Transpl Int (1999) 12: 176–181


ORIGINAL ARTICLE

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# Increasing prevalence of cardiovascular disease in kidney transplant patients with Type 1 diabetes

Received: 19 March 1998
Accepted: 18 December 1998

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**Abstract** Type 1 diabetes was evaluated as a risk factor in kidney transplantation with respect to cardiovascular disease and with focus on changes over time. From 1985 to 1993, 159 Type 1 diabetic patients received first kidney transplants in Göteborg. Actual 5 year-survival of diabetic patients was 75 % compared to 94 % for matched controls, $P < 0.0001$, and survival of grafts was 60 % compared to 75 %. In the diabetic group, high age and preexisting coronary heart disease were additional, independent risk factors. When patients were divided into three groups according to time of transplantation, survival was found to improve initially but then declined, $P = 0.03$. Patients in the last group were older and 39 % had pre existing vascular disease. The fact that Type 1 diabetic patients now reach end-stage renal failure at a higher age and with more established vascular disease calls for careful evaluation of a larger proportion of the transplant candidates.

**Key words** Cardiovascular disease · case-control study · diabetes Type 1 · diabetic nephropathy · Kidney transplantation · survival

## Introduction

To the present day, many groups have reported the outcome of kidney transplantation to Type 1 diabetic patients in optimistic terms [1, 4, 10, 11, 20, 26]. On the other hand, much interest has been focused on diabetes as a risk factor for death and transplant failure, and on possibilities of evaluating and reducing this risk [3, 8, 13, 16, 17, 18]. Some of the divergence might be due to the mode of evaluation of results. Comparisons have been made with an older non-diabetic transplant population or with diabetic patients in dialysis [4, 5, 6, 26]. The selection of patients for transplantation may have differed [6]. The present study compares patient and graft survival in a large and well-defined recent group of Type 1 diabetic patients with contemporary controls matched for age, all recipients of first kidney transplants. The minimum follow-up time was 5 years. Based on our early positive experience [10, 11], even patients with a history of coronary heart disease were accepted.

## Patients and methods

The Transplant Unit in Göteborg serves 40 % of the Swedish population. From January 1985 to January 1993, 1095 kidneys were transplanted to 1000 patients, 874 of whom received first transplants. In order to describe the consequences of the underlying renal disease for the outcome of transplantation, we reviewed the records and reevaluated the underlying renal diagnosis in each case. The details of this work have been described previously [22].

Type 1 diabetes was defined as onset of disease before the age of 31, with insulin-dependence from the start. Cases not fulfilling both criteria were excluded. Type 1 diabetic patients with uremia caused by renal disease other than diabetic nephropathy were also excluded. In the period studied, a total of 159 Type 1 diabetic patients with diabetic nephropathy received a first kidney transplant, 18 % of the total transplant population. One hundred patients received a kidney transplant only and 59 received a combined pancreas-kidney graft (CPK).

**Table 1** Demographic data for kidney transplant patients with Type 1 diabetes and their matched controls. Age values are median (range)

| | Diabetic patients $n = 159$ | Control patients $n = 159$ |
|---|---|---|
| Males | 58% | 58% |
| Age, years | | |
| at diabetes onset | 11 (1–30) | |
| at the start of renal replacement therapy | 39 (19–64) | 38 (18–59) |
| at the time of transplantation | 39 (19–66) | 39 (18–64) |
| Preemptive transplantation | 32% | 25% |
| Type of transplant | | |
| Cadaveric kidney only | 38% | 75% |
| Simultaneous kidney and pancreas | 37% | – |
| Living donor | 25% | 25% |
| Donor age, years | 45 (13–71) | 45 (4–75) |

### Patient selection

Before transplantation, coronary heart disease was recognised as a risk factor, but patients with modest symptoms of angina or a history of myocardial infarction were accepted. Only eight patients were investigated by coronary angiography. Screening of asymptomatic patients for coronary disease was not practised. In the present review, a history of cardiovascular morbidity before transplantation was recorded separately as ischemic heart disease (angina or myocardial infarction), peripheral vascular disease (claudication or amputations) or cerebrovascular events (stroke or transient ischemic attacks). Each patient was then classified as either having a pretransplant vascular disease or not. Eight of the CPK patients had preexisting vascular disease but only one of them had ischemic heart disease.

