

# Survival of Patients With Type 1 Diabetes Receiving Renal Replacement Therapy in 1980–2007

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**OBJECTIVE** — Risks of end-stage renal disease and premature death in patients with type 1 diabetes have declined over the past decades. Data on the survival of patients receiving renal replacement therapy (RRT) are, however, limited. We investigated whether survival of patients with type 1 diabetes receiving RRT has improved over time and whether improvement can be attributable to progress in dialysis treatment or diabetes care.

**RESEARCH DESIGN AND METHODS** — An incident cohort of all patients with type 1 diabetes ( $n = 1,604$ ) starting chronic RRT in Finland between 1980 and 2005 were followed until death or end of follow-up on 31 December 2007. The control group ( $n = 1,556$ ) consisted of patients with glomerulonephritis who started RRT. All patients were identified from the Finnish Registry for Kidney Diseases.

**RESULTS** — Median survival time of patients with type 1 diabetes increased progressively from 3.60 years during 1980–1984 to >8 years in 2000–2005. In 2000–2005, the unadjusted relative risk of death was 0.55 compared with 1980–1984. After adjustment for the most important variables, the corresponding relative risk of death was only 0.23. For patients with glomerulonephritis, the adjusted relative risk decreased to a lesser extent to 0.30 ( $P = 0.007$ ).

**CONCLUSIONS** — Survival of patients with type 1 diabetes and end-stage renal disease has improved since the 1980s despite a conspicuous increase in the age of patients who start RRT, suggesting not only true progress in dialysis therapy and overall treatment of patients with end-stage renal disease but possibly also improved management of diabetes.

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**D** iabetes is the most important cause of end-stage renal disease (ESRD) in industrialized countries, reflecting the rapidly growing number of patients with adult-onset diabetes (1,2). The incidence of type 1 diabetes, however, varies significantly among countries and is the highest in the world in Finland (3). At the end of 2007, the incidence and prevalence of ESRD due to type 1 diabetes were 13 and 128 per million inhabitants, respectively (4). The latter accounts for 17.2% of patients receiving chronic dialysis. In a recent Finnish study, the risk of

ESRD in patients with type 1 diabetes was 2.2% after 20 years and 7.8% after 30 years from the diagnosis of diabetes (5). In addition, the risk had decreased over the past decades, which is in line with the declining incidence observed in many other countries (6).

A European study with data from 10 national registries showed a decrease in the mortality rates of patients with type 1 diabetes receiving renal replacement therapy (RRT) during the time period 1991–2000 (7). In a Danish registry study that covered the time period 1990–2005, the

overall survival rate of patients with diabetes receiving RRT had improved by 15% per 5 calendar years, but the survival rate of patients with type 1 diabetes was not assessed separately per time period (8). Moreover, registry data from Australia and New Zealand from 1991 to 2005 showed no significant change in the survival of patients with type 1 diabetes receiving RRT over time, although the survival of patients with type 2 diabetes as well as of that of patients without diabetes had improved (9). The authors also reported that the prognosis of patients with type 1 diabetes remained poor regardless of good access to kidney transplantation. Taken together, despite continuous advances in the management of diabetes and the prevention of diabetic nephropathy, there are only scarce data on whether the prognosis of patients with type 1 diabetes receiving RRT has improved.

Our aim was, therefore, to investigate whether the survival of patients with type 1 diabetes receiving RRT has improved. We used comprehensive data for all patients with type 1 diabetes who had started chronic RRT in Finland during the time period 1980–2005, which enabled a considerably longer follow-up period than that in previously published studies.

## RESEARCH DESIGN AND METHODS

Our incident cohort study included all patients with type 1 diabetes as the cause of renal failure who had started chronic RRT (hemodialysis, peritoneal dialysis, or kidney transplantation) in Finland from 1 January 1980 to 31 December 2005 ( $n = 1,604$ ). The patients were followed from the day of the first dialysis treatment until death or the end of the follow-up period on 31 December 2007 or until recovery of kidney function or the patients had moved abroad or were lost to follow-up. As a control group we included all patients with chronic glomerulonephritis who had started RRT during the same time period ( $n = 1,556$ ). The control group was chosen to represent a primary renal disease and hereby obtain information that could separate the impact of development of RRT and diabetes care. Patients with glomerulone-

