Nephrol Dial Transplant (2006) 21: 770–775
doi:10.1093/ndt/gfi278
Advance Access publication 9 January 2006

Original Article

NDT
Nephrology Dialysis Transplantation

Time trends in the epidemiology of renal transplant patients with type 1 diabetes mellitus over the last four decades

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Abstract

Background. Diabetes mellitus (DM) type 1 is an important contributor to end-stage renal disease (ESRD) among younger transplant recipients. However, little is known about the changes in epidemiological characteristics of this population. Especially, time to reach ESRD may have changed in type 1 diabetic patients referred for transplantation, resulting in higher age at time of grafting. Such time trends may allow anticipating future developments regarding the demand for organ replacement in this patient group.

Methods. We retrospectively analysed 173 patients with type 1 DM undergoing renal transplantation at our institution, stratified into four groups according to year of reaching ESRD (A = 1973–1983, B = 1984–1990, C = 1991–1995 and D = 1996–2002). For each group we determined age at diagnosis of DM, age at time of reaching ESRD and age at time of transplantation. From these data, the interval from diagnosis of DM to ESRD and from ESRD to transplantation was calculated. The results were analysed in relation to gender, year of and age at onset of diabetes.

Results. Patients reaching ESRD in more recent years (group D) tended to be both younger at diagnosis of DM and older when reaching ESRD, resulting in higher mean age at transplantation (35.0, 37.5, 39.6 and 41.0 years in groups A, B, C and D, respectively). Accordingly, median duration to ESRD has significantly been prolonged over the last five decades in patients with type 1 DM undergoing renal transplantation (group A: 21.0, B: 20.7, C: 22.3 and D: 28.5 years; $P < 0.0001$), this finding being more pronounced in female patients.

Conclusions. The results of our analysis are compatible with a change in epidemiology in patients undergoing kidney transplantation. Older age at time of reaching ESRD may impact significantly on the demand for renal grafts, as patients are already clearly older nowadays when being transplanted. From our data it cannot be concluded whether this development is due to a change in the progression of diabetic nephropathy or may simply reflect a change in the selection of type 1 diabetic patients referred for transplantation.

Keywords: diabetes mellitus type 1; diabetic nephropathy; end-stage renal disease; progression

Introduction

Epidemiological data suggest that the incidence of nephropathy among patients with type 1 diabetes is stable [1] or even dropping [2–4]. However, as the incidence of diabetes mellitus (DM) continues to increase [5], diabetic nephropathy has become a major cause of renal failure in the Western world [6,7]. The frequency of diabetic patients initiated on renal replacement therapy very much depends on both the referral criteria and the rate of progression from onset of diabetes to end-stage renal disease (ESRD). Thus, it is of paramount socioeconomic interest whether the epidemiological characteristics and the course of diabetic nephropathy in patients referred for transplantation has changed over the last decades. Both changes in the criteria for eligibility to receive a renal allograft and improvements in diagnosing, managing and treating diabetic patients may have resulted in a change in characteristics of patients referred for transplantation and their course of progression to renal failure. Better antihypertensive therapy [8], the use of angiotensin-converting enzyme (ACE) inhibitors [9–11], intensive insulin treatment [12] and the combined implementation of these measures [13] seem to impact positively on the course of diabetic nephropathy in general.

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However, no long-term data are available on the progression to ESRD for the subgroup of patients that undergo kidney transplantation. Therefore, we have analysed the epidemiological characteristics of type 1 diabetics among our transplant patient population regarding temporal changes over the last decades by dividing them into groups according to the year they had reached ESRD.

