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ARTICLE

Comorbidities and survival of patients with type 1 diabetes on renal replacement therapy

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Abstract
Aims/hypothesis Comorbidities are frequent among type 1 diabetes patients on renal replacement therapy, yet the effect of comorbidities on survival is unknown. Our aim was to estimate this effect.
Methods An incident cohort of all patients with type 1 diabetes entering chronic renal replacement therapy (n=656) in Finland between 2000 and 2008 was followed until death or the end of follow-up on 31 December 2008. All data were obtained from the Finnish Registry for Kidney Diseases, which collects information on comorbidities at the start of renal replacement therapy. The main outcome measure was relative risk of death according to comorbidities.
Results At start of renal replacement therapy, 22% of the patients with type 1 diabetes had coronary artery disease, 19% peripheral vascular disease, 11% cerebrovascular disease, 33% left ventricular hypertrophy and 7% heart failure. All these comorbidities were significant predictors of death in univariate analyses (RR 1.6–4.9). The 5 year survival probability of patients without comorbidities was 74%, while it was 56% and 37%, respectively, for those with one or more than one comorbidity. When the comorbidities were studied in a multivariate model, adjusting for age and sex, peripheral vascular disease (RR 1.9), left ventricular hypertrophy (RR 1.7) and heart failure (RR 2.5) remained independent risk factors for death. Calculations indicated that one-third of deaths in the study population could be attributed to comorbidities.
Conclusions/interpretation Among patients with type 1 diabetes entering renal replacement therapy, comorbidities are common and strong predictors of death. Therefore, it is essential to identify and adequately treat comorbidities.

Keywords Comorbidity · End-stage renal disease · Mortality · Registry · Renal replacement therapy · Survival · Type 1 diabetes

Abbreviations
ESRD End-stage renal disease
RRT Renal replacement therapy

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Introduction

Type 1 diabetes is a major cause of end-stage renal disease (ESRD), and accounts for 4–17% of all patients entering renal replacement therapy (RRT) in the USA and Finland [1, 2]. Patients with type 1 diabetes have a two- to fourfold mortality compared with the general population [3, 4], and if type 1 diabetes is complicated by ESRD, then mortality increases further to more than tenfold [5]. In fact, two

recent studies from Finland and the USA revealed that patients with type 1 diabetes and normoalbuminuria showed no excess mortality beyond the general population, but ESRD was associated with 18 and 30 times higher standardised mortality ratios, highlighting the importance of chronic kidney disease as the major risk factor for mortality in patients with type 1 diabetes [6, 7]. We have, however, recently shown that survival of patients with type 1 diabetes on RRT has improved over the past three decades and that this may be related to improvements in RRT and diabetes care [8].

Comorbidities such as coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes and cancer have been shown to be important risk factors for death among ESRD patients [9]. In those with diabetes (type 1 and type 2 diabetes combined), comorbidities are also more frequent and survival substantially worse compared with other ESRD patients [10, 11]. The effect of comorbidities on survival, however, has not been estimated separately in patients with type 1 diabetes on RRT.

Our aim was therefore to estimate the prevalence and effect of comorbidities on survival in a nationwide incidence cohort of patients with type 1 diabetes receiving RRT.

Methods

All data were obtained from the Finnish Registry for Kidney Diseases. This registry receives information from all nephrological units in Finland and has an estimated 97–99% coverage of all Finnish patients on RRT since 1965. The registry is maintained by the Finnish Liver and Kidney Association which is fully financed by the Finnish government. The registry contains information on age, sex, cause of ESRD, type of RRT (peritoneal dialysis, haemodialysis or kidney transplantation), laboratory results and cause of death. Since 2000, extensive data at start of RRT on the presence of coronary artery disease, peripheral vascular disease, left ventricular hypertrophy, heart failure, cerebrovascular disease, and treatment of hypertension and dyslipidaemia have been collected using a ‘tick the correct box’ system. The causes of ESRD are coded according to the ICD-10 codes (www.who.int/classifications/icd/en/). This enables separation between type 1 and type 2 diabetes. All patients gave written informed consent to use their data anonymously in registry reports and for research purposes.

All patients with type 1 diabetes who entered chronic RRT from 1 January 2000 to 31 December 2008 according to the Finnish Registry for Kidney Diseases were included in the study (n=656). In addition, we selected a control group that included all patients 18 years or older with diseases other than type 1 or type 2 diabetes as the cause of renal failure starting RRT during the same time period (n=2,801). A total of 4,421 patients started RRT in Finland during 2000–2008.

The patients were followed from the start of RRT until death, recovery of kidney function, loss of follow-up, moved abroad or to the end of the follow-up period on 31 December 2008. Observed comorbidities at the start of RRT were peripheral vascular disease, coronary artery disease, cerebrovascular disease, left ventricular hypertrophy, and heart failure. Information on comorbidities was available from 86% (left ventricular hypertrophy) to 96% (coronary artery disease) of the patients. Age, sex, obesity (BMI categories), and blood pressure were included in multivariate analysis, and 75% of the patients had information for all analysed variables and could be included in the analysis. In order to evaluate the possibility of selection bias, survival was compared between patients with and without information on all variables.

Statistical methods Comparisons between groups were performed by χ^2 test for categorical variables. Logistic regression was used for adjusted comparison of comorbidity prevalences between patient groups. Survival probabilities were calculated using Kaplan–Meier curves and differences between patient groups were assessed using the logrank test. Relative risks of death as a function of comorbidities and other explanatory variables were estimated using Cox proportional hazards regression, with death as the event and censoring at 31 December 2008 or at last date of follow-up. Two-sided p values lower than 0.05 were considered statistically significant. All possible first-degree interactions between the explanatory variables were considered by including interaction terms in Cox regression with and without adjustment for age and sex. Interaction means that the effect of one variable on survival differs according to the level of another variable. Interactions were considered significant if the two-sided p value was lower than 0.001 (Bonferroni adjustment was used to calculate this reduced p value in order to decrease risk of detecting interactions just due to multiple testing). Statistical analyses were performed using SPSS version 17.0.

Results

Baseline characteristics Of the 656 patients with type 1 diabetes included in the study, 209 died during follow-up, two moved abroad and two regained kidney function. The cause of death was cardiovascular in 56% (n=117) of the deceased patients. Patients with type 1 diabetes were

considerably younger than the patients without diabetes (46 vs 62 years, $p<0.001$) at the start of RRT. Of the patients with diabetes, 64% were men and 53% entered haemodialysis as the first mode of dialysis treatment. Mean time from diagnosis of diabetes to start of RRT was 31 years. During follow-up, 39% ($n=258$) of the patients received a renal transplant, and these patients had been on dialysis therapy on average 1.6 years.

Prevalence of comorbidities, obesity and medication for hypertension and dyslipidaemia Prevalence of comorbidities was high, with an average of 1.2 comorbidity per patient, and 52% of patients having at least one comorbidity. Left ventricular hypertrophy, coronary artery disease and peripheral vascular disease were the most common comorbidities (Table 1). Patients with coronary artery disease were divided into two groups, those previously invasively treated (bypass surgery or angioplasty) and those non-invasively treated.

Comparison with patients without diabetes Patients with type 1 diabetes had more comorbidities and had medication for dyslipidaemia and hypertension more often than non-diabetic patients, even though the mean age was 15 years lower among the patients with type 1 diabetes. Adjustment for age and sex made this difference even more evident (Table 1). Relative risk of death was 2.1 (95% CI 1.8–2.5) for type 1 diabetes patients compared with patients without diabetes when adjusting for age and sex, and 1.8 (95% CI 1.5–2.2) with further adjustment for comorbidities.

Effect of comorbidities on risk of death In univariate analysis all observed comorbidities (peripheral vascular disease, coronary artery disease, cerebrovascular disease, left ventricular hypertrophy and heart failure) were associated with an increased risk of death. After adjustment for age and sex, the association between invasively treated coronary artery disease and mortality disappeared. Heart failure was associated with the highest risk, whereas BMI was not correlated to risk of death (Table 2). Furthermore, diastolic blood pressure correlated negatively with the risk of death in univariate analysis, but the correlation disappeared after adjustment for age and sex.

With mutual adjustment for all variables listed in Table 2, age at start of RRT, peripheral vascular disease, left ventricular hypertrophy and heart failure were independent predictors of death, whereas coronary artery disease, cerebrovascular disease, BMI and blood pressure were not (Table 2).

Because of incomplete information on comorbidities, 24.7% of the patients with type 1 diabetes were excluded from the multivariate analysis. There was, however, no difference in survival between those patients included or excluded. Furthermore, when the initial treatment modality was added into the multivariate model, the results remained unchanged.

Number of comorbidities and risk of death Risk of death increased gradually with increasing number of comorbidities. In age- and sex-adjusted analysis, patients with more

Table 1 Prevalence of comorbidities, hypertension and medication use

Characteristic	Proportion (%)			
	Type 1 diabetes	No diabetes	Unadjusted *p* value	Adjusted *p* value[a]
Peripheral vascular disease	19	9	<0.001	<0.001
Coronary artery disease	22	23	0.73	<0.001
Non-invasively treated	10	14	0.021	<0.001[b]
Invasively treated	12	10	0.038	<0.001
Cerebrovascular disease	11	9	0.36	<0.001
Left ventricular hypertrophy	33	28	0.019	<0.001
Heart failure	7	9	0.10	0.004[b]
Systolic BP >125 mmHg	91	81	<0.001	<0.001
Diastolic BP >75 mmHg	76	67	<0.001	0.097
Hypertension medication	96	83	<0.001	<0.001
Dyslipidaemia medication	68	41	<0.001	<0.001
Overweight (BMI >30 kg/m^2)	14	16	0.262	0.823
Underweight (BMI <20 kg/m^2)	6	9	0.004	<0.001

[a]Age- and sex-adjusted *p* value for the overall significance between the groups

[b] Adjusted risk of comorbidity is significantly higher in patients with type 1 diabetes

Table 2 Effect of comorbidities on risk of death among patients with type 1 diabetes on RRT

Characteristic	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)	