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## Why do some diabetic patients on the kidney transplant waiting list not receive a transplant?

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**Abstract** The waiting list (WL) history of 405 diabetic patients placed on the kidney transplantation WL for the years 1993–2000 was examined. By 31 December 2000, 295 (73 %) patients had received a transplant. Of the remaining 110 patients 53 (13 %) were still on the WL; 27 of these were temporarily withdrawn, i.e. non-active, 46 others (11 %) had died and 11 (3 %) had been permanently removed. Patient follow-up continued until the end of 2002. Although the mean total time on the WL of the non-transplanted was twice that of the transplanted patients there were no significant differences in the mean active times on the WL. The mean cumulative withdrawal time of the transplanted and those on the active WL was less than 10 % of their total time on the

list, but for the patients who had died or were withdrawn on 31 December 2000 it exceeded 50 %, usually because of diabetic complications. The 5-year survival of the transplanted patients was greatly superior to that of the non-transplanted, as expected. However, the better survival of the transplanted patients is not necessarily proof of a better treatment modality but rather a consequence of the exclusion from transplantation of patients suffering from diabetic complications. It is not justified to compare the survival of transplantable and non-transplantable WL patients.

**Keywords** Kidney transplantation · Waiting list · Diabetes · Dialysis · Patient survival

### Introduction

Despite substantial improvements in graft and patient survival following kidney transplantation in people with diabetes, their prognosis remains worse than that of patients with primary kidney disease. Life-long immunosuppression and co-morbidity are factors that influence the poor outcome of these patients. In any case, transplantation appears to extend significantly the survival of the diabetic patient when compared to those who receive only dialysis treatment [1, 2, 3].

The requirement for a good HLA match and poor availability of organs are patient-independent factors

that prolong the waiting time for kidney transplantation. As elsewhere, the mean waiting time for kidney transplantation is increasing in Finland. This is true even though the discrepancy between the number of patients placed on the waiting list and the annual number of transplantations here is far exceeded by that reported, e.g. from the United Network for Organ Sharing (UNOS) area [4].

There are many patient-dependent reasons for which patients are temporarily removed from the waiting list for extended periods of time. These may result in the delay of transplantation beyond the optimal time for an individual patient and may even result in exclusion from

transplantation. In order to re-assess the pre-listing work-up and waiting list management here, we studied the causes and lengths of withdrawals from the waiting list of the cohort of diabetic patients who had been accepted for cadaveric kidney transplantation during an 8-year period. Furthermore, those patients were followed-up for an additional 2 years.

## Patients and methods

During the 8-year period from 1 January 1993 to 31 December 2000, 405 patients with diabetic end-stage renal disease (12.6 % of whom were type II diabetics) were placed on the single national waiting list in Helsinki for a first cadaveric kidney transplantation. Referring hospitals belonging to the national network provided the pre-listing workup and a crude clinical scoring for their candidates for transplantation. Generally, the workup was similar to that for all kidney transplantation candidates. It included screening for possible infection foci and cancer and the status of viral antibodies. Particular emphasis was given to the cardiovascular status of the patients. Appropriate examinations were performed for cardio-respiratory capacity as well as cardiovascular and peripheral vascular disease. Those patients who were over 40 years old and/or smokers underwent thorough examinations to exclude coronary artery disease. Furthermore, any necessary interventions, e.g. angioplasties, were carried out. As a general rule, a BMI < 30 was required for acceptance on the waiting-list.

Nephrologists regularly monitored the patients on the waiting list and reported their findings to the transplant centre at 3-month intervals. When complications rendered the patient unfit for transplantation or when extensive examinations were required, the patients were temporarily removed from the waiting list, i.e. declared *non-active*. Those individuals were returned to the list as soon as the nephrologist considered them fit for surgery. The transplant centre in Helsinki monitored the waiting list, as well as the list of temporarily withdrawn patients, with the remitting hospitals each month. With this policy the centre here, with an annual volume of 160–190 cadaver kidney transplantations, has had only one or two intended transplantations cancelled for medical reasons per year.