Subjects and methods

The present study is a retrospective chart analysis of all patients with type 1 DM which were transplanted at the university hospital of Zurich (USZ) from May 1974 through July 2002. Our institution is the only transplant centre for Zurich, as well as for the eastern and southern part of Switzerland, exclusively covering an area with a mostly Caucasian population of about 2 million people. Patients transplanted at the USZ have been diagnosed and treated for chronic renal failure either by ourselves or were referred by nephrologists practising in the residential areas of the patients analysed in this study. Medical records of all patients undergoing renal transplantation at the USZ are collected, updated and archived at our institution. From these central records, patients with the diagnosis of type 1 DM were identified by personnel not involved in further data analysis. The main criteria for identification were the diagnosis made by the referring physician along with a typical medical history of acute onset of hyperglycaemia and insulin dependence. Seven patients were excluded because of incomplete or ambiguous data. The primary end-point of our analysis was the time interval between onset of DM and the occurrence of ESRD. The time point of onset of diabetes was based on the date of diagnosis as noted in the medical records of the referring physician. ESRD was defined by the initiation of dialysis treatment or the performance of first renal transplantation (mainly for subjects receiving a kidney from a living donor). Secondary end-points were age at onset of DM and ESRD. Patients were stratified into four groups according to the year of onset of ESRD (A = 1973–1983, B = 1984–1990, C = 1991–1995 and D = 1996–2002). The intervals in each stratum were chosen to achieve groups balanced for time span covered and strata size. Also, we aimed to assign subjects in order to have one group that, at least in theory, was substantially 'exposed' to newer therapeutic strategies, i.e. the use of ACE inhibitors, or intensified insulin therapy. As the number of patients referred for transplantation was increasing over time, most probably reflecting a more liberal referral policy in latter years, the resulting groups are not homogenous for both criteria (number of patients and time span). However, the outcome of our analysis was found to be independent of how groups were formed.

Data are presented as means ± SD and as range, unless indicated otherwise. Time between diagnosis of DM to ESRD is given as median and 95% confidence interval by group and displayed graphically using a failure plot that reverses the *y*-axis to show the number of failures rather than the number of survivors. Comparison between groups was performed with ANOVA and post-test analysis with Kramer–Tukey test.

Results

Among the 1779 patients that had undergone renal transplantation at our centre since 1973, 180 (10.1%) were identified from central records with the diagnosis of type 1 DM and were evaluated for inclusion into our analysis. Of the 173 patients available for analysis, all are of Caucasian origin. They developed DM between 1944 and 1983, covering a timeframe of almost 40 years. Some 138 patients underwent transplantation of a kidney in combination with either a pancreas ($n = 133$, since January 1974) or pancreatic islet cells ($n = 6$, since January 2000). The remainder received a kidney transplant alone ($n = 35$), with four of them having a living donor source of their organ. The 173 patients were stratified into groups A–D according to the year of ESRD occurrence. Twenty-four patients underwent transplantation without prior dialysis treatment. The characteristics of the entire group, as well as of the individual strata, are shown in Table 1. The ratio of male to female patients was even for the combined groups, whereas a predominance of women was noted in strata A and D. Mean age at diagnosis of type 1 DM was 12.7 years for the entire cohort, the oldest patients belonging to group C. Patients reaching ESRD in the most recent period were clearly younger at onset of DM compared with all other groups. In contrast, patients with the most recent onset of renal failure from diabetic nephropathy (group D) were significantly older at time of reaching ESRD compared with all other groups ($P = 0.0038$, Table 1). Consequently, the time to ESRD after onset of DM became increasingly longer in patients diagnosed with diabetes in more recent years ($P < 0.0001$, Table 1). The cumulative incidence of ESRD in this population of patients with DM type 1 undergoing kidney transplantation over time is shown graphically in Figure 1. The percentage of patients having reached ESRD 20 years after diagnosis of type 1 DM was 45.9 in group A, 46.0 in group B and 25.5 in group C. In contrast, the prevalence of ESRD after 20 years of diabetes in group D was only 12.8% (log-rank $P < 0.0001$). Finally, the slower progression to ESRD in type 1 DM patients diagnosed in more recent years resulted in a higher age of these patients at time of transplantation ($P = 0.010$, Table 1).