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**Table 1—Demographic data and characteristics of patients according to patient group (type 1 diabetes or glomerulonephritis) and the start period of RRT**

Patient group	Start period of RRT					All	P value*
	1980–1984	1985–1989	1990–1994	1995–1999	2000–2005		
<b>Type 1 diabetes</b>							
Median age (years)†	34.8	38.5	39.4	43.3	44.6	42.3	<0.001
≥55 years (%)	2	5	12	15	18	11.9	<0.001
Male sex (%)	64	67	57	66	65	63.8	0.108
Peritoneal dialysis (%)‡	55	66	55	49	48	53.5	<0.001
Kidney transplantation within 2 years (%)‡	60	52	47	40	35	44.6	<0.001
Cause of death (%)							
Cardiovascular	62	67	66	64	71	65.8	0.425
Infection	18	18	17	19	13	17.1	0.631
n	205	281	317	361	440	1,604	
<b>Glomerulonephritis</b>							
Median age (years)†	43.5	48.9	55.3	56.5	57.2	53.1	<0.001
≥55 years (%)	26	34	50	52	55	45.2	<0.001
Male sex (%)	70	71	71	72	74	71.8	0.824
Peritoneal dialysis (%)‡	29	40	41	34	27	33.9	<0.001
Kidney transplantation within 2 years (%)‡	76	60	46	43	38	50.4	<0.001
Cause of death (%)							
Cardiovascular	49	50	55	47	44	49.5	0.424
Infection	27	25	17	25	23	23.3	0.217
n	242	276	304	338	396	1,556	

Data are median or %. \*P value for the overall significance between the groups of RRT start periods. †At the start of RRT. ‡From the start of RRT.

phritis caused by systemic diseases were excluded.

We used data from the Finnish Registry for Kidney Diseases, which has an estimated 97% coverage of all Finnish patients receiving chronic RRT since 1965. Kidney disease diagnoses have been stored as ICD-9 and later as ICD-10 codes, which enable separation between type 1 and 2 diabetic nephropathy. The registry is maintained by the Finnish Kidney and Liver Association, which is fully financed by the Finnish government. All patients provided written informed consent and permission to use the data anonymously in registry reports and for research purposes.

Data extracted for this study included information on demographics and patient characteristics: age, sex, cause of ESRD, mode of initial RRT (hemodialysis, peritoneal dialysis, or kidney transplantation), information on subsequent kidney transplantation, and cause of death (Table 1).

The diagnosis of ESRD was confirmed by kidney biopsy in 80 of the 1,604 patients with type 1 diabetes (5%) and a minimum of 980 of the 1,556 patients with glomerulonephritis (63%). In the glomerulonephritis group, at least 43% had the diagnosis based on biopsy during 1980–1994 and during 1995–2005 the

biopsy incidence was 73–85%, resulting in overall biopsy percentage of at least 63%. A widely accepted clinical practice is to avoid kidney biopsy in patients with type 1 diabetes if there are other signs of microvascular end-organ damage, such as diabetic retinopathy.

A total of 8,719 patients started RRT and of these 18.4% ( $n = 1,604$ ) had type 1 diabetes and 17.8% ( $n = 1,556$ ) had glomerulonephritis as the cause of ESRD. The study period was divided into five intervals: 1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2005. Table 1 describes the study population within these time periods. We further divided the patients into four age-groups based on the age at the start of RRT: <35 years (444 patients), from 35 to 44 years (586 patients), from 45 to 54 years (383 patients), and ≥55 years (191 patients). A total of six patients with type 1 diabetes and 19 with glomerulonephritis had a kidney transplant as the primary treatment. The majority of these preemptive transplantations took place during 1980 to 1984.

