Long-term Mortality After Kidney Transplantation in a Nationwide Cohort of Patients With Type 1 Diabetes in Finland

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OBJECTIVE

To examine time trends in mortality rates and causes of death in patients with type 1 diabetes and end-stage renal disease on dialysis and after kidney transplantation.

RESEARCH DESIGN AND METHODS

In a nationwide retrospective cohort analysis, all patients with type 1 diabetes in Finland who received a kidney transplant alone were compared with patients who remained on dialysis. The main outcome was patient survival after starting dialysis. The cohort was divided into dialysis, functioning kidney transplant, and dialysis after transplant loss. Causes of death were retrieved and standardized mortality ratios calculated.

RESULTS

We studied 2,383 patients. Patients survived a median of 15.9 years after a successful transplant, 11.2 years if transplant function was lost, and 2.9 years if they remained on chronic dialysis. Standardized mortality ratio decreased in all subgroups during the past four decades: from 2005 onwards, it was 3.9 in patients receiving a kidney transplant, 11.5 in patients with graft loss, and 32.5 in patients on dialysis. The most common cause of death in all patients was ischemic heart disease (45%) followed by infection (18%), which was more common in patients on dialysis.

CONCLUSIONS

Kidney transplantation is the treatment of choice for patients with type 1 diabetes and end-stage renal disease because it substantially reduces the excess death risk when compared with dialysis. Even when kidney graft function is lost, the excess death risk is still considerably lower. Although overall mortality has decreased over the years, premature death due to ischemic heart disease remains high.

Type 1 diabetes (T1D), a common disease in children and young adults, is associated with high risk of both acute and chronic complications. Diabetic nephropathy is a severe complication in patients with T1D, and in Finland, recent data show that 7.0% of the patients progress to end-stage renal disease (ESRD) after 30 years of T1D (1), whereas in the U.S., 25% have been shown to progress to ESRD after 40 years of T1D (2). Moreover, registry data show that between 4 and 17% of patients starting renal replacement treatment (RRT) have T1D (3,4). It is well known that patients with ESRD carry a manifold increased risk of premature mortality when compared with the general population, and this is particularly true for patients with T1D (5,6).

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Even though the treatment of choice for patients with ESRD is kidney transplantation (KT), earlier studies have shown that the independence from dialysis has not reversed the excess mortality observed in transplanted patients (7). This is surprising given that during the past four decades, there have been remarkable improvements in not only surgical techniques but also immunosuppressive medications. Although there have been several improvements in diabetes care, the mortality rates for individuals with T1D after KT have remained higher compared with subjects without diabetes, and this constitutes a major challenge for the health care system due to multiple comorbidities in this patient group (8). Of note, combined kidney and pancreas transplantation provides better survival than KT alone, particularly in the case of deceased donors (9). Over the last three decades, the number of pancreas transplantations grew remarkably. As of December 2014, >29,000 pancreas transplants in the U.S. and 19,000 outside the U.S. had been performed. Also noteworthy is that during the last decade, the rate of pancreas transplantation has declined by 20% in the U.S., probably due to a decline in organ donor quality (10). Despite the advances, KT recipients die prematurely most commonly due to cardiovascular disease, infections, or malignancy (11,12).

The incidence rate of T1D is increasing at a rate of 3–5% per year (13), and this is particularly true for Western countries. Notably, Finland has the highest T1D incidence rate in the world (14) and access to nationwide comprehensive registries, which provides a unique opportunity to study the factors affecting patient survival in this patient group. Our aim was therefore to examine the time trends of mortality and cause of death in a nationwide cohort study of patients with T1D after KT.