In order to identify potential epidemiological factors associated with the observed differences in progression to ESRD, we further analysed our data. As the male to female ratio was unequal among individual strata, we wondered whether gender difference might account for the results described above. Therefore, we separately analysed our data for male and female patients regarding age at onset of diabetes, age at reaching ESRD and the interval between these events. As a cohort, female patients were 2.6 years younger compared with men at onset of diabetes ($P = 0.022$), consistent among all groups (data not shown). In contrast, women developed end-stage renal failure ~1.5 years earlier than men. Consequently, female

Table 1. Patient characteristics, time to ESRD and renal transplantation in subjects with type 1 DM stratified according to year of reaching ESRD

	All groups $n=173$	Group A (1973–1983) $n=37$	Group B (1984–1990) $n=50$	Group C (1991–1995) $n=47$	Group D (1996–2002) $n=39$	*P*-value
Gender (male:female)	85:88	15:22	25:25	24:23	14:25	0.2171
Age at Dx of DM (years)	12.7 ± 7.4 (0.16–43.6)	12.0 ± 6.3 (0.16–30.0)	13.8 ± 8.9 (2.9–43.6)	14.2 ± 7.4 (2.9–29.9)	10.3 ± 5.7 (0.32–22.9)	0.0615
Age at ESRD (years)	36.7 ± 8.2 (22.8–63.7)	33.4 ± 6.1 (25.0–48.6)	35.9 ± 9.3 (23.8–63.7)	37.8 ± 7.6 (22.8–56.5)	39.8 ± 7.9 (26.0–59.3)	0.0038
Interval from start DM to ESRD (years)	24.0 ± 7.1 (3.5–54.8)	21.4 ± 5.0 (13.6 ± 32.3)	22.1 ± 6.5 (3.5–44.6)	23.6 ± 5.4 (14.3–39.8)	29.4 ± 8.7 (15.8.-54.8)	<0.0001
Isolated kidney Tx (*n*)	35	7	13	7	8	ND
LRD Tx (*n*)	4	0	0	0	4	ND
Age at Tx (years)	38.3 ± 8.4 (23.7–64.5)	35.0 ± 6.4 (26.0–51.0)	37.5 ± 9.4 (26.7–64.5)	39.6 ± 8.2 (23.6–62.2)	41.0 ± 8.0 (27.3–62.6)	0.0100

Results are given as means ± SD. Dx, diagnosis; Tx, transplantation; LRD, living related donor.

patients, in general, had a slightly longer interval from onset of diabetes to reaching ESRD. However, this finding was inconsistent when analysed among groups according to period of reaching ESRD. Another possible factor that may have affected time of progression to renal failure is age at diagnosis of diabetes. As mentioned earlier, patients developing ESRD in more recent years (i.e. group D) tended to be younger when they were diagnosed with diabetes. Indeed, a weak correlation between age at diagnosis of DM and time to reach renal failure was detectable for all four groups (Figure 2; $r=-0.37$). However, for every given age, time to develop ESRD tended to be longer in patients with more recent occurrence of renal failure. This conclusion may be flawed as it is prone to selection bias. Patients with a very long duration of diabetes at onset of ESRD are more likely to be considered for transplantation when being diagnosed with DM at younger age, as they won't be as old at time of transplant as a patient with onset of DM at higher age and slow progression to ESRD. Finally, age at diagnosing diabetes may be related to the year at onset of the condition. As shown in Figure 3, patients tended to be younger when diagnosed with diabetes in earlier times ($r=0.32$). On the other hand, when analysed separately according to year of reaching ESRD, patients with more recent occurrence of renal failure were younger in general at any given year of DM diagnosis. Again, a note of caution needs to be raised and the probability of selection bias be considered. The likelihood to be transplanted in 1974 or beyond (when our transplant programme was initiated), and thus being included in our analysis, was higher for younger patients diagnosed with DM in the later years of the 1940s (or early years of the 1950s). Being of higher age at onset of diabetes in 1947, for example, would probably have precluded individuals from transplantation >27 years later, as they most likely would have been considered to be too old.