### Statistical methods

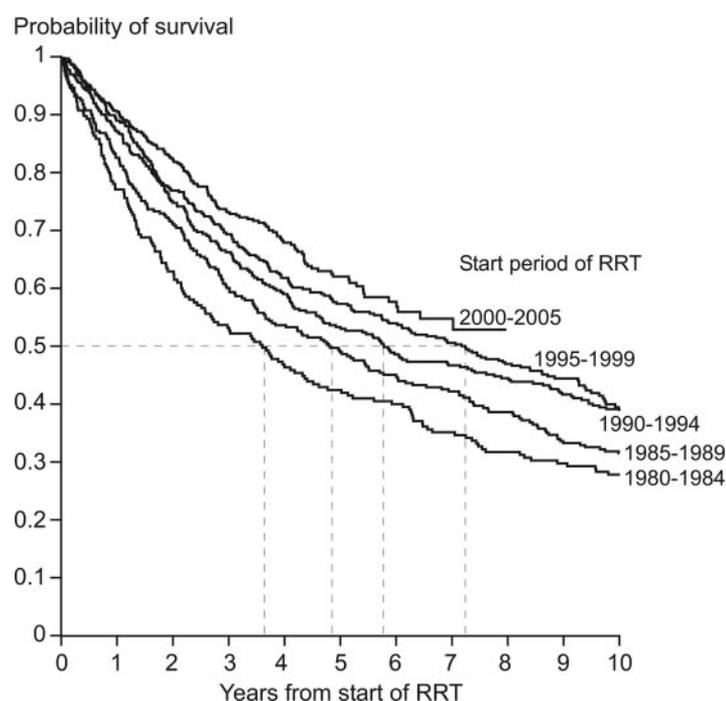
Comparisons between groups were performed using the  $\chi^2$  test for categorical variables. We calculated survival probabilities with the Kaplan-Meier method,

with death as the event, and patients were censored at 31 December 2007 or at the date of last follow-up. Median survival times were estimated from the Kaplan-Meier curves, and differences in survival probabilities between groups were assessed using the log-rank test. We used Cox proportional hazards regression to perform multivariable modeling of survival probabilities. Two-sided  $P < 0.05$  was considered statistically significant. For statistical analyses we used SPSS (version 16.0). All possible first- and second-degree interactions between the explanatory variables were considered in the Cox model building.

## RESULTS

### Descriptive results

The patients with type 1 diabetes showed a significant increase in median age and an overall decrease in peritoneal dialysis mode. The initial RRT mode was hemodialysis in 46.1%, peritoneal dialysis in 53.5%, and kidney transplantation (preemptive) in 0.4%. Sex distribution remained the same with two-thirds being men. The probability to receive a kidney transplant within 2 years from the RRT start diminished from 60% in 1980–1984 to 35% in 2000–2005 (Table 1).



**Figure 1**—Survival probability of type 1 diabetic patients beginning RRT according to start period of RRT. Dashed lines denote cut points for median survival times.

### Crude survival of patients with type 1 diabetes

Of the 1,604 patients with type 1 diabetes, 1,047 (65.3%) had died, and 557 patients were censored (alive at the end of follow-up on 31 December 2007,  $n = 548$ ; regained own kidney function,  $n = 5$ ; moved abroad,  $n = 4$ ; and lost to follow-up,  $n = 0$ ). Cardiovascular causes remained the main cause of death and comprised 65.8% of deaths (Table 1). Median survival time increased throughout the span of our study, from 3.60 years (95% CI 2.50–4.70) to 7.24 (95% CI 5.74–8.74) from the time period 1980–1984 to 1995–1999 (Fig. 1). Median survival time of patients starting RRT during 2000–2005 could not be calculated because it was longer than the maximal follow-up time, thus indicating a median survival time of >8 years. The median survival times increased significantly in all of the age-groups (Fig. 2). The absolute risk of death within 5 years from the start of RRT dropped from 51% in 1980–1984 to 33% in 2000–2005. The unadjusted relative risk (RR) of death was 0.55 for patients that entered RRT in 2000–2005 compared with those that entered in 1980–1984 (Table 2). In the different age-groups the corresponding RRs were even lower, varying between 0.31 and 0.38, indicating a confounding effect of age. In univariate analysis, the risk of

death increased by 4.1% (95% CI 3.4–4.7%) per year of age at the start of RRT. Sex was not associated with risk of death ( $P = 0.360$ ). Patients having hemodialysis as the initial mode of RRT had 1.4-fold risk (95% CI 1.2–1.6) of death compared with patients that entered peritoneal dialysis. Death risk was much higher in patients who did not receive a kidney transplant within 2 years (RR 4.0 [95% CI 3.5–4.6]).

