with normal RAC. We can only speculate that it was due to an ocular cause, involving an imbalance between anti-neovascular and vascular factors in the ischemic retina. The non-ocular risk and protective factors are indisputably of great significance in predisposing the diabetic retina for the development of retinopathy. However, it is necessary to appreciate that it is the ocular factors which determine how, when, and to what extent this predisposition will develop[7].

A frequent finding is the progression of cataract. For this reason, these patients must undergo surgery. As DR is developed in all patients, the risk of its progression post-operatively is high[12]. The cause for this acceleration is apparently long-term immunosuppression and corticoid administration. The effect of long-term immunosuppression on DR is still subject to research.

It can be reasonably concluded that combined transplantation is a stabilizing element for DR, mainly because of subsequent normoglycemia and BP compensation.

There is no doubt that combined transplantation has a psychosocial impact even at the end stages of DR, since it releases the blind patient from dependence on self-monitoring and insulin administration.

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REFERENCES

1. Early Treatment Diabetic Retinopathy Study Group. Ophthalmology, Suppl *1–7*, (1991).
2. Fegerberg, S.E. (1980) Control of blood glucose and diabetic vascular disease. Acta Endocrinol. *94/235*, 42–43.
3. Hamilton, A., Ulbig, M., Polkinghorne, P. (1996) Management of Diabetic Retinopathy. BMJ Publishing Group, London, 1–13.
4. Olk, L., Lee, C. (1993) Diabetic Retinopathy. J. B. Lippincott comp., Philadelphia.
5. Kampik, A., Ulbig, M. (1986) Is proliferative diabetic retinopathy an indication for pancreatic transplantation. Transplant Proc. *18/4* Suppl.3, 62–63.
6. Bartoš, V., Pelikánová, T. (1996) Praktická diabetologie. Maxdorf, Praha 197–223.
7. Sosna, T., Saudek F. (1995) Is successful pancreas transplantation a protective factor for diabetic retinopathy? Eur. J. Ophthalmol. vol. *5*/No 2A, Suppl, 137.
8. Bandello, F., Vigano, C., Secchi, A. (1991) Effect of pancreas transplantation on diabetic retinopathy: 20-case report. Diabetologia, *34,* Suppl l, 92–94
9. Konigsrainer, A., Miller, K., Steurer, W. (1991) Does pancreas transplantation influence the course of diabetic retinopathy? Diabetologia, *34* Suppl 1, 86–88.
10. Di Landro, D. Koengsrainer, A., Oefner, D. (1996) Experience with 100 combined renal transplantations in single center, Nephron *72* (4), 547–51.
11. Traeger, J., Monti, L. (1986) Early diabetic nephropathy as an indication for pancreatic transplantation. Transplant Proc., *18/4* Suppl.3, 64–65.
12. Freeman, R. W. (1993) Practical Atlas of Retinal Disease and Therapy, Raven Press, New York, 130–132.