### Control patients

For each Type 1 diabetic patient, a contemporary control, also a first transplant patient, matched for age ± 5 years, sex, kidney source i.e. living donor or cadaveric donor, was obtained from the consecutive file of kidney transplants. Their diagnoses were comparable with the general population described previously [22].

Table 1 presents demographic data for Type 1 diabetic patients and their controls. The proportion of cadaveric donors was equal, but about half of the diabetic patients received a combined pancreas-kidney transplant from the same cadaveric donor. Donor age was similar for patients with and without diabetes, but among the diabetic patients, CPK recipients had significantly younger donors, median 35(16–56) years, $P < 0.0001$. Preemptive transplantations, i.e. transplantation without previous dialysis, had been performed in about one third of the Type 1 diabetic patients, not significantly different from the controls ($P = 0.11$). Diabetic patients who did not receive preemptive transplants had a mean dialysis treatment time of 9 months. To enable comparisons over time, the entire population of 1095 transplants in Göteborg from January 1985 to January 1993 was divided into three subgroups according to time of transplantation, January 1985 to June 1987 ($n = 344$), July 1987 to December 1989 ($n = 356$), and January 1990 to January 1993 ($n = 395$). The proportion of patients with Type 1 diabetes was 19%, 21% and 15%, respectively ($P = 0.18$).

### Transplantation procedures

Living donor-transplantation, if possible with an HLA-identical sibling, is our preferred form of transplantation. With cadaveric donors, matching for HLA antigens was not attempted, except within the Scandiatransplant collaboration, where agreements existed on exchange of cross-match negative kidneys to patients with HLA antibodies, and of kidneys with no foreign antigens. Only 14% of the cadaveric transplants in this period had no foreign HLA DR antigen. Maintenance immunosuppression was based on cyclosporin A and prednisolone. The transplant patients of 1985–87 took part in a randomised study to evaluate the effect of adding azathioprine [15]. No significant effect of azathioprine was demonstrated, but since completion of that study the combination of all three drugs has been the standard. Methylprednisolone in bolus doses on four consecutive days was used as antirejection therapy, followed by antithymocyte globulin or monoclonal antibodies in resistant cases. Blood pressure management was carried out with care, supine values above 140/90 being accepted only in patients with pronounced orthostatic blood pressure fall. The pancreas transplant programme in Göteborg was initiated in 1985. We have always used a segmental pancreas with exocrine deviation to the urinary bladder. The immunosuppression described above was used with the additon of antithymocyte globulin for the first postoperative week [23].

### Follow-up

Patients living in the Göteborg area are monitored at our out-patient clinic. Other patients are seen by their local nephrologists, who submit at least annual reports to our centre. In addition, patients were seen at follow-up visits, 6 months, and 1, 3, 5, and 10 years after transplantation. Records from both sources were reviewed with respect to manifestations of diabetic complications. Patients were followed until death, regardless of graft loss and any retransplants. Eight patients who received pancreas transplants after successful kidney transplantation were evaluated with their original group. All surviving Type 1 diabetic patients and controls were followed for a minimum of five years. Only one patient, a member of the control group, was lost to follow-up after that. The follow-up time was 108, 58–155 months, (median range) for surviving diabetic patients and 105, 60–159 months, for the control patients.

### Statistics

Unless otherwise stated, values are mean ± standard deviation. Cumulative survival was calculated according to Kaplan-Meier, tested by Mantel Cox, and with Cox, proportional hazards test, stepwise. Graft survival was not censured for loss due to patients' death. Other comparisons between groups were made using the $\chi^2$ test for frequencies, and ANOVA, Mann-Whitney's U-test or Kruskal-Wallis for values.

## Results

Cumulative survival of diabetic patients was markedly lower than that of matched control patients, $P < 0.0001$. Five-year actual survival was 75% compared to 94% for the controls. Within the diabetic group, five-year survival of CPK patients was 86%, compared to 64% for recipients of cadaveric kidneys alone, and 74% for