### Adjusted survival of patients with type 1 diabetes

Adjustment for age and sex revealed a more substantial improvement in the prognosis, with RR of death of 0.33 for patients with type 1 diabetes starting RRT in 2000–2005 compared with 1980–1984. After further adjustment for initial mode of dialysis and having or not having received a kidney transplant within 2 years from the start of RRT, the RR of death dropped even more prominently to 0.23 (Table 2). The risk of death decreased, however, both in patients who received a kidney transplant and in those who did not (RR 0.20 [95% CI 0.11–0.37] and 0.25 [0.19–0.33], respectively).

### Interaction analysis

In the type 1 diabetic group we observed no statistically significant first- or second-

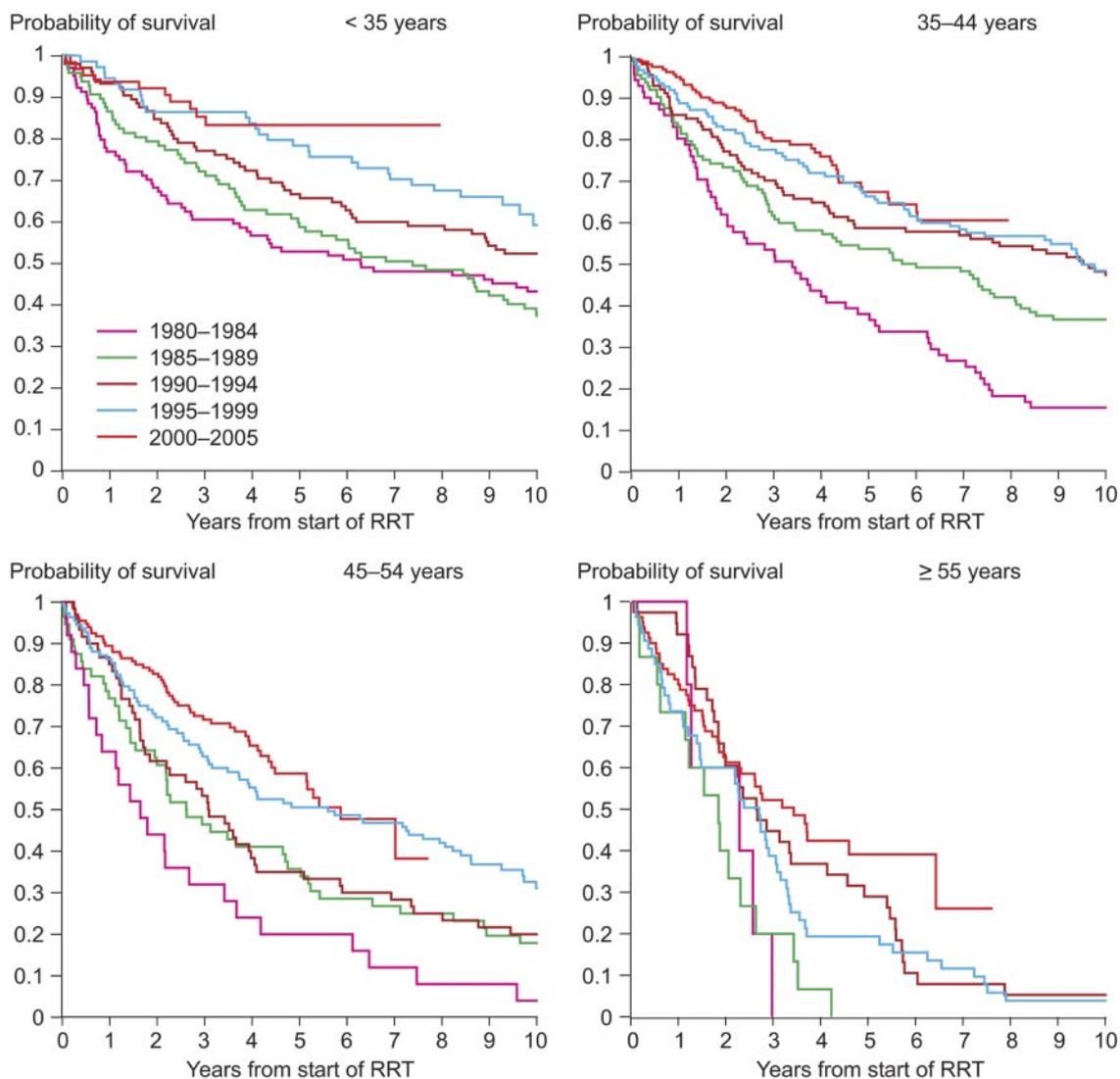
degree interactions between the variables RRT start period, age at start of RRT, sex, initial mode of dialysis, and having or not having received a kidney transplant within 2 years from the RRT start.