Our allocation policy for renal transplantation requires ABO-blood group compatibility, sharing of at least two antigens in the HLA-AB and one antigen in the HLA-DR loci, together with a negative T-cell cross-match test against donor spleen cells. The patients are selected for transplantation first, according to the HLA-match, and second, with regard to their total waiting time. Special attention is given to immunised patients and to those with extended waiting times, as previously described [5, 6].

Total waiting list time was taken as the period from admission on to the waiting list to either transplantation or to permanent removal from the list. *Active* time on waiting list was that time the patient was actually eligible for transplantation and had not been temporarily taken off the active list.

By 31 December 2000, i.e. the end of the enlisting period of the study, kidney transplantation had been performed on 295 of the 405 enlisted patients. The withdrawals from the waiting list of all patients were examined in addition to the status of the 110 patients who were not transplanted. The withdrawal data were collected from the original manual waiting-list forms. Short (< 7 days) removals due to, e.g., respiratory infections, were excluded from the analysis, as minor illnesses are not systematically reported to the transplantation centre. Temporary withdrawals lasting more than 1 month were defined as being *long*.

The 64 non-transplanted patients alive on 31 December 2000 were further followed-up until 31 December 2002, when their status was re-assessed.

During the enlisting period of this study, 1,034 other, non-diabetic, patients had been placed on the waiting list for their first cadaveric transplantation, with 780 (75 %) of them having received a transplant by 31 December 2000. In addition to the diabetic patients of this study, our kidney transplantation waiting list comprised, on that day, 230 non-diabetic patients, 55 (24 %) of whom were temporarily withdrawn.

Statistical significances of differences in distributions were analysed with the chi-squared test, that of differences in means with the *t*-test or ANOVA, and of the medians with the median test. Survival data were calculated with the Kaplan and Meier product-limit method and compared with the log-rank test. A *P* value of < 0.05 was considered significant. The probability of transplantation and death or permanent removal from the list was also estimated with the competing risk method [7].

## Results

The 405 diabetic patients who were placed on to the kidney transplantation waiting list for the first time during the study period were grouped according to their status on 31 December 2000. Of these, 295 received a kidney transplant, while 46 others had died without having been transplanted. Eleven patients were permanently removed, while 53 others remained on the waiting list. Of these, 27 had, however, been temporarily withdrawn. Thus, 51 % of the diabetic patients and, for comparison, 24 % of the non-diabetic patients were temporarily taken from the waiting list on that day ( $P < 0.001$ ).

The demographic data of the transplanted and non-transplanted groups at the time of entering the waiting

list were quite similar. Respectively, the mean BMI in the patients was 23.4 and 24.5, while men accounted for 62 % and 68 % of the patients (N.S.). Sixty-one percent of transplanted patients had been on peritoneal dialysis, whereas 52 % of the non-transplanted had had this treatment (N.S). The transplanted patients had spent a shorter time on dialysis before entering the waiting list (Table 1). Their median dialysis time was 4.5 months, in contrast to 6.0–7.3 months in the non-transplanted groups ( $P < 0.001$ , median test). The transplanted patients were, on average, younger, having a mean age of 41.3 years (range 20–76), as compared to 45.2 years (range 21–68) for those not transplanted ( $P < 0.001$ ), and fewer of them had type II diabetes, 10.2 % vs 18.2 % ( $P < 0.05$ ). No significant differences were found in HLA immunisation, HLA-A, B, or DR distribution, number of HLA-homozygotes or ABO-blood group distribution between the transplanted and non-transplanted groups. There were no significant differences between the groups in the clinical scores used by the remitting nephrologists.

#### Waiting times

The total and the active times on the waiting list are shown in Table 1 and Fig. 1, with notable differences appearing between the groups. Total waiting times were shortest in the transplanted group, with a median time of less than one-quarter that of the permanently withdrawn group. Patients who had been temporarily withdrawn remained over twice as long on the waiting list as their counterparts who had undergone transplantation (ANOVA and median test  $P < 0.0001$ ). However, the active times on the list were similar in all groups (ANOVA and median test  $P < \text{N.S.}$ ). Transplanted patients and those on the active waiting list on 31 December 2000 had been temporarily removed, on average, less than

10 % of their total waiting time. The remaining other patients had been withdrawn for some half of their waiting time.