RESEARCH DESIGN AND METHODS

Study Population

The study population included all Finnish patients with T1D who progressed to ESRD and received a KT after initiation of dialysis. Data were obtained from the Finnish Kidney Transplant Registry covering the period from 1964 to November 2016. We excluded recipients of simultaneous pancreas and kidney transplants, pancreas after kidney transplants, and kidney retransplantations. The reason for excluding pancreas transplantation is that in Finland, there were only 78 such cases by November 2016. Data for the D cohort (patients who remained on dialysis) include data from 1975 onward that were drawn from the Helsinki University Hospital District database, which represents nearly one-third of all patients on dialysis in Finland. Vital status and causes of death were obtained from the Finnish Cause of Death Register, and death certificates were reviewed in uncertain cases. Furthermore, mortality data were verified with the database of the Finnish Diabetic Nephropathy Study (FinnDiane), which is a nationwide, ongoing multicenter study with the aim of identifying genetic and clinical risk factors for nephropathy in T1D (15).

The variables procured from the databases were date of initiation of dialysis, age at start of dialysis, age at transplantation, type and number of KTs, recipient and donor sex, type of donor, donor age, HLA mismatches, panel-reactive antibody titers, delayed graft function occurrence, acute rejection episodes, KT loss date, patient's death date, and cause of death. We divided the cohort according to the treatment modality: patients who remained on dialysis (D), those who received a kidney transplant but returned to dialysis after losing graft function (KT-D), and patients who maintained kidney allograft function (KT). The patients' flowchart is available in Supplementary Fig. 1. Causes of death were retrieved initially as recorded in the death certificates and further regrouped for era comparison. The causes of death were regrouped for comparison as follows: ischemic heart disease (including fatal acute myocardial infarction, heart insufficiency, arrhythmia, and sudden death), fatal stroke (including both hemorrhagic and ischemic), peripheral vascular disease (PVD) (defined as a complication of atherosclerotic vessels of the limb including amputation, gangrene, and sepsis as a consequence of an infected limb), infections (excluding those as a consequence of PVD), malignancies, intoxications, thrombosis, heart valve diseases, suicide, trauma, others, and undetermined. Follow-up started from the date at dialysis initiation and ended either at the time of death or 1 November 2016.

Era Analysis

We analyzed the mortality rate in four eras, defined by major changes in the immunosuppression regimen in Finland: before 1990 (before the widespread use of cyclosporin A), between 1990 and 1999 (cyclosporine A, azathioprine, and corticosteroids), from 2000 to 2005 (replacement of azathioprine with mycophenolate mofetil), and from 2006 onward (increased use of tacrolimus instead of cyclosporine A and induction therapy).

Statistical Analysis

Results are expressed as the median and interquartile range (IQR) for continuous variables or frequencies for categorical variables. Comparison between groups was performed by either ANOVA or *t* test, as needed. Panel-reactive antibodies were subdivided with a cutoff of 20% (low vs. intermediate/high sensitization). In a similar fashion, HLA-AB mismatches were categorized with a cutoff of 2, HLA-DR mismatches with a cutoff of 1, and total HLA mismatches with a cutoff of 3. Categorical variables were compared with χ^2 test, and we adjusted the *P* values with the Bonferroni method. Patient survival was considered the outcome variable in Kaplan-Meier analyses, and log-rank test was used for group comparison. Patient survival was compared by their median survival time, with 95% CIs compared in the KT, KT-D, and D groups. Absolute risk of death was compared at the 5-year and 15-year points after start of dialysis. Hazard ratios (HRs) with 95% CIs for 5-year mortality secondary to ischemic heart disease were provided by Cox regression analysis and adjusted for all of the variables available from the three groups: age at initiation of RRT, type of RRT, and year at initiation of RRT and sex. Standardized mortality ratios (SMRs) were calculated as the ratio between the number of observed deaths and number of expected deaths derived from rates in the Finnish background population drawn from Statistics Finland. SMRs were calculated for the entire cohort and separately for sex, treatment modality, and time period. All *P* values were two-tailed, and significance was set

at a level of 0.05. Statistical analyses were performed with SPSS software (version 19; SPSS Inc., Chicago, IL) and SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Ethical Committee of Helsinki University Hospital.