Discussion

The results of this retrospective analysis, covering a period of almost 40 years, reveal relevant temporal trends in the epidemiological characteristics of patients with type 1 DM referred for renal transplantation. Patients having reached ESRD more recently are significantly older at time of both renal failure and transplantation compared with all other groups. Moreover, a significant prolongation from onset of diabetes to ESRD in transplant patients with more recent development of renal failure (group D, 1996–2002) can be observed.

The findings of our study may be accounted for by several causes, the most likely being changes in the selection and referral criteria of patients with diabetic nephropathy for transplantation. Specifically, medical practice with regard to acceptance of older patients and diabetics with polymorbidity may have changed

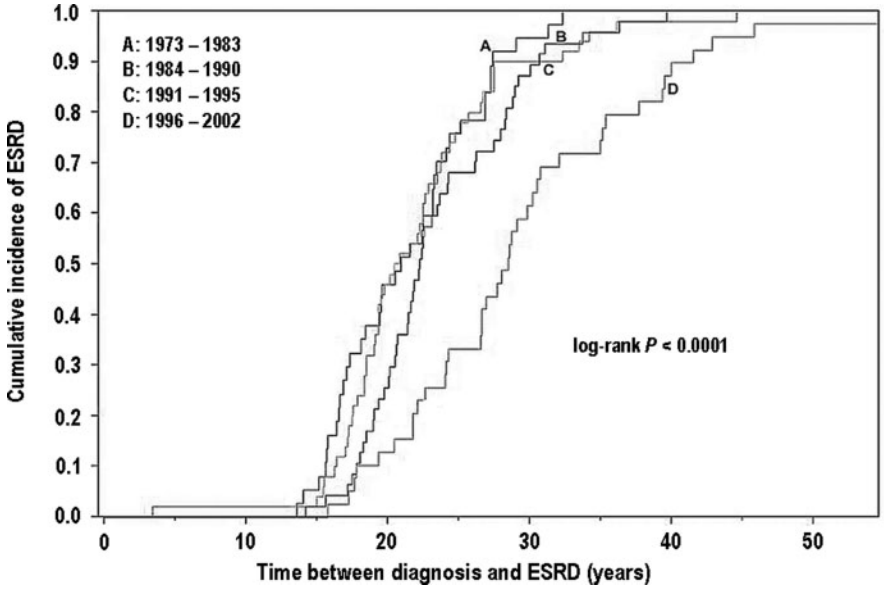

Fig. 1. Cumulative incidence of ESRD in patients with type 1 DM referred for transplantation: time interval from diagnosis of DM to reaching ESRD. Patients with DM type 1 referred for transplantation have been randomized according to the year of reaching ESRD. Time between diagnosis of DM to ESRD is displayed graphically using a failure plot that reverses the *y*-axis to show the number of failures rather than the number of survivors. Comparison between groups was performed with ANOVA and post-test analysis with Kramer–Tukey test. The results show a significant prolongation in the median duration from onset of diabetes to renal failure for patients referred for transplantation reaching ESRD most recently (group D).