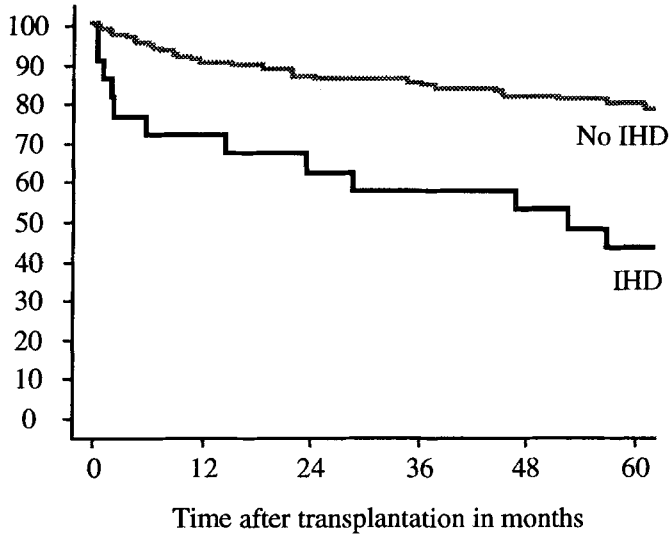


**Fig. 1** Actuarial survival of Type 1 diabetic patients with and without preexisting ischemic heart disease (IHD), according to Kaplan-Meier. $P < 0.0001$. The number of patients at risk with and without IHD is 21/138 at time zero, 13/118 after 24 months and 9/108 after 60 months.

living donor recipients, $P = 0.02$. Causes of death for diabetic patients and controls are listed in Table 2. Myocardial infarction, cardiac failure, sudden death, stroke and other vascular diseases accounted for 53 deaths in the diabetic group (14 in CPK patients) versus 13 among the controls. Patients with preexisting vascular disease had reduced survival rates compared with those without, $P < 0.0001$. When the various manifestations of preexisting vascular disease were tested in a univariate analysis, the most profound difference was seen between patients who had preexisting ischemic heart disease and those who had not ($P < 0.0001$) (Fig. 1). In the stepwise Cox' proportional hazards analysis, preexisting ischemic heart disease and age at the time of transplantation were both entered as significant, $P < 0.0001$ and $P = 0.003$, respectively, but the type of transplantation, i.e. CD, LD or CPK, was not.

As expected, considering the lower survival rates of diabetic patients, cumulative survival of the kidney grafts also differed significantly between Type 1 diabetic patients and controls ($P = 0.0001$). Actual 5-year values were 60% compared to 75% for the controls. Within the diabetic group, kidney graft survival was 68% for CPK patients, 49% for cadaveric donor recipents, and 66% for patients with living donors (not significant). Table 3 shows the causes of graft loss. Graft loss as a consequence of a patient's death was more frequent among diabetic patients than among control patients ($P = 0.0001$). Graft loss due to rejection within 6 months was not different, but late rejections were more frequent among diabetic patients ($P = 0.02$).

**Table 2** Causes of death in 159 kidney transplant patients with Type 1 diabetes (59 with a combined pancreas-kidney transplant, CPK) and their matched controls

| | Diabetic patients | | Control patients |
|---|---|---|---|
| | all | (CPK) | |
| Myocardial, cardiac failure | 20 | (2) | 8 |
| Sudden death/found dead | 13 | (7) | 2 |
| Stroke | 9 | (3) | 1 |
| Universal arteriosclerosis | 11 | (2) | 2 |
| Malignancy | 3 | | 5 |
| Infections | 8 | (2) | 5 |
| Intoxication/suicide | – | | 1 |
| Cachexia/uremia | 2 | | 1 |
| Pulmonary embolism | 2 | (2) | 1 |
| Total number | 68 | (18) | 26 |

**Table 3** Causes of kidney graft loss in 159 kidney transplant patients with Type 1 diabetes (59 with a combined pancreas-kidney transplant, CPK) and matched controls. * denotes significantly higher incidence in diabetic patients

| | Diabetic patients | | Control patients |
|---|---|---|---|
| | all | (CPK) | |
| Never functioning | 3 | (1) | 1 |
| Rejection within 6 months | 19 | (3) | 15 |
| Rejection later than 6 months* | 31 | (12) | 16 |
| Artery thrombosis | 3 | (1) | 4 |
| Recurrence of glomerular disease | – | | 7 |
| Glomerulopathy, unclassified | – | | 5 |
| Infection/intercurrent disease | 5 | (3) | 1 |
| Patient's death* | 32 | (7) | 8 |
| Total number | 93 | (27) | 57 |

A comparison between diabetic patients in the three subgroups according to time of transplantation is shown in Table 4. Patients in the last group were significantly older at the time of transplantation ($P = 0.046$) and had a longer duration of diabetes than patients in the other groups ($P = 0.021$). Otherwise, the baseline data were similar. Fig. 2 shows survival of diabetic patients. The survival rates improved from the first to the second period and then declined, $P = 0.03$. The number of cardiovascular deaths during the initial 5 years differed significantly between the three periods, $P = 0.0003$. In the first period, 9 of 16 deaths were of cardiovascular origin. The corresponding numbers in the middle and last periods were 3 of 6 and 17 of 18, respectively. In the control group, patient survival remained excellent throughout the three study periods, Fig. 3.