RESULTS

Study Population

Out of 2,543 patients with T1D who developed ESRD and initiated dialysis, 1,283 kidneys were transplanted to 1,192 patients as of 31 October 2016 after a variable time on dialysis before transplantation. The first patient with T1D received a KT in August 1976. There were no cases of patients dying on the transplant waiting list, and there were no preemptive transplantations. After first transplant failure, only 59 patients (25%) were retransplanted. In March 2010, the national pancreas transplantation program started in Finland, and as of 1 November 2016, 78 patients received a pancreas along with kidney transplant. After excluding retransplantation cases and pancreas-transplanted patients, a total of 2,383 patients remained and were included in this study. All patients were Caucasians. Follow-up data were missing from 68 patients (no known address in Finland). The accessibility of KT has changed across time: 40% of all patients with T1D who developed ESRD before 1990 were transplanted. The accessibility increased between 1990 and 1999 to 51% and between 2000 and 2005 to 53%. We observed a decline in the accessibility of KT occurring in the last 10 years (43%).

Compared with patients who experienced kidney allograft loss, KT patients with a functioning allograft were less sensitized and had less acute rejections. However, the KT patients with a functioning allograft had more HLA-AB and total mismatches, were older at transplantation, and more often had delayed graft function. The D patients were older at initiation of RRT (i.e., dialysis) than the KT-D (median 45.7 [IQR 16.9] vs. 35.6 [11.6] years; $P < 0.001$) and KT patients (45.7 [16.9] vs. 41.2 [13.3] years; $P < 0.001$). Also, the KT patients were older than KT-D patients (41.2 [13.3] vs. 35.6 [11.6] years; $P < 0.001$). Demographic data are detailed in Table 1.

Patient survival was compared among the D, KT-D, and KT subgroups from the date of initiation of dialysis therapy. The results are shown in Fig. 1. At the end of the second year of follow-up, 631 D patients had already died. By preserving KT function, patients' survival was longer (median survival time 15.5 years [95% CI 14.4–16.6]) compared with those who remained on dialysis (median survival time 2.4 years [2.2–2.5]) (Fig. 2). The most substantial difference between the absolute risk of death was during the first years from the start of dialysis. Therefore, the 5-year risk of death in the KT patients was 11.5% (95% CI 9.5–13.4), whereas it was 77.9% in the D patients (77.3–78.4).

Even when graft function was lost, KT-D patients lived longer (median survival time 10.7 years [95% CI 9.8–11.7]) than D patients, and the 5-year risk of death was 20.2% (95% CI 16.0–24.2). The corresponding risks of death within 15 years were 49.2 (47.0–51.4), 67.1 (64.9–69.1), and 96.5 (96.5–96.6) in the KT, KT-D, and D patients, respectively.

Overall, SMRs in D patients were 48.1 (95% CI 45.2–51.1), in KT-D 21.2 (18.3–24.5), and in KT 7.8 (7.1–8.7). The combination of sex and type of treatment showed that women in the D group had a 110.2-fold (95% CI 99.2–122.1) increased risk of premature death compared with the women in the background population, whereas in men, the risk was increased 36.9-fold (95% CI 34.2–39.8). The corresponding figures for women in the KT-D group were 45.5 (95% CI, 35.4–57.7) and in the KT group 13.2 (10.9–15.9). In men, SMRs were 16.5 (13.8–19.7) in KT-D and 6.6 (5.8–7.5) in KT patients.