### Comparison between patients with type 1 diabetes and glomerulonephritis

Of the 1,556 patients with glomerulonephritis, 823 (52.9%) had died and 733 were censored (alive on 31 December 2007,  $n = 719$ ; regained own kidney function,  $n = 8$ ; moved abroad,  $n = 4$ ; and lost to follow-up,  $n = 2$ ). The initial RRT mode was hemodialysis in 64.8%, peritoneal dialysis in 33.9%, and kidney transplantation (preemptive) in 1.2%. Median survival time of patients with glomerulonephritis was significantly higher than that of patients with type 1 diabetes but did not show any significant increase during the follow-up (11.50 years on average). The unadjusted RR of death was 0.88 in patients starting RRT in 2000–2005 compared with 1980–1984. With adjustment for other variables, the RR was 0.30, indicating a clear improvement of prognosis also in the glomerulonephritis group (Table 2). The risk of death decreased more among patients with type 1 diabetes than among patients with glomerulonephritis ( $P = 0.007$ ), as indicated by interaction analysis between diagnostic group (type 1 diabetes and glomerulonephritis) and the RRT start period with adjustment for age, sex, treatment mode, and kidney transplant status at 2 years. During 1980–1984, the risk of death for patients with type 1 diabetes receiving RRT was 3.5-fold compared with patients with glomerulonephritis, but the risk decreased to be only 2.7-fold during 2000–2005.

**CONCLUSIONS** — We observed a considerably improved prognosis of patients with type 1 diabetes receiving RRT since 1980. The RR of death was 77% lower for patients beginning RRT in 2000–2005 compared with 1980–1984. Our results are based on a nationwide database with long-term coverage of all dialysis and kidney transplant patients in Finland. To our knowledge, our study is the first to show improvement in the prognosis of patients with type 1 diabetes receiving RRT during a follow-up as long as 28 years.

Interestingly, our study shows a progressive increase in median survival time of patients with type 1 diabetes receiving



**Figure 2**—Survival probability of patients with type 1 diabetes beginning RRT according to start period of RRT and age at start of RRT. Survival probabilities were statistically significantly different between start year periods in all age-groups ( $P < 0.005$ ).

chronic RRT from 3.60 to  $>8$  years and with similar survival improvement across all age-groups and throughout the follow-up period 1980–2007 (Fig. 2). Our results are in line with the observations of Sørensen et al. (8), who found that the overall survival rate of ESRD patients with type 1 or type 2 diabetes had improved by 15% per 5 calendar years. Our findings are also in accordance with an earlier European study by van Dijk et al. (7) that included a larger number of patients with ESRD but had a markedly shorter follow-up time, in which there was only a modest age- and sex-adjusted 2-year mortality reduction for all patients with type 1 diabetes, but a more pronounced 49% reduction in those patients that received a kidney transplant comparing years 1991–1994 to 1995–1998. Our study, however,

is the first focusing only on patients with type 1 diabetes and expanding the observation period to almost three decades.

It is noteworthy that the prognosis in this cohort improved over time despite the fact that some patient characteristics were changing in a direction that should be unfavorable with regard to prognosis. In particular, the median age of patients with type 1 diabetes increased by nearly 10 years over the duration of our study period, and the glomerulonephritis group aged to an even greater extent. The proportion of elderly subjects increased in both groups. Mean age of patients at the time of type 1 diabetes diagnosis, however, has not changed, but the time before development of ESRD has increased (5). We also observed a diminishing proportion of patients starting peritoneal dialy-

sis, which is the treatment mode that correlated with the better prognosis. Moreover, the probability of receiving a kidney transplant declined clearly. Thus, the improved prognosis could possibly be explained by better overall management of the patients with chronic kidney disease before and during RRT, as well as by developments in dialysis techniques and diabetes care.