**Table 4** Demographic data and outcome of transplantation for kidney transplant patients with Type 1 diabetes according to time period. * difference between groups statistically significant, $P < 0.05$

| | Jan 1985–June 1987 ($n = 49$) | July 1987–Dec 1989 ($n = 61$) | Jan 1990–Jan 1993 ($n = 49$) |
|---|---|---|---|
| Proportion of total population | 23% | 29% | 23% |
| Age, years | | | |
| at onset of diabetes | 12 ± 8 | 11 ± 6 | 11 ± 7 |
| at the time of transplant | 38 ± 8 | 37 ± 7 | 40 ± 7* |
| Diabetes duration | 26 ± 8 | 26 ± 6 | 29 ± 6* |
| Preemptive transplantation | 25% | 29% | 28% |
| Time in dialysis, months | 10 ± 8 | 13 ± 10 | 15 ± 14 |
| Pre transplant vascular disease | 20% | 28% | 39% |
| Pre transplant ischemic heart disease | 8% | 11% | 20% |
| Age of donor, years | 45 ± 15 | 42 ± 16 | 41 ± 16 |
| Type of transplant | | | |
| Cadaveric kidney only | 41% | 38% | 37% |
| Simultaneous pancreas | 28% | 38% | 45% |
| Living donor | 31% | 25% | 18% |
| 5-year graft survival | 57% | 72% | 49%* |

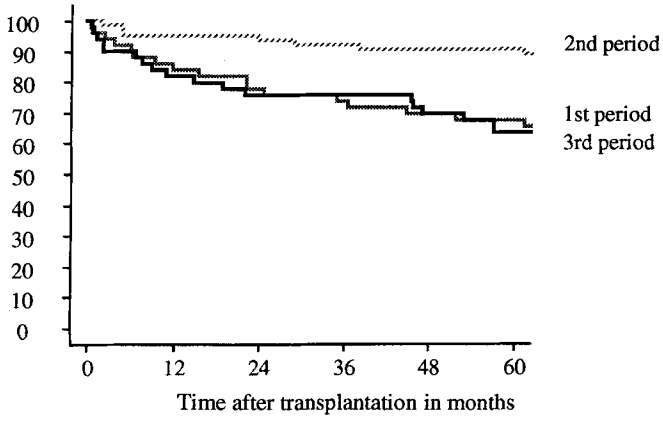


**Fig. 2** Actuarial survival of Type 1 diabetic patients during three different periods between 1985 and 1993, according to Kaplan-Meier. $P = 0.03$. The number of patients at risk in the first, second and third period (January 1985–June 1987 / July 1987–December 1989 / January 1990–January 1993) is 49/61/49 at time zero, 37/57/37 after 24 months and 32/54/29 after 60 months

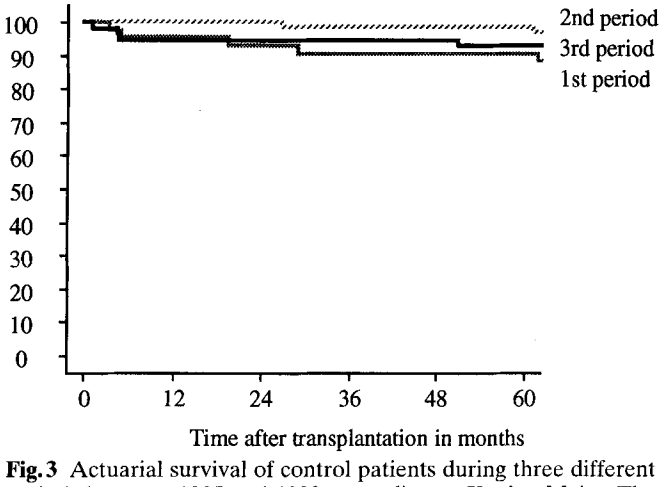


**Fig. 3** Actuarial survival of control patients during three different periods between 1985 and 1993, according to Kaplan-Meier. The number of patients at risk in the first, second and third period is 42/61/56 at time zero, 39/60/53 after 24 months and 37/58/50 after 60 months

## Discussion

Our analysis showed a much reduced survival of patients with Type 1 diabetes in comparison with their closely matched controls. The method of presentation stresses this difference as patients were followed after graft loss, death while in dialysis is included. This approach reflects the prognosis, i.e. the true outcome for Type 1 diabetic patients who undergo kidney transplantation, rather than results of the transplantation procedure as such. Moreover, we matched for patient age, which would otherwise have been higher in the control patients. Two small studies from the United Kingdom are the only previous case-control studies to our knowledge [9, 19]. In one, differences in survival were only of borderline significance, while the results in the other study concur with our findings [9].