Temporary withdrawals had occurred in 116 of the 295 transplanted patients, in nine of the 26 actively waiting, in all of the 27 temporarily withdrawn, in nine of the 11 permanently withdrawn and in 43 of the 46 patients who had died (chi square  $P < 0.001$ ), starting after 100, 268, 71, 116, and 142 days (median) after listing, respectively (median test N.S.).

Figure 2 shows the total times on the waiting-list and temporary withdrawal periods for the individual patients in the groups who, on 31 December 2000, had not been transplanted, i.e. they were either temporarily withdrawn ( $n = 27$ ) or permanently withdrawn or had died ( $n = 57$ ). The withdrawal periods predominated throughout the waiting time, starting in many cases shortly after the patient had been placed on to the waiting list. Together, of these 84 patients, 75 had long temporary removals, with the median time from entering the waiting list to the beginning of the first withdrawal being 117 days.

#### Causes of long withdrawals

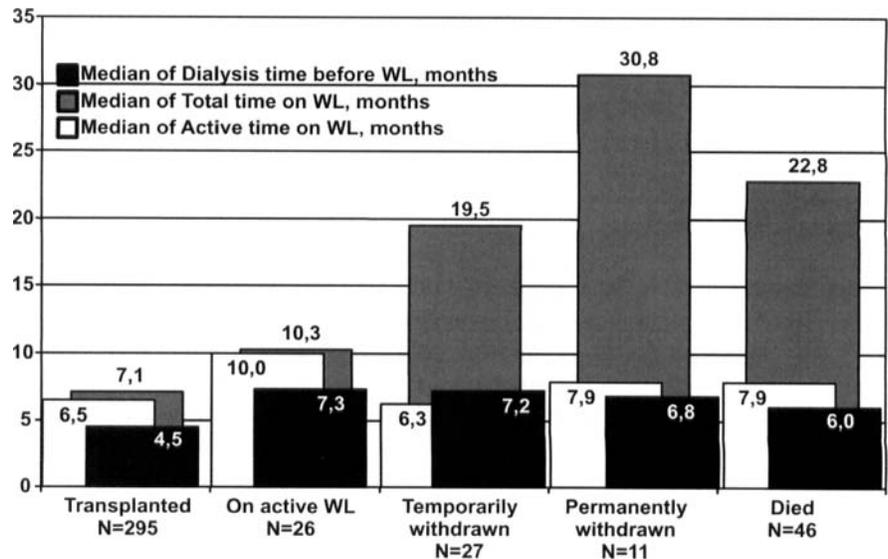
The causes were often multiple. The principal reasons for the long temporary withdrawals are shown in Table 2. The distributions of the causes between the groups were significantly different ( $\chi^2 P < 0.001$ ). Dialysis-related infections were similar in the groups. The annual risk for diabetes-related micro-vascular and macro-vascular complications, particularly peripheral infections/ulcers, was substantially higher in those patients who, on 31 December 2000, had been neither transplanted nor on the active list. In those patient groups also, the overall annual risk for long withdrawals had been higher.

**Table 1** Data from 405 diabetic patients entered on the Helsinki kidney transplantation waiting list (WL) in 1993–2000. The patients are grouped according to their status on 31 December 2000

Parameter	Patient status on 31 December 2000					P
	Transplanted	On active WL	Temporarily withdrawn	Permanently withdrawn	Died	
Number of patients	295	26	27	11	46	
Dialysis time before WL, mean (median), range (months)	5.6 (4.5) 0–39.6	7.7 (7.3) 1.0–20.5	10.5 (7.2) 2.1–34.4	8.1 (6.8) 2.8–17.7	8.5 (6.0) 0.6–53.8	< 0.001*
Total time on WL, mean (median), range (months)	9.9 (7.1) 0–58.3	12.0 (10.3) 0.4–35.2	20.1 (19.5) 0.4–51.7	29.5 (30.8) 4.5–56.6	23.9 (22.8) 2.4–49.9	0.0001**
Active time on WL, mean (median), range (months)	8.8 (6.5) 0.0–56.5	10.8 (10.0) 0.3–29.0	7.6 (6.3) 0.0–26.5	13.5 (7.9) 1.8–34.2	11.0 (7.9) 1.4–36.6	NS
Proportion of waiting time on active list	91.7 %	92.5 %	45.2 %	44.4 %	50.7 %	
Median follow-up (years)	6.4	2.8	3.6	4.5	6.9	< 0.001*
Type II diabetes	10.8 %	7.7 %	33.3 %	9.1 %	17.4 %	< 0.025***

