KIDNEY AND KIDNEY-PANCREAS TRANSPLANTATION IN DIABETIC RECIPIENTS

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SUMMARY - Type 1 as well as Type 2 diabetic patients in end-stage renal failure and with no contraindications to kidney transplantation have a greater probability of survival with a functioning kidney graft than if they remain on dialysis. Five-year patient and pancreas graft survival rates for simultaneous kidney-pancreas transplantation are currently 81 and 67% respectively. The main benefit of this operation is to achieve insulin independence and improved quality of life. However, surgical morbidity is higher and the immunosuppressive regimen more powerful than for kidney transplantation alone. The 5-year survival rate for kidney transplantation in Type 2 patients without severe cardiovascular disease is 81%, although a high incidence of peripheral vascular complications can be expected. Renal transplantation should be considered in diabetic patients with a life expectancy of more than 5 years, no contraindications to immunosuppressive treatment, and low per operative risk. Combined kidney-pancreas transplantation should be considered in Type 1 patients under 50 years of age with no or moderate cardiovascular complications and a thorough understanding of the risks and benefits of the procedure.

Key-words: kidney, kidney-pancreas, transplantation, diabetes.

RÉSUMÉ - Transplantation rénale et rein-pancréas chez les diabéti ques. Les diabétiques, aussi bien de type 1 que de type 2, en insuffisance rénale terminale et sans contre-indication à la greffe rénale ont une probabilité de survie supérieure étant greffés que restant en dialyse. Après transplantation combinée rein-pancréas, la survie à 5 ans des patients et des greffons pancréatiques est actuellement de 81 et 67 %, respectivement. Le bénéfice majeur de cette intervention est l’obtention de l’insulino-indépendance et, dès lors, une meilleure qualité de vie. Le prix à payer, par rapport à une greffe de rein isolée est un risque plus élevé de complications chirurgicales et une immunosuppression plus lourde. Chez le diabétique de type 2 sans complications cardiovasculaires majeures la transplantation de rein isolée permet d’espérer une survie à 5 ans de 81 %. Il faut néanmoins s’attendre à une incidence élevée de complications vasculaires périphériques. La transplantation rénale doit être envisagée chez tout diabétique qui (1) a une espérance de vie estimée à au moins 5 ans (2) n’a pas de contre-indication au traitement immunosuppresseur (3) a un risque opératoire faible. La transplantation combinée rein-pancréas doit être envisagée chez les diabétiques de type 1 âgés de < 50 ans sans atteintes cardiovasculaires sévères et bien informés des enjeux de la double greffe.

Mots-clés : rein, rein-pancréas, transplantation, diabète.
Diabetic nephropathy has become the leading cause of end-stage renal failure (ESRF) worldwide. In the United States, 40% of patients starting renal replacement therapy (RRT) in 1997 had diabetes (Type 1: 12%; Type 2: 28%) [1]. In Europe, the proportion of diabetic subjects (mostly Type 2) among new patients starting RRT has increased steadily but more slowly, from 11% in 1984 to 18% in 1994, with large variations among countries and regions [2, 3].

As in other ESRF patients, renal transplantation (TP) should be the first-line option to consider in diabetic subjects because of the indisputably better quality of life afforded by this treatment as compared to dialysis therapies. However, many diabetic patients are precluded from renal TP because of advanced age and/or severe comorbidity. In fact, renal TP is currently considered in a minority of diabetic patients entering a programme of RRT in our countries. In 1998, diabetic subjects accounted for only 4.5 and 7.4% of patients on the waiting list for renal TP in France and the French-speaking part of Belgium respectively [4, 5]. The higher survival of diabetic patients after renal TP than on dialysis, as well as the improved outcome of combined kidney-pancreas TP in Type 1 patients and isolated kidney TP in Type 2 patients should encourage a broadening of the indications for TP in these categories of recipients.

**SURVIVAL AFTER RENAL TRANSPLANTATION AS COMPARED TO DIALYSIS**

In the absence of a prospective, randomised study comparing survival in patients undergoing TP and on dialysis, a valid approach is provided by a limited number of retrospective studies in which selection biases have been carefully minimised. In a German study, 46 Type 1 patients who received a renal graft between 1978 and 1997 were compared with 46 Type I patients who registered for renal TP but remained on dialysis without being transplanted [6]. The groups were matched for age, sex, diabetes duration, length of dialysis (up to registration) and date of registration for TP. Survival was significantly higher (80 and 74%, vs 62 and 38% at 5 and 10 years respectively) in transplanted than dialysed patients. Coronary and peripheral vascular events were also significantly more frequent in dialysed patients [6].

Although no similar study is available for Type 2 patients, a Canadian multicentric study on the survival of patients over 60 years of age at the onset of RRT provides interesting data [7]. Thirty-three transplanted patients were matched (for age, number of comorbid conditions and length of dialysis up to transplantation) with 66 who did not undergo TP. Survival probability was found to be twice as high in the transplanted group.