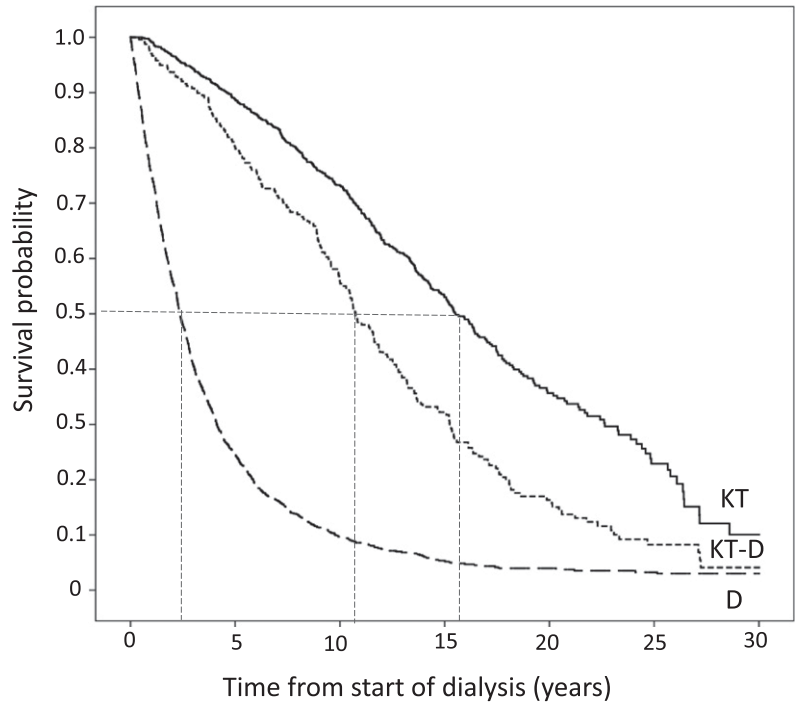
Time Trends in Mortality

The number of cases in each time period were as follows: before 1990, 593 (24.9%); between 1990 and 1999, 664 (27.9%); between 2000 and 2005, 441 (18.5%); and from 2006 onwards, 685 (28.7%). We observed that SMRs decreased in all treatment modalities

Table 1—Demographic data

	D (*N* = 1,273)	KT-D (*N* = 237)	KT (*N* = 873)	*P*
Patient sex, male/female, *n* (%)	828 (65)/445 (35)	150 (65)/87 (35)	571 (63)/302 (37)	0.832
Age at RRT, years, median (IQR)	45.7 (16.9)	35.6 (11.6)	41.2 (13.3)	<0.001
Age at KT, years, median (IQR)	—	37.4 (12.1)	43.6 (14.3)	0.011
Months on dialysis before KT, median (IQR)	—	15.8 (20.0)	15.4 (20.9)	0.160
Donor sex, male/female, *n* (%)	—	142 (60)/95 (40)	495 (57)/378 (43)	0.020
Donor age, years, median (IQR)	—	44.0 (23.0)	47.0 (20.0)	0.548
DD/LD, *n* (%)	—	232 (98)/5 (2)	835 (96)/38 (4)	0.110
HLA-AB MM ≤2 vs. >2, %	—	97.9 vs. 2.1	88.6 vs. 11.4	0.001
HLA-DR MM ≤1 vs. 2, %	—	94.0 vs. 6.0	90.9 vs. 9.1	0.082
Total HLA MM ≤3 vs. >3, %	—	96.6 vs. 3.4	88.3 vs. 11.7	<0.001
Maximum PRA I, low sensitization, %	—	38.8	67.8	<0.001
Maximum PRA II, low sensitization, %	—	22.2	50.0	0.038
Occurrence of DGF, %	—	20.3	27.8	0.020
Acute rejection episodes, %	—	28.3	15.9	<0.001
Patient survival, years, median (95% CI)	2.2 (2.0–2.3)	10.6 (9.6–11.7)	15.7 (14.5–16.8)	<0.001
Age at death, years, median (IQR)	49.5 (18.4)	48.3 (15.0)	52.3 (13.6)	<0.001

Low sensitization means panel-reactive antibodies <20%. DD, deceased donor; DGF, delayed graft function; LD, living donor; MM, mismatch; PRA, panel-reactive antibody.



No. At risk							
D	1273	246	73	27	18	13	10
KT-D	238	189	127	66	25	8	2
KT	874	675	436	204	76	25	5

Figure 1—Kaplan-Meier survival estimates after start of dialysis for patients on dialysis without a kidney graft (D), those with failed kidney grafts (KT-D), and those with functioning kidney grafts (KT). Median survival times shown as gray dashed lines.

over time. For the D patients, there was a 55% reduction in the SMRs from the first (before 1990) to the last period (2006 onward). Similarly, the corresponding decrease in the KT-D and KT patients was 58% between the first and last time periods. Detailed results are displayed in Fig. 2. Noteworthy is that in the most recent era, the KT SMRs were 88% lower than SMRs in the D group, and even when graft function was lost, the SMR was 65% lower.

