SUMMARY - Pancreatic transplantation is the best method of replacing the endocrine function of the gland in Type 1 insulin-dependent diabetic patients. At the end of 1996, 9,000 pancreas transplants had been reported to the International Pancreas Transplant Registry. For 1994-1996, one-year pancreas survival rates were 81% for simultaneous pancreas and kidney transplantation (n = 1,516), 71% for pancreas after kidney (n = 141) and 64% for pancreas alone (n = 64). In patients with a functional graft, glycosylated haemoglobin, fasting blood sugar, and 24-h metabolic profiles are normal. The effect of pancreatic transplantation on secondary complications often appears after several years of normal pancreatic function. Successful transplantation is associated with an improvement in different aspects of the quality of life. The decision to perform pancreatic transplantation depends on the balance between the risks of transplantation, mainly surgical or related to immunosuppression, and those of diabetes development. The advantages and drawbacks of pancreatic transplantation and insulin therapy need to be honestly and carefully analysed for specific populations of diabetic patients as well as for each individual. At present, simultaneous pancreatico-renal transplantation is the best treatment for diabetic patients with chronic renal failure. Transplantation of the pancreas alone in non-uraemic patients may also be considered in carefully selected subjects. Diabetes & Metabolism 1998, 24, 195-199.

Key-words: pancreas transplantation, results, indications, secondary complications.

RÉSUMÉ - La transplantation pancréatique : résultats et indications. La transplantation pancréatique est la meilleure méthode de remplacement de la fonction endocrine du pancréas chez les patients diabétiques insulinodépendants de type I. À la fin de 1996, 3 000 transplantations pancréatiques étaient rapportées au Registre International de Transplantation Pancréatique. Pour la période 1994-1996, la survie du greffon pancréatique était de 81 % à un an pour la transplantation rein-pancréas simultanées (n = 1 516), de 71 % pour le pancréas après rein (n = 141) et de 64 % pour la transplantation de pancréas seul (n = 64). Chez les receveurs porteurs d’un greffon fonctionnel, l’hémoglobine glycosylée, la glycémie et les profils métaboliques sont normaux. L’effet de la transplantation pancréatique sur les complications secondaires apparaissent après plusieurs années d’une fonction pancréatique normale. Le succès de la transplantation est associé à une amélioration dans différents aspects de la qualité de vie. La décision de réaliser une transplantation pancréatique dépend de la balance entre les risques opératoires ou de l’immunosuppresion, et les risques évolutifs du diabète. Les avantages et les inconvénients de la transplantation pancréatique et de l’insulinotherapie doivent être honnêtement et attentivement analysés pour une population diabétique spécifique et sur le plan individuel. Actuellement, la transplantation simultanée rénale et pancréatique est le traitement le plus adapté pour les diabétiques avec insuffisance rénale chronique. La transplantation du pancréas isolé chez les patients non urémiques est une option qui s’adresse à certains patients sélectionnés. Diabetes & Metabolism 1998, 24, 195-199.

Mots-clés : transplantation pancréatique, résultats, indications, complications secondaires.
Pancreatic transplantation has become the best method of replacing the endocrine function of the gland in Type 1 insulin-dependent diabetic patients. Since the first attempts at the end of the 1960s, more than 10,000 transplants have been performed, half during the past decade. Results have considerably improved, reaching the patient and graft survival rates observed after transplantation of other solid organs such as kidney, liver, or heart. Simultaneously, the morbidity and mortality of the surgical procedure have decreased, while progress in immunosuppression has led to greater efficacy and less toxicity. As a result of these improvements, the indications for pancreatic transplantation are gradually moving towards transplantation earlier in the course of the diabetic disease.

**RESULTS**

The International Pancreatic Transplant Registry offers a unique source of information. The registry summarises large numbers of grafts. However, data need to be analysed with due caution since they are collected in numerous centres. Individual centres usually publish more homogeneous and often better results.