Even though some selection biases may persist in these studies, they strongly suggest that Type 1 as well as Type 2 patients in ESRF and with no contraindications to TP have higher survival with a functioning kidney graft than if they had remained on dialysis. These results have recently been confirmed by a large survey using data from the U.S. Renal Data System [8]. The authors compared the survival of patients undergoing TP with that of those awaiting a graft. After adjustment for age, race, sex, geographic region, time from first dialysis to placement on the waiting list, and year of initial placement on the list, it was found that the relative risk of death among transplant recipients was 73% lower in all categories of diabetic patients (82, 73 and 54% respectively in those 20-39, 40-59 and 60-74 years of age at the time of placement on the list). The projected years of life remaining were 8 for patients who remained on the waiting list vs 19 for those who received a transplant (8 vs 25 in the 20-39 year category, 8 vs 22 in the 40-59 year category, 5 vs 8 in the 60-74 year category). The type of diabetes was not mentioned in this study.

**SIMULTANEOUS KIDNEY-PANCREAS TRANSPLANTATION**

More than 10,000 pancreatic transplants have been performed worldwide, and the vast majority have involved a simultaneous kidney graft [9]. For simultaneous kidney-pancreas TP, patient and pancreas graft survival rates were respectively 92 and 79% at 1 year and 81 and 67% at 5 years [10], and kidney graft survival rates were similar to those achieved after kidney TP alone. Recent advances in surgical practice and immunosuppressive treatment have contributed to the increasing success of this operation.

Until recently, the standard practice was to drain the pancreas into the bladder, which allowed rejection to be monitored by measurement of urinary amylase concentration. Unfortunately, bladder drainage is frequently complicated by metabolic acidosis as well as by several urologic problems including haematuria, urinary tract infection, chemical cystitis or urethritis, which occasionally require surgical conversion of pancreatic drainage to the intestine [11]. To eliminate these complications, most centres have now adopted enteric drainage, which has the additional advantage of being a more physiological portal than systemic venous drainage [12]. One disadvantage is the inability to monitor pancreas rejection directly, although this has become less important with the dramatic reduction in the acute rejection rate afforded by the use of newer immunosuppressants.

Most centres currently use antibody induction therapy and triple drug maintenance immunosuppression (the most popular combination being tacrolimus + mycophenolate + prednisolone). Controlled trials are ongoing to determine whether the benefits of de-
creased rejection and better early graft survival achieved with these powerful regimens are not compromised later by increased risk of infection and malignancy [12].

The indisputable benefits of a successful kidney-pancreas transplantation are the achievement of euglycaemia and insulin independence (together with improved quality of life) and the prevention of recurrence of diabetic nephropathy. It has been more difficult to prove that this operation prevents long-term diabetic complications such as retinopathy, neuropathy and macroangiopathy [11]. Encouragingly, Cheung recently documented early improvement in diabetic microangiopathy, as assessed in the conjunctival microcirculation [13]. The effect on established target-organ lesions may only be apparent later. Thus, Fioretto et al. showed that histological lesions of diabetic nephropathy were unchanged at 5 years in eight recipients of an isolated pancreas transplant, but regressed at 10 years following pancreas TP [14].

In summary, the main benefit of simultaneous kidney-pancreas TP is insulin independence and a markedly improved quality of life. However, surgical morbidity is higher, and a more powerful immunosuppressive regimen is required than with kidney TP alone.

RESULTS OF RENAL TRANSPLANTATION IN TYPE 2 PATIENTS

Surprisingly, only one report has been published on the specific outcome of Type 2 patients after renal TP [15]. This prompted us to review our experience with 23 Type 2 patients transplanted between 1983 and 1996 [16]. The mean age of these patients at the time of TP was 57 years (range 41-73), and they were selected on the basis of estimated low cardiovascular risk (only 8 and 7 respectively had previously experienced a coronary or a peripheral vascular event). Patient survival at 1, 5 and 8 years after TP was 91, 81 and 72 % respectively. Actuarial risk for coronary and peripheral vascular disease (complication) at 5 years was 18 and 51 % respectively.

In summary, type 2 patients with no or moderate cardiovascular disease have excellent survival after renal TP. However, a high incidence of peripheral vascular complications can be expected.

WHICH DIABETIC PATIENTS IN ESRF ARE SUITABLE FOR TRANSPLANTATION?

As for other ESRF patients, renal TP should be considered in the diabetic patient with a life expectancy of more than 5 years, no contraindications to immunosuppressive treatment (such as another end-stage organ failure or severe infectious disease), and low perioperative risk [2]. Special attention should be paid to the possibility of coronary disease.

In patients with a history or symptoms of coronary disease, as well as in those with a high-risk profile (over 60 years of age, diabetes for more than 25 years, history of smoking, ischaemic changes on the EKG, peripheral vascular disease), coronary arteriography is mandatory. Asymptomatic low-risk patients should be screened by the best locally available non-invasive technique, i.e. thallium/MIBI stress (or dipyridamole) scintigraphy [17] or dobutamine stress echocardiography [18]. When coronary arteriography reveals stenoses amenable to revascularisation, this should be done before transplantation [19].

High-risk patients should also be screened for athromatous lesions of carotid and iliac arteries.

We currently restrict combined kidney-pancreas transplantation to Type 1 patients under 50 years of age with no or moderate cardiovascular complications and a thorough understanding of the risks and benefits of the procedure [2].

Both selection for TP and the prognosis following TP critically depend on the severity of cardiovascular complications when RRT is started. Regrettably, early treatment of cardiovascular risk factors is still too often neglected. For example, a prospective study of diabetic patients admitted for RRT in Germany revealed that only 5 % of patients were normotensive and only 5 % had lipid-lowering treatment [20]. The effort to improve access to TP and survival after TP actually starts a long way upstream from ESRF.

REFERENCES