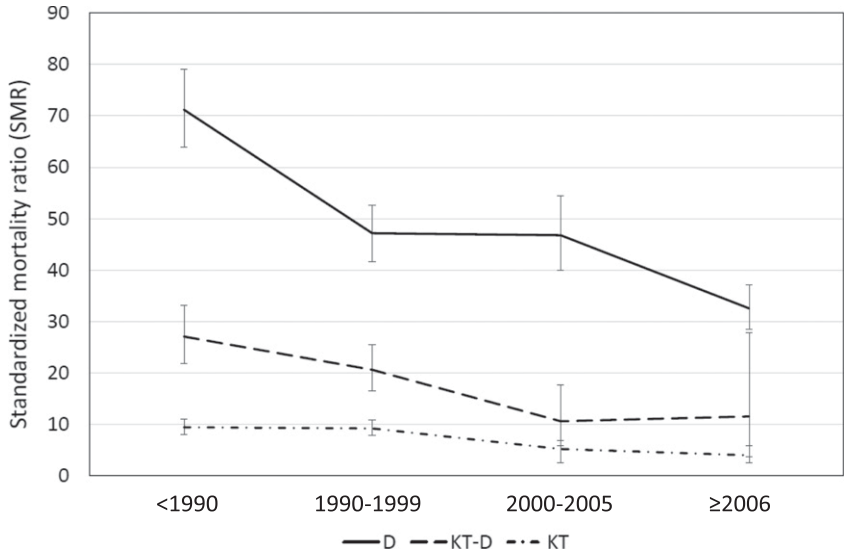


Figure 2—Time trends in SMRs stratified by treatment modalities: D (dialysis), KT-D (dialysis following failure of kidney graft), and KT (functioning kidney graft).

Causes of Death

We retrieved death certificates from 1,659 patients, of whom the cause of death was undetermined in 133 (8%). Across time and ESRD treatment modality, ischemic heart disease was the leading cause of death. The differences between the most common causes of death are depicted in Table 2. A complete enumeration of all causes of death according to treatment modality and time period is exposed in Supplementary Table 1.

We observed that deaths secondary to ischemic heart disease before 1990 reached 43% (249 out of 578 deaths). Between 1990 and 1999, between 2000 and 2005, and after 2006, the frequencies of ischemic heart disease deaths among all recorded deaths were 45%, 48%, and 46%, respectively. To allow comparison between groups with different duration of follow-up, we calculated the 5-year mortality rates secondary to ischemic heart disease as well as the HRs. The explanatory variables included in the model were age at dialysis, sex, era of treatment, and modality of type of kidney replacement treatment. The only significant variable in the model was the modality of RRT: a functioning KT decreased the risk of premature cardiovascular mortality at 5 years from dialysis start by 87% (HR 0.129 [95% CI 0.009–0.183]; $P < 0.001$), and, even in those who returned to dialysis, the risk of premature mortality was reduced by 84% (HR 0.161 [95% CI 0.102–0.252]; $P < 0.001$). The detailed results of the Cox regression analysis are available in Supplementary Table 2.

CONCLUSIONS

In the current study, we show sustained improvement during the last 40 years in the survival of patients with T1D in Finland who developed ESRD and were on RRT. The conspicuous progress in diabetes care, drug therapies, dialysis techniques, surgical procedures, and surveillance of patients with KTs is the likely explanation for the lowered risk of premature mortality in this cohort. It is of note that the decrease in mortality was independent of RRT modality. Similar results were observed in Finnish patients with T1D with ESRD compared with patients with ESRD with glomerulonephritis, but that particular investigation

Table 2—Main causes of death in relation to the kidney replacement treatment type