\*Median test, \*\*ANOVA and median test, \*\*\*chi-squared test

**Fig. 1** The total and active times on the waiting list (WL) in 405 diabetic patients entered on the kidney transplantation waiting list 1993–2000, by the patients' status on 31 December 2000



**Patient outcome**

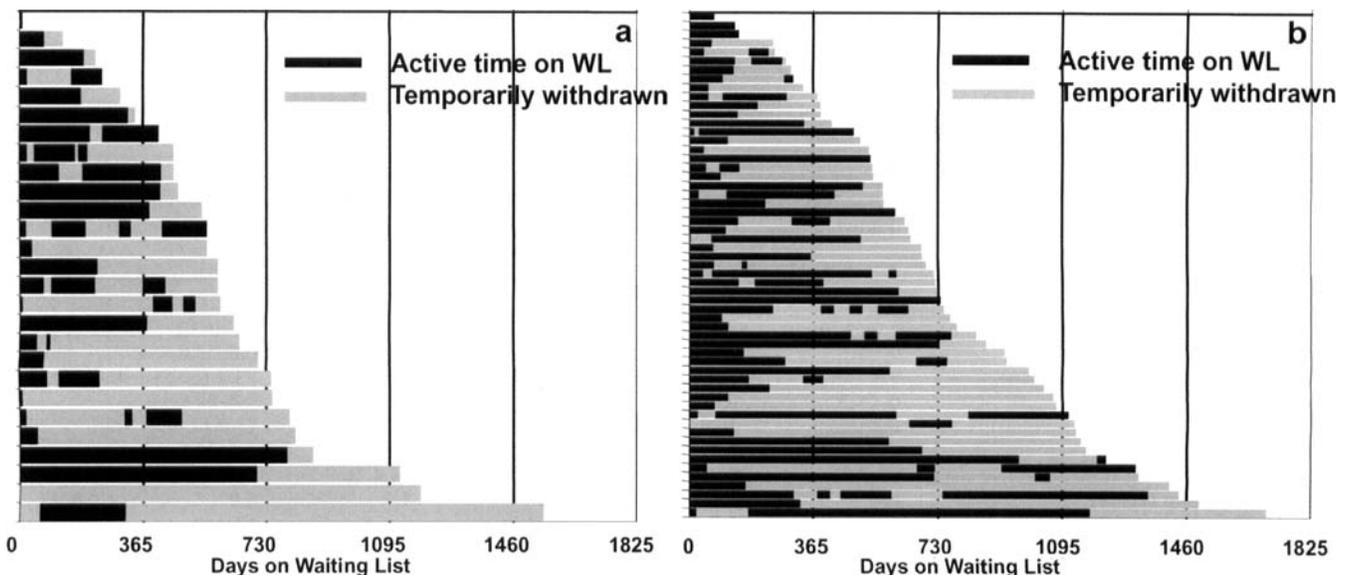
When all the 405 diabetic patients were analysed with the competing risk method, the probability of removal from the list by permanent withdrawal or death at 0.5, 1, 2, 3, and 5 years was 4.1%, 8.3%, 11.3%, 14.9%, and 16.4% respectively, and by transplantation, 27.7%, 46.8%, 69.5%, 75.5%, and 81.3%.

From the day of acceptance to the waiting list, the 5-year survival rate of the transplanted patients was

89 %, and their graft survival rate was 93 % at 1 year and 82 % at 5 years. In the non-transplanted patients the 5-year survival rate was 34%.

On 31 December 2000, 269 of the 295 transplanted patients were alive. During the 2-year follow-up period, 11 of these patients died. The change of status of the 64 patients who were alive but not transplanted on 31 December 2000 are shown in Table 3. A majority of the group on the active list had received a kidney transplant by 31 December 2002, whereas only one-quarter of the temporarily removed group had been transplanted ( $\chi^2 P < 0.005$ ). More than half of the temporarily withdrawn group had, 2 years later, either been withdrawn or died. One-half of the permanently withdrawn group had died, as had one-fifth of the temporarily withdrawn.