During the follow-up time of our study, the number of patients with type 1 diabetes starting RRT in Finland has increased from 205 in 1980–1984 to 440 in 2000–2005. Their relative proportion, however, out of all patients starting RRT has decreased progressively from 22 to 15%. Despite the decreasing relative incidence, the relative prevalence of patients with type 1 diabetes of all patients receiv-

Table 2—RR of death according to the start period of RRT among patients with type 1 diabetes and patients with glomerulonephritis

RRT start period	Risk of death within 5 years of RRT start	Unadjusted RR	Adjusted RR*	Adjusted RR†
Type 1 diabetes (n = 1,604)				
1980–1984‡	0.51 (0.51–0.64)	1	1	1
1985–1989	0.45 (0.45–0.57)	0.87 (0.72–1.06)	0.72 (0.59–0.87)	0.64 (0.52–0.77)
1990–1994	0.41 (0.41–0.52)	0.70 (0.58–0.85)	0.53 (0.44–0.65)	0.44 (0.36–0.54)
1995–1999	0.38 (0.38–0.48)	0.66 (0.54–0.81)	0.43 (0.35–0.52)	0.33 (0.27–0.41)
2000–2005	0.33 (0.33–0.43)	0.55 (0.44–0.68)	0.33 (0.26–0.41)	0.23 (0.19–0.29)
Glomerulonephritis (n = 1,556)				
1980–1984‡	0.23 (0.23–0.35)	1	1	1
1985–1989	0.25 (0.25–0.36)	1.01 (0.82–1.25)	0.86 (0.69–1.06)	0.76 (0.61–0.94)
1990–1994	0.33 (0.33–0.44)	1.21 (0.98–1.50)	0.72 (0.58–0.90)	0.60 (0.48–0.75)
1995–1999	0.31 (0.31–0.41)	1.17 (0.93–1.46)	0.59 (0.47–0.74)	0.49 (0.38–0.62)
2000–2005	0.23 (0.23–0.33)	0.88 (0.68–1.14)	0.37 (0.28–0.49)	0.30 (0.23–0.40)

Data are RR (95% CI). \*Adjusted for age at the start of RRT, and sex. †Adjusted for age at the start of RRT, sex, initial mode of dialysis, and having or not having received a kidney transplant within 2 years of the RRT start. ‡Reference group.

ing RRT has remained constant at ~17%. This confirms the improved survival of patients with type 1 diabetes receiving RRT as shown in our current study.

To estimate the possible effect of progress in diabetes care, we chose patients with glomerulonephritis as the control group because it is obvious that among patients with glomerulonephritis an improved prognosis could not be caused by better diabetes care. Furthermore, we excluded patients with systemic glomerulonephritis because they could be regarded as potentially sicker than patients with disease affecting only the kidneys. We found a more substantial survival benefit over time for patients with type 1 diabetes compared with patients with glomerulonephritis, indicating that advances in diabetes care and management of diabetes complications may have partly contributed to our observation of improved prognosis of patients with type 1 diabetes.

Over the last few decades, management of diabetes has evolved remarkably in terms of insulin regimens and more intensive blood glucose monitoring. Disposable insulin syringes became widely available in the early 1970s, and home glucose monitoring and semisynthetic and synthetic human insulin reached wider use in the 1980s. With the emergence of multiple insulin injections in the 1990s followed by the development of rapid-acting insulin regimens, patients with type 1 diabetes were able to maintain more stable blood glucose control and closer-to-target A1C levels. In our study population, however, the level of A1C has shown only slight changes during the past

years: the mean value was 8.4% in 1992 (when these data were routinely gathered for the first time) and was almost the same in 2007 (8.0%). Nevertheless, this finding does not exclude other potential improvements such as fewer hypo- and hyperglycemic events, with probable beneficial effects on mortality. By taking into account the obvious developments in diabetes care, it is likely that the level of A1C was higher in the 1980s, thus increasing the likelihood of a negative outcome in these patients.