Cause of death	D	KT	KT-D	Total	*P*
Infection*	195 (18.2)	52 (13.7)†	50 (25.1)†	297 (17.9)	0.003
Malignancy*	18 (1.6)†	23 (6.1)†	2 (1.0)†	43 (2.6)	<0.001
IHD*	480 (44.4)	178 (47.1)	87 (43.7)	745 (44.9)	0.633
Stroke*	123 (11.4)†	62 (16.4)†	32 (16.1)†	217 (13.1)	0.017
PVD*	48 (4.5)†	7 (1.8)†	5 (2.5)	60 (3.6)	0.048
Total main causes‡	864 (79.8)	322 (85.1)	176 (88.4)	1,362 (82.0)	
Total number of deaths§	1,082 (84.9)	378 (43.3)	199 (83.9)	1,659 (69.6)	
Number of patients at risk	1,273	873	237	2,383	

IHD, ischemic heart disease. *Number of cases (percentage of the total number of deaths). †Statistically significant. ‡Sum of main causes of death (percentage of the total number of deaths). §Total number of deaths (percentage of patients at risk).

was focused on the survival of patients starting RRT at different time periods and not on the effect of kidney allograft loss on survival (16). Moreover, a similar reduction in mortality rates has been observed in Swedish patients with T1D, although that study did not focus on patients with ESRD (17). Of note, we show in this study that the survival of a patient with T1D after transplantation improved up to the year 2000, thereafter reaching a plateau. The lack of long-term improvement in KT survival in the last two decades has been well described before, irrespective of the kidney disease etiology (18). In our study, we observed a conspicuous improvement in the survival of patients with T1D who developed ESRD and received a KT in Finland between 1990 and 1999, after which further improvement has been more modest. This observation is in line with previous studies (19).

Several studies have suggested that intensive glycemic control may lower the risk of long-term complications, such as ESRD. Thus, the Diabetes Control and Complications Trial (DCCT) showed a reduction in the requirement of kidney replacement therapy when diabetes was treated intensively (20). Along with a reduction in the overall mortality in individuals with T1D, a reduction in the mortality of patients with ESRD has also been reported (2,16). Our findings are in line with those observed in other cohorts, but it is of note that our study was also able to discriminate the magnitude of improvement among different RRT modalities.

It is well known that mortality increases proportionally with the decrease in kidney function. Thus, in patients with ESRD, the treatment of choice is organ transplantation. Particularly, patients with T1D who develop ESRD are at high risk of premature death due to cardiovascular disease if they remain on dialysis treatment (21,22). However, not all patients with ESRD are candidates for KT, and the reason is usually that they may be too frail with too many comorbidities. We observed that D patients were older at initiation of RRT. We hypothesized that this group could have been more frail, with a longer duration of diabetes and its complications. Unfortunately, we do not have data on comorbidities before initiation of RRT to allow a comparison between groups. Thus, the comparison between the D and KT populations is hampered by selection bias. This is particularly true for the candidates for combined pancreas and KT, which is usually offered to younger and healthier recipients (23). The combined pancreas-KT program started in Finland only after 2010. The inclusion criteria for this program were particularly strict at the beginning, such as age under 55 years and absence of cardiovascular disease. As of 30 November 2016, combined pancreas-KT only accounted for 78 cases. For these reasons, we excluded such cases from this investigation. The selection bias impacts the conclusions one can draw from this study, as we cannot prove causality or consider other confounding factors affecting the candidacy for transplantation. Nevertheless, we compared KT patients who maintained allograft function until death versus those who lost their grafts. We observed that patient survival was 13 years longer than for D patients and ~5 years longer compared with those in the KT-D group. Thus, preserved KT function after first transplantation was associated with improved patient survival. Protective factors were low titers of panel-reactive antibodies and less acute rejection episodes. Although we do not have kidney graft biopsies confirming the cause of graft loss, we hypothesize that immunological injury has been an important factor for graft loss. Worse HLA matching, delayed graft function, and age did not seem to affect KT survival in this population. Shortening time on dialysis might effectively lower the risk of premature mortality, as previously demonstrated in a cohort of Korean patients with either T1D or type 2 diabetes (24). Both preemptive KT and living organ donation are rising as important practices, as has already been stated (23). Unfortunately, many of these patients, and their relatives, might not have been properly informed about the benefit of preemptive transplantation and are ultimately being transplanted after the initiation of dialysis (25). By the time our study population developed ESRD, preemptive transplantation was not in practice in Finland, and this policy changed by 2015. Even living donation has been underused, constituting only 2 to 3% of all kidney transplants. For this reason, we could not study the impact of preemptive transplantation or living donation in our population. Noteworthy is that the retransplantation rate was low. Possible reasons for the low odds of being retransplanted were increased comorbidity and longer waiting time for a second KT due to sensitization. In this cohort, there were no cases of patients dying while on the transplant waiting list, probably because of the relatively short waiting time for a KT in Finland (15.6 months in this cohort). However, it is possible that some patients were removed from the waiting list if a severe complication that changed the candidacy for transplantation occurred.