**Fig. 2a, b** Waiting-list history of diabetic patients accepted on the Helsinki kidney transplantation waiting list in 1993–2000 and who (a) were temporarily withdrawn ( $n = 27$ ) or (b) were permanently withdrawn or had died ( $n = 57$ ) on 31 December 2000



**Table 2** The causes of long (> 30 days) withdrawals of 405 diabetic patients entered on the Helsinki kidney transplantation waiting list (WL) in 1993–2000, expressed as the number of episodes per patient year on waiting list (number of episodes in brackets). The patients are grouped according to their status on 31 December 2000

Parameter	Patient status on 31 December 2000				
	Transplanted	On active WL	Temporarily withdrawn	Withdrawn	Died
Number of patients	295	26	27	11	46
Exit-site infection	0.046 (11)				
Peritonitis	0.117 (28)	0.039 (1)	0.089 (4)	0.096 (2)	0.064 (6)
Other infections/peripheral ulcers	0.075 (18)	0.117 (3)	0.224 (10)	0.482 (10)	0.308 (29)
Cardiovascular	0.033 (8)	0.117 (3)	0.089 (4)	0.096 (2)	0.096 (9)
Cerebrovascular	0.012 (3)	0.078 (2)	0.045 (2)	0.096 (2)	0.064 (6)
Travel	0.004 (1)				
Personal reasons	0.004 (1)		0.022 (1)		0.021 (2)
Surgery	0.012 (3)				0.011 (1)
Peripheral vascular	0.046 (11)	0.039 (1)	0.022 (1)		0.011 (1)
Cancer				0.048 (1)	0.011 (1)
Overweight	0.008 (2)	0.039 (1)	0.089 (4)		0.021 (2)
Other	0.058 (14)		0.112 (5)	0.048 (1)	0.021 (2)
Total	0.416 (100)	0.428 (11)	0.693 (31)	0.868 (18)	0.626 (59)

## Discussion

The donor problem makes the optimal timing for every patient to receive a kidney impossible within a cadaver-organ transplant programme. Diabetic patients in particular require early or even pre-emptive transplantation, according to some authors, and should, therefore, be given priority [8]. These demands are, in part, based on the assumption that diabetic patients fare poorly on dialysis; this is, however, difficult to analyse objectively. Comparisons of survival of transplanted diabetic patients with that of the entire diabetic patient population on dialysis [9] suggest that bias does indeed exist, as only “good” patients tend to be listed. The comparisons are more relevant when only those patients who were accepted on to a waiting list are considered [1, 10, 11, 12]. Vianello et al. [12] described clinical scores on admission to the waiting list as being significantly worse among the non-transplanted than the subsequently transplanted listed patients. In addition, nearly 40 % of patients in their study were unsuitable for transplantation when called in. This is in contrast to the present study, where cancellations were rare.

Comparisons of survival rates between transplanted and non-transplanted waiting list patients assume that the groups are comparable and that the timing of transplantation after a patient has been added to the waiting list is an essentially random process, as implied

in an editorial by Hunsicker [13]. That might not be completely true, but a level of bias could easily establish itself in the selection of patients. In the present study, an attempt was made to analyse one possible cause of this selection bias.

The policy of the Helsinki centre offers places on the cadaveric kidney transplantation waiting list to patients who already require dialysis, irrespective of the underlying cause of their uraemia. That policy follows the recommendation not to favour one patient group over another [14] and aims to present all patients with an equal opportunity for renal transplantation. Even though graft survival in diabetic patients here, as in other centres, approximates that of non-diabetic patients, the survival rate of the former group is indeed inferior [5, 15, 16]. Preliminary results here, with regard to overall diabetic patient material, suggest that the waiting time for transplanted diabetic patients is similar to that of other patient groups. Furthermore, a long period of dialysis before transplantation appears to be detrimental to patient survival following transplantation. This is in concert with the study by Meier-Kriesche et al. [17].