considerably over time. In addition, the epidemiology of type 1 diabetes and the 'natural course' of diabetic kidney disease may have changed over the last decades due to environmental and medical factors. Epidemiological factors, such as age at onset of diabetes, may be of importance in the development of the disease and its related complications. Indeed, our analysis revealed a clear trend to younger age at diagnosis of diabetes in patients referred for transplantation in the more recent past (Table 1) and an inverse correlation between age at diagnosis of DM and time to reach ESRD (Figure 2). These findings suggest that patients diagnosed with diabetes at younger age have a more favourable course of kidney disease. Whether age by itself does account for this cannot be decided from our analysis. Not many long-term epidemiological data exist regarding age at onset of diabetes. A trend towards younger age at diagnosis has been noted for the last 15–20 years in several European countries, such as Italy [14], Finland [15] and England [16]. Interestingly, no similar trend could be noted in our transplant cohort, as patients tended to be older when diagnosed with DM in later years during the time period covered by our study (Figure 3). However, there is a clear downward shift towards younger age at diabetes diagnosis in patients reaching ESRD more recently. This finding may suggest that younger age at diagnosis is an independent risk factor contributing to a more favourable course of diabetic nephropathy. Alternatively, younger age at diagnosis of DM might also reflect better screening efforts to detect and treat diabetes, resulting in later occurrence and/or slower progression of secondary complications, such as diabetic nephropathy. However, a cautionary note is necessary with regard to these conclusions, as no information is available on the course of nephropathy in diabetic patients not referred for renal transplantation. Thus, our findings are attributable exclusively to the subgroup of transplanted diabetics assessed in this analysis. Finally, overall improvement in medical care

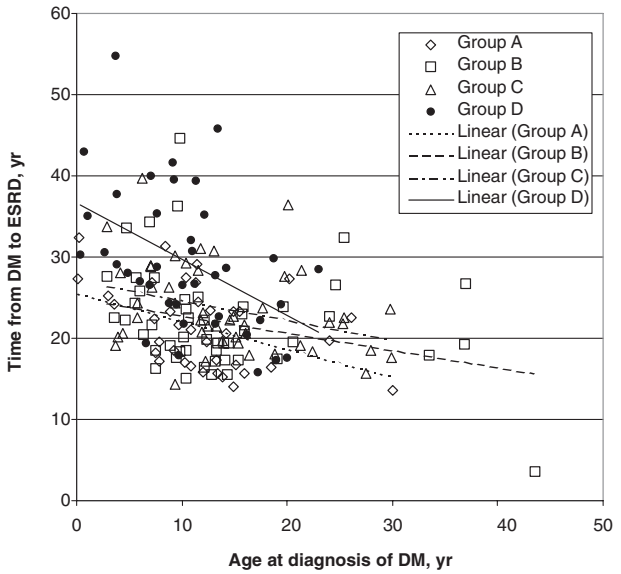

Fig. 2. Correlation analysis between age at diagnosis of type 1 DM and time to reach ESRD. An inverse correlation between age at diagnosis of DM and time to reach renal failure was detectable for all four groups (A: $r = -0.43$, $P = 0.0075$; B: $r = -0.29$, $P = 0.0392$; C: $r = -0.34$, $P = 0.0213$; D: $r = -0.46$, $P = 0.0036$). However, for every given age, time to develop ESRD tended to be longer in patients with more recent occurrence of renal failure.

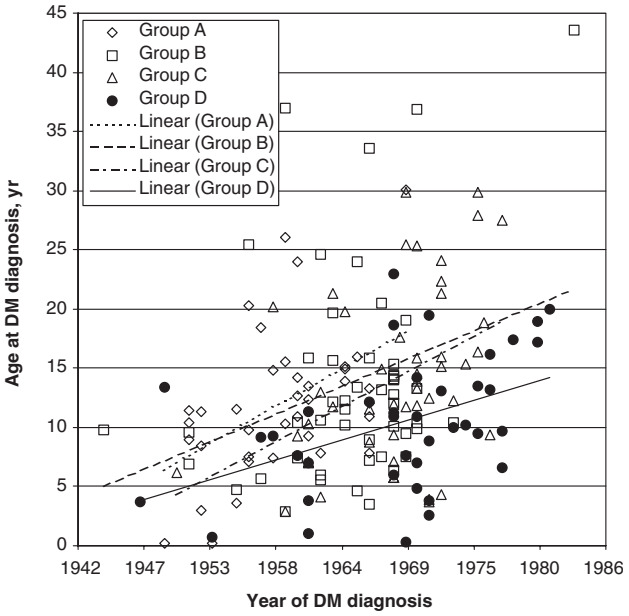

Fig. 3. Correlation analysis between year of diagnosis of type 1 DM and age at time point of diagnosis. Patients tended to be younger when diagnosed with diabetes in earlier times (A: $r = 0.49$, $P = 0.0022$; B: $r = 0.30$, $P = 0.0339$; C: $r = 0.41$, $P = 0.0045$; D: $r = 0.44$, $P = 0.0051$). Moreover, when analysed separately according to year of ESRD, patients with more recent occurrence of renal failure were younger in general at any given year of DM diagnosis.