We observed that the SMRs decreased in all patients with T1D with ESRD over time, but even those who maintained the kidney allograft function had a fourfold increased risk of premature death compared with the background population. Nevertheless, the KT group had an SMR 65% lower than KT-D and 88% lower than D. Of note, the highest SMRs were seen in women on dialysis, probably because of the low risk of mortality of this age-group in the background population.

The second aim of this study was to evaluate the causes of death over the

past 40 years. Our results confirm those previously published in which cardiovascular disease was the leading cause of death in patients with ESRD (26,27). We observed that it remained at the top over the 40-year period. Noteworthy is that before transplantation, all patients are routinely screened for malignancies, infections, and cardiovascular disease. Although all transplant candidates with diabetes are screened for coronary artery disease with a variety of tests, the *American Journal of Cardiology* clearly stated that routine cardiac screening of asymptomatic transplant candidates has not been shown to decrease mortality (28). This issue has been confirmed in two large randomized trials, Detection of Ischemia in Asymptomatic Diabetics (DIAD) and Factor 64, focused on patients with type 2 diabetes (29,30). No studies similar to these have been performed in patients with T1D. In our study, we also observed a higher frequency of ischemic heart disease in transplant recipients, but the fatal event occurred earlier in the patients on dialysis. Of note, death in all groups occurred at a premature age. This fact raises doubts about the efficacy of cardiovascular screening prior to transplantation. Fatal stroke events in our study were lower than rates that the Diabetes Epidemiology Research International (DERI) group observed in Japanese patients with T1D receiving dialysis (11.4% vs. 38.9%) (31). Unfortunately, we could not retrieve data from all of the patients concerning the use of statins, aspirin, or renin-angiotensin system blockers. This limits the possibility of analyzing the impact of these confounders on the risk of death.

Infection-related mortality was more prevalent in D than in KT patients, despite the use of immunosuppression. The risk was especially high in patients in the KT-D group, probably due to the additive effect of uremic toxins and immunosuppression on leukocyte function. Our results are in line with a recent report from the European registries (11). The higher cardiovascular mortality in this population might explain the lower risk of dying secondary to a malignancy, as it is a competing factor. Of note, acute complications such as alcohol-related events or violence as cause of death have not been as prevalent in our investigation as has been reported in patients with T1D without ESRD (32).

The main strength of this study is the data sources, including all patients with T1D who received a KT from the beginning of the transplant activities in Finland, and we missed follow-up data from only 2.7% of them. In addition, we reviewed 1,659 death certificates, and in only 8%, was the cause of death undetermined. This provides a comprehensive and accurate picture of the comorbidities that affect patient survival.

To conclude, over the years, overall mortality has decreased in patients with ESRD on RRT. However, mortality due to cardiovascular complications remains high, and patients die young. Infectious deaths were more common in D patients than in KT patients despite the use of immunosuppression. Efforts should be set on maintaining kidney function after transplantation, as it decreases mortality.

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