The most unfortunate group is those diabetic patients who, after a long stay on the waiting list, are either abandoned or die without ever having received a kidney transplantation. This was also demonstrated in the present study when the patients' probability of removal from the list by permanent withdrawal or death was calculated. The risk was very small early after listing, but

**Table 3** Two-year follow-up of the 64 diabetic patients who had been entered on the waiting list 1993–2000 and were alive but not transplanted on 31 December 2000

Patient status on 31 December 2000	Number	Patient status on 31 December 2002			
		Transplanted	On waiting list	Withdrawn	Died
On active waiting list	26	18 (69 %)	4 (15 %)	4 (15 %)	–
Temporarily withdrawn	27	7 (26 %)	4 (15 %)	10 (37 %)	6 (22 %)
Permanently withdrawn	11	1 (9 %)	–	5 (46 %)	5 (46 %)

increased markedly as the total waiting time lengthened while the patients were off the active list and thus ineligible for transplantation.

It could be speculated from the pre-listing dialysis times in this study that the non-transplanted groups had more co-morbidity-associated delays in becoming listed. However, the pre-listing scoring system gave no indication of that. It must be admitted that this may be partly explained by the weakness of our relatively crude scoring system, as so many of the non-transplanted patients were withdrawn soon after listing, usually because of complications and co-morbidity of their primary disease. Those withdrawals from the active list comprised a major part of their total waiting time.

The proportion of diabetic patients who were temporarily removed from the list at the end of recruitment was twice that of their non-diabetic counterparts on the list. Overall, the proportion of patients temporarily withdrawn was higher in the present study than in many centres in the survey described by Danovitch et al. [4]. Thus, the issues described in the our study are of major importance in the management of our waiting list with a traditionally high proportion of patients with diabetes and the absolute and proportional increase in the number of transplant candidates with type II diabetes.

With the kidney allocation policy in force here, temporary withdrawals should not diminish the patients' chance of obtaining a transplant when back on the list. This is because when they re-join the active waiting list, after the HLA-match, the total waiting time is taken into account as a secondary criterion in recipient selection.

The reporting of the patients' medical condition from the various dialysis units to the transplant centre appears satisfactory. Only a few transplant candidates have been deemed unsuitable for transplantation when a kidney has become available.

Diabetic complications and their prolonged treatments may force some patients to remain on dialysis, and, understandably, they fare poorly on it. This offers an explanation for the apparent gain in life expectancy of transplanted patients when compared with those still on the waiting list [1, 3]. Schnuelle and colleagues [2] noted that complete and reliable data on temporary and permanent removal from the waiting list would be required to assess the benefits of transplantation reliably in this respect. This has been one of the aims of our study.

One could postulate that diabetic kidney transplantation candidates who left the waiting list without transplantation were victims of an unfair allocation policy. Their total waiting time was many times longer than that of those who were transplanted. This difference in waiting time consisted, however, only of time off the active list, which in most cases started only a short time after the patient had entered the list. It was a bit surprising that, in all groups, patients left the waiting list after a similar period on the active list, some by transplantation, others by withdrawal or death. Except for the long withdrawals, no other explanatory factors could be found between the groups. The demographic data, which could affect allocation, did not differentiate the transplanted and non-transplanted patients.

Although not an easy task, it is of paramount importance that a diabetic patient not face unnecessary delays in joining a waiting list. Examinations in the pre-transplant workup should be undertaken before terminal uraemia occurs. With this in mind, however, terminal uraemia may develop more quickly than anticipated. Sometimes the patient's own reluctance to enter dialysis may also influence the outcome. Finally, unexpected complications of the primary disease may ruin any carefully planned suites of screening procedures.

As a result of our study a process has been established to provide for nationally uniform recommendations for pre-transplant screening and assessment in addition to periodic re-assessment of cardiovascular and peripheral vascular status during the waiting time, particularly if prolonged. This relatively small group of transplant candidates must be granted undelayed access to vascular investigations and necessary interventions, both before and after acceptance onto the kidney transplantation waiting list.

In conclusion, the results of this study show the bias in comparisons of survival between transplanted and non-transplanted diabetic waiting list patients. The extended withdrawals, at least among patients with diabetes, promote the selection of the "better" patients to obtain a kidney transplant. Further, an active policy in screening for transplantability and increased resources for investigation and treatment are required throughout the time the patient is heading towards renal transplantation, both during the workup and while on the waiting list.

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