and pharmacological treatment over the last decades is likely to be the most important factor to account for a more prolonged course to ESRD after initiation of diabetes. Among those measures, the most likely to have such a beneficial impact are intensified blood sugar control and insulin treatment [12], better antihypertensive control [8], screening for nephropathy by monitoring the occurrence of microalbuminuria and, last but not least, the introduction of angiotensin-modifying drugs, such as ACE inhibitors and angiotensin 2-receptor antagonists [9–11]. As ACE inhibitors were approved in Switzerland in 1980, the majority of our cohort may have been treated with this type of drug at some time. Obviously, patients reaching ESRD more recently were more likely to be exposed over a longer cumulative time to ACE inhibitors compared with patients experiencing renal failure earlier [median duration of exposure (years): 16.1 in group D, 11.3 in group C, 6.1 in group B and 0.1 in group A].

The design of our study does not allow discriminating the factors responsible for the apparently slower progression of kidney disease in the subgroup of diabetic patients with nephropathy selected for renal transplantation and referred more recently. Also, the findings of our analysis may not be attributable to the overall population of diabetics with kidney disease. In a retrospective analysis of 1075 patients diagnosed with juvenile type 1 DM of the Allegheny County Registry, 104 (13%) developed ESRD, with a significant decline in 20-year cumulative incidence rate among all patients diagnosed with diabetes between 1965 and 1969, 1970 and 1974 and 1975 and 1979 (9.1%, 4.7% and 3.6%, respectively; $P = 0.01$) [17]. The average time from onset of DM to ESRD, however, did not change significantly during the observation period among groups, but was in a range comparable to our results (±29 years). Although the Allegheny data may not be directly comparable with our study, the differing findings may suggest that type 1 diabetics referred for renal transplantation may represent a positive selection of patients with more favourable characteristics resulting in slower progression to renal failure.

Besides the applicability strictly to patients with type 1 DM undergoing kidney transplantation, our analysis has several limitations inherent to its retrospective design with only limited clinical data available. The time point of ESRD occurrence may not have been determined stringently for all patients, as we used initiation of dialysis or date of transplantation to define renal failure. There is no universal agreement among physicians on when to initiate renal replacement therapy and policies may have changed over the years. However, in earlier days dialysis was probably started at a later stage of renal insufficiency than in more recent years. Consequently, this would be even more supportive of our notion that progression to ESRD has been slowed over the years. Unfortunately, our data do not allow distinguishing whether this alteration in course is due to a change in the interval from onset of diabetes to kidney disease or to slower progression of diabetic nephropathy to renal failure.

Despite these limitations and to our best knowledge, this is the first analysis that has assessed changes in the epidemiological characteristics and the progression of nephropathy over a time-span of almost 40 years in patients with type 1 DM undergoing renal transplantation. The findings show a trend to occurrence of ESRD at a later time in life, compatible with a slower progression from onset of diabetes to renal failure in patients referred for transplantation. The reasons for this development are, as yet, unclear and will have to be evaluated further. However, the epidemiological implications are of relevance, as the change in progression to ESRD has already resulted in a substantially higher age at renal transplantation. This has a beneficial impact with regard to organ shortage.

Acknowledgements. The authors wish to thank the transplant coordination team from the university hospital of Zurich for their support in collecting patient data.

Conflict of interest statement. None declared.

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Received for publication: 14.7.05
Accepted in revised form: 26.10.05