On the other hand, quality and dose of dialysis therapy have also improved over the years. During the 1980s most hemodialysis patients were treated with basic techniques and low-flux cellulose dialyzers, with no access to on-line hemodiafiltration or modern synthetic high-flux dialyzers with better biocompatibility. Use of these has been expanding since the mid-1990s, allowing enhanced uremic toxin clearance and flexibility of hemodialysis treatment. With peritoneal dialysis therapy, the present availability of biocompatible fluids with better tolerability and solute removal and icodextrin-containing fluid (with superior ultrafiltration capability without excess glucose load) has increased the efficacy of peritoneal dialysis. In addition, the number of patients receiving peritoneal dialysis using automated overnight peritoneal dialysis machines has increased, leading to 1) greater toxin clearance, 2) better adjustment of peritoneal dialysis to everyday life with improved adherence and overall patient compliance to therapy, and 3) possibly diminished peritonitis episodes

(10,11). In our patient population with type 1 diabetes, the mean number of weekly hemodialysis sessions increased from 2.9 (95% CI 2.8–3.0) to 3.1 (95% CI 3.0–3.3) from 1992 to 2007, with mean weekly treatment hours rising from 11.4 (95% CI 10.9–12.0) to 13.5 (95% CI 12.8–14.2). During the same time the percentage of those patients with type 1 diabetes who entered peritoneal dialysis therapy and initially used an automated machine rose from 2 to 27. It is a well-known fact that achieving target uremic toxin clearance improves survival in patients receiving dialysis (12), and thus the increase in dialysis dose could have led to improved survival in our study population. The dialysis dose, however, was approximately the same both for the patients with type 1 diabetes and patients with glomerulonephritis, suggesting that any survival advantage related to progress in dialysis technology should be similar in both groups.

It could also be speculated that patients with type 1 diabetic nephropathy are in more intensive monitoring by health care professionals compared with patients without diabetes. Patients with type 1 diabetes are closely followed up from childhood with routine visits to the health care system, which probably have preventive effects on cardiovascular complications (13). The comprehensive management of patients approaching ESRD includes control of blood pressure and calcium-phosphorus level and treatment with erythropoiesis-stimulating agents, which are known to have an effect on cardiovascular outcomes (14). However, in acknowledging that ~66% of those pa-

tients with type 1 diabetes who died during our study period died of cardiovascular causes, there is a need for further studies to explore how comorbidities and other related factors before and during ESRD influence the outcome of patients receiving RRT.

Our study has some limitations. First, the results might not be generalizable to other countries, as the incidence of type 1 diabetes is among the highest in the world in Finland. Therefore, much attention has been focused on improving quality of diabetes care, which may explain part of the favorable progress in prognosis of the Finnish patients. Second, for most of the patients with type 1 diabetes we did not have kidney biopsy confirmation of the diagnosis because the long-term practice in Finland is to perform a biopsy only in rare patients when other microvascular, diagnosis-confirming findings are absent. Third, we did not have data on patient level details of diabetes treatment (e.g., type of insulin or type of blood pressure medication) or dialysis treatment (e.g., type of vascular access). Thus, we do not exactly know which aspects of treatment improvement have been responsible for the improved prognosis. On the other hand, the strength of the study is that it is based on an exceptionally comprehensive nationwide database with complete coverage of Finnish patients with ESRD. This excludes selection bias and allows longer follow-up of patients with type 1 diabetes receiving RRT than published before.

In summary, the survival of Finnish patients with type 1 diabetes and ESRD has consistently and significantly improved since the beginning of the 1980s despite the progressively older age of patients starting RRT. During the same time period, survival in the control group (patients with glomerulonephritis) has also improved but to a lesser extent. This result indicates a beneficial contribution of both dialysis-related factors and progress in diabetes care and highlights the importance of comprehensive diabetes care in patients receiving chronic renal replacement therapy.

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M.H. and J.H. wrote the first draft and finalized the manuscript, researched data, contributed to discussion, and reviewed/edited the manuscript. P.-H.G. contributed to discussion and reviewed/edited the manuscript. C.G.-R. conceived the original idea of the study, contributed to discussion, and reviewed/edited the manuscript. P.F. conceived the original idea of the study, researched data, contributed to discussion, and reviewed/edited the manuscript.

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