About one third of our diabetic patients received, simultaneously with the kidney, a pancreas graft. They represented a positive selection with less cardiovascular morbidity before transplantation. Survival was better in this group. The result of the Cox proportional hazards analysis shows that the positive patient selection was more significant than any effect of the pancreas transplant.

Graft survival in diabetic patients was also affected. There was an increased risk of graft loss due to the death of patients. Furthermore, late "rejection" was more frequent. This may seem difficult to explain, but chronic rejection is no real entity. Only a minority of the graft biopsies showed true vascular rejection. Unspecific changes of fibrosis, glomerular sclerosis and tubular atrophy were more often the only findings. These changes are related to hypertension, athero- and arteriolosclerosis, hyperlipidemia and ischemia, which are all frequent in diabetic patients.

The inferior patient survival in our study was mainly related to manifestations of cardiovascular disease. This experience has previously been reported by several investigators [6, 7, 9, 13, 16, 19, 25]. As expected, the survival rate was significantly lower among diabetic patients with preexisting vascular disease [8, 13, 19].

The last few years have seen great changes in the treatment of diabetes in Scandinavia. Better technical equipment, better educated patients, and better methods of measuring long-term glycemic control have led to improved metabolic control. As a consequence, the incidence of diabetic nephropathy has decreased [2]. When present, the progression to terminal uremia is slower, due to better treatment of hypertension, the widespread use of ACE-inhibitors, and better metabolic control [14, 21, 24]. The patients we describe have had access to these improvements only during the latter part of their disease. However, the longer duration of diabetes observed in recipients in the last subgroup is probably a consequence of better care.

In our diabetic population, patient survival over time improved from the first to the second subgroup, presumably because of advancements in the general care of patients at the time, in particular, better management of infections. Due to progression of cardiovascular disease, survival again declined from the second to the third subgroup. This may be related to the fact that these patients were older, had longer diabetes duration, and a high rate of established ischemic heart disease before transplantation. Previous studies have also demonstrated an impact of patients' age and an increased prevalence of coronary heart disease with age and duration of diabetes [8, 13, 18]. This development can be expected to continue, adversely affecting the results of transplantation. The number of uremic Type 1 diabetic patients will probably decline, but those found will be more severely affected by macrovascular disease. This changing picture requires changed policies.

Transplantation is a great investment and must only be undertaken when the outlook for the following few years is fair. One way to handle high-risk patients is to turn them down as transplantation candidates. We must conclude that our acceptance policy has probably been too liberal with respect to cardiovascular disease. On the other hand, transplantation may be of greater benefit to Type 1 diabetic patients than to other patients with renal failure, because improved renal function will reduce their symptoms of neuropathy and anorexia.

The need for careful pretransplant assessment of uremic diabetic patients has been stressed [8, 12, 13, 17, 18, 25]. However, as pointed out by the Patient Care and Education Committee of the American Society of Transplant Physicians, the scientific basis for defining an algorithm in asymptomatic patients is limited [8]. Coronary angiography with revascularisation of significant stenoses has been reported to markedly improve survival in asymptomatic patients, but the series was small and the outcome in the conservatively treated group unexpectedly poor [17]. The authors concluded that a larger multicentre trial is needed. This has not yet been carried out. Based on their preliminary study, Manske et al proposed coronary angiography to be performed routinely, except in patients with a low risk, identified by strict clinical criteria [18].Very few of our patients would fulfill these.

Most investigators prefer non-invasive screening in asymptomatic patients, proceeding to coronary angiography when the test suggests ischemia [3, 8]. However, the value of the various tests has not been assessed in diabetic patients with end-stage renal disease [8]. Screening procedures seem to be less frequently used in Europe than in the U.S. [5, 9, 19]. No European policy has been proposed. Widening the indications for coronary angiography would require extensive new resources. Furthermore, there is limited experience as to how to treat the various detected abnormalities. This is a matter to be further investigated.

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