At the end of 1996, 9,000 pancreas transplants had been reported to the International Pancreas Transplant Registry [1], although this number was probably an underestimation since only 2,100 cases (104 in 1996) were reported from European countries. Bladder drainage for duct management was used in the majority of cases (92% of U.S. cases). However, more physiological enteric drainage of exocrine secretion has recently regained popularity. When 1987/96 U.S. data for bladder drainage were analysed according to the three major recipient categories — simultaneous pancreas and kidney transplantation (SPK) in diabetic patients with chronic renal failure (n = 3,989), pancreas after kidney (PAK) in diabetic patients with a functional renal graft (n = 375), and pancreas alone (PTA) in non-uremic diabetic patients (n = 229) — patient survival rates at one year were respectively 92%, 92% and 91%. Graft survival rate was 79% in the SPK group and thus significantly higher (P = 0.001) than for PAK (60%) and PTA (57%) groups. In the SPK group, kidney survival at one year was 88%. An improvement in graft survival rates was demonstrated for all categories. For 1994-1996, one-year pancreas survival rates were 81% for SPK (n = 1,516), 71% for PAK (n = 141) and 64% for PTA (n = 64).

For all categories of transplants, minimisation of HLA mismatches was associated with a significantly lower risk of graft loss. The positive impact of HLA-matching was best seen in the group of recipients who died with a functioning graft. For SPK cases, the risk of graft loss at one year for 0, 1, 2-3 and 4-6 mismatches was 0%, 9%, 4% and 5% respectively. For PAK, it was 0%, 12%, 19% and 26%. Although the number of patients was small (n = 35), it was striking that no immunological loss was observed before one year in any category for all pancreas recipients with 0 mismatch grafts.

Progress in immunosuppression has been associated with improved results. In the SPK and PTA categories, anti-T-cell therapy (antilymphocyte globulins, antithymocyte globulins, OKT3 monoclonal antibodies) has significantly lowered the risk of graft loss. In the SPK category, the graft survival rate was 81% with OKT3 (n = 1,600), 78% with ALG or ATG (n = 1,715) and 75% with neither (n = 457; P < 0.001). In the PTA category, one-year survival was 59% when ALG or ATG was used (n = 132), 57% with OKT3 (n = 76) and 26% (n = 13) when neither was used. When Ciclosporin and Tacrolimus were compared in PTA, no differences were observed in one-year graft survival rates, although the number of immunological losses was higher with Ciclosporin than Tacrolimus (9% and 0% respectively; p > 0.2).

**INDICATIONS**

Unlike heart, lung or liver transplantation, pancreatic transplantation is not a lifesaving procedure. Patients have to be carefully selected in order to reduce morbidity and mortality. Investigations of myocardial and cerebral vascularisation are mandatory. Coronary arteriography has to be performed when thalium scintigraphy is not normal, and angiography of the cerebral arteries when the carotid Doppler is not normal. Severe vascular abnormalities need to be corrected prior to transplantation. Cancer and a developing viral or bacterial infection, as well as other contraindications to organ transplantation, must be respected.

Indications should be discussed on the basis of the results of pancreatic transplantation in terms of normalisation of glucose metabolism, the effect on secondary complications and quality of life.

Normalisation of glucose metabolism after pancreatic transplantation has been well-demonstrated. In patients with a functional graft, glycosylated haemoglobin, fasting blood sugar, and 24-h metabolic profiles are normal [2, 3]. In the absence of rejection, the quality of the function is maintained at long term. However, total pancreatic grafts show a better response to intravenous or oral glucose tolerance tests than do segmental grafts [4].

For two main reasons, the effects on secondary complications are more difficult to demonstrate. Firstly, most pancreatic transplantations are performed at a late stage of the diabetic disease in patients with severe secondary lesions. The effect of pancreatic transplantation often appears after several years of normal pancreatic function [5-8]. Secondly, the capa-
city of pancreatic transplantation to reverse nephropathy has been demonstrated by studies in patients receiving a pancreas several years after a kidney graft. Renal biopsies taken at the time of pancreatic transplantation and then several years later have shown improvement of glomerular lesions [9].

The decision to perform pancreatic transplantation depends on a balance between the risks of transplantation, mainly surgical or related to immunosuppression, and the risks of diabetes development.

**Insulin-dependent diabetic patients with chronic renal failure** – In this category of patients, the choice is between dialysis (continuous ambulatory peritoneal dialysis, haemodialysis), renal transplantation alone, or pancreatorenal transplantation.

Data on the course of diabetic patients on dialysis are difficult to find in the literature. In France, according to the 1995 UREMIDIAB study [10], the prevalence of diabetic patients in the dialysed population was 14.2%, and the incidence was 17.7%. Thirteen percent of the population had Type 1 diabetes. Four years after starting dialysis, only 10% of diabetic patients (Type 1 and 2 combined) were alive. In Europe, according to the 1994 report on management of renal failure [11], patient survival after renal replacement (dialysis and renal transplantation) in diabetic patients (Type 1 and 2 combined) was between 50% and 55% at 2 years, but only 25% five years after the start of treatment. In 1995, dialysis accounted for 80% as the first mode of treatment for non-paediatric patients [12]. Survival curves for patients starting treatment in 1981, 1984 or 1988 showed virtually no differences. Restriction of the overall survival analysis to patients reported to have diabetic nephropathy as the primary renal disease and who were 15 to 34 years of age at the start of treatment led to only a slight increase in survival (55% at 3 years). Forty percent of these patients were supported by a functional graft. Thus, there is a clear need for more complete and more precise studies. However, directly or indirectly, these data demonstrate that the results of dialysis in diabetic patients are poor. The main causes of failure are related to difficulties of vascular access, infectious complications, myocardial and cerebrovascular complications and the development of secondary diabetic complications.

For many years, kidney transplantation alone has been the treatment of choice for uraemic in diabetic patients, mainly because of the greater life expectancy and better quality of life that it provides. However, a patient with a successful renal graft is not in the same condition as a diabetic patient without renal failure since the risks of surgery and immunosuppression are to be added to those of diabetes. Although it can enhance the quality of life, simultaneous pancreas transplantation is not performed in many centres because it may cause complications not encountered when only a kidney is transplanted. At present, the additional risks of mortality and morbidity with pancreas transplantation are respectively estimated to be 1% to 2% and 10 to 15% [13, 14]. Are these risks worth taking to achieve a potential additional improvement in the quality of life by becoming non-diabetic as well as dialysis-free? In the literature, only incomplete answers have been given to this question up to the 1990s.

The 1992 annual report of the USRDS (United States Renal Data System) is a landmark [15]. Patient and kidney survival were compared in two groups of patients receiving an SPK or a renal transplantation alone. No statistically significant differences were observed in patient survival in this large series (n = 3,168) of patients 18 to 45 years of age who received a cadaveric kidney between 1986 and 1989. Nine point seven percent of SPK patients and 9.8% of KTA patients died during the study period up to the end of 1990. Kidney graft survival was significantly higher for SPK patients than for KTA patients. During the first year following transplantation, 16.8% of SPK grafts and 25.2% of KTA kidney grafts failed. This study indicated that the risk of death associated with SPK was not greater than with KTA. Furthermore, the risk of kidney graft failure was lower among SPK transplants than KTA up to 29 months after transplantation and possibly longer. From this report, as well as from many publications from individual centres [16-18], simultaneous pancreas-kidney transplantation now appears to be the best treatment for uraemic diabetic patients. However, careful selection of recipients is necessary, and this selection may influence the interpretation of results.

**Non-uraemic diabetic patients** – Diabetic patients with a functional kidney graft are a particular category of non-uraemic subjects. They have a long history of diabetes, and the risk of secondary complications is high. They receive immunosuppressive treatment to maintain renal graft function. Theoretically, they are excellent candidates for PAK. However, the results of PAK are not as good as those of SPK, probably because of genetic differences between the kidney donor and pancreas donors. In these patients, the indication of pancreatic transplantation depends on the course of secondary complications and the day-to-day problems of insulin therapy. Because of their immunosuppressed condition, they might be the best candidates for islet transplantation, especially when they belong to the group of SPK in which a pancreatic graft has failed for technical reasons and pancreatic retransplantation represents a risk related to local or general conditions.

Pancreatic transplantation has many advantages: secretion by the graft of C peptide and amylin, the other hormone of β cells; normalisation of glucose metabolism with (systemic venous drainage) or without hyperinsulinaemia (portal venous drainage); and improved metabolic profiles. Immunosuppressants...
are given per os, and monitoring of the graft is simple (usually one blood sample per month after one year). There are no diet restrictions. When performed before secondary complications occur, or when they are not serious, pancreatic transplantation may cure or improve neuropathy, retinopathy, nephropathy and macroangiopathy. Results in terms of quality of life are excellent.

The drawbacks of pancreatic transplantation are related to surgical risks and long-term risks and side effects of immunosuppression.

The main advantages of exogenous insulin are the relative simplicity of treatment and monitoring, which however require multiple daily injections and capillary glycaemia, possibly influencing the quality of life of the patient. Intensive therapy delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy. In the Diabetes Control and Complications Trial study [19], the risk of retinopathy was reduced by 76 % as compared to conventional therapy, and the progression of retinopathy was reduced by 54 %. However, intensive therapy did not reduce the incidence of ketoacidosis but increased (threefold) that of severe hypoglycaemic coma and weight gain. There was no change in the quality of life. Exogenous insulin has its drawbacks because of the absence of amylin and C-peptide secretion that may protect against secondary complications. Daily injections and monitoring as well as diet may represent a psychological burden. Insulin concentrations are unphysiological in the absence of a feedback mechanism. The balance between hypoinsulinaemia and hyperinsulinaemia and hyperglycaemia and hypoglycaemia is difficult to adjust. Lipodystrophy at injection sites and allergy may be a problem in some patients.

Ideally, pancreatic transplantation should be performed earlier in the course of the disease, before the appearance of secondary complications including nephropathy. As results have improved considerably during the past 5 years, the indication of pancreatic transplantation alone has become the main subject of controversy in pancreatic transplantation.

As a preliminary consideration, the respective advantages and drawbacks of pancreatic transplantation and insulin therapy need to be honestly and carefully analysed for specific populations of diabetics as well as for each individual.

In diabetic patients without renal failure, the choice of pancreatic transplantation should be determined by the balance between the risks of surgery and immunosuppression on the one hand and the risks of secondary diabetic complications and complications of insulinotherapy on the other.

The three key questions are:

- Will pancreas transplantation have a positive, neutral or negative effect on patient survival?
- Will the benefits of insulin independence offset the side effects of antirejection drugs?
- Will the management of immunosuppression be less, more or equally difficult than/as management of diabetes?

The cooperation of diabetologists and transplant surgeons is mandatory in order to select patients for whom pancreatic transplantation will reduce the risks of severe complications of diabetes while offering a better quality of life.

The population of diabetic patients is not homogeneous. At the present time, candidates for pancreatic transplantation can be selected among various categories of diabetic subjects. In some patients with labile diabetes, immunosuppression could be an acceptable alternative, and some patients with frequent hypoglycaemic episodes requiring constant family attention could also benefit from pancreatic transplantation, especially when HbA1C is high. Some patients with poor compliance with insulin injections and monitoring might prefer immunosuppressive drugs.

Trials comparing insulin therapy with transplantation of the pancreas alone could be performed at the onset of diabetics or after a delay, for example, of 10 years of microalbuminuria. However, before considering these types of studies, results of pancreatic transplantation alone need to be improved, and immunosuppression must progress.

### CONCLUSION

The results of pancreatic transplantation have improved considerably during the past decade. Normalisation of glucose metabolism is regularly obtained in successful pancreatic transplantation. The effects on secondary diabetic complications still need to be confirmed. However, improvements of neuropathy and stabilisation of retinopathy have been demonstrated in several studies after a few years of graft function. Successful transplantation is associated with an improvement in different aspects of the quality of life.

At the present time, simultaneous pancreateicorenal transplantation is the best treatment for diabetes with chronic renal failure.

Improvements in surgical techniques and better handling of immunosuppression, including the use of new immunosuppressive agents, should make PTA more feasible in non-ureaemic diabetes. Candidates could be chosen among subjects with advanced autonomic and peripheral neuropathy, or oscillating ketoacidosis and hypoglycaemia, or rapidly developing retinopathy and loss of visual acuity.

In the future, pancreatic transplantation could also be used prophylactically to prevent secondary complications. This possibility will be based on the study of genetic susceptibility to complications. At the present time, genetic markers are lacking, although microalbuminuria has been shown to be an early marker of nephropathy in some patients. Elevated Na/Li counter-
transport may prove to be an interesting marker if its capacity to predict the development of nephropathy is confirmed.

Candidates for pancreatic transplantation alone could also be selected from the prepubertal diabetic population: the younger the onset of diabetes, the greater the risk of complications. However, well-controlled insulin treatment during childhood and adolescence is not without psychological consequences. Transplantation could be considered when patients reach their majority and can participate in the choice of the most suitable treatment.

Only well-conducted, prospective, randomised studies can compare the potential advantages of transplantation (implying the use of immunosuppression) over those of remaining diabetic for many years.

These new indications open up exciting prospects for pancreatic transplantation. Diabetologists and transplant surgeons need to cooperate to select the patients who will benefit the most from pancreatic transplantation.

REFERENCES

1 International Pancreas Transplant Registry, Minneapolis. 1997, 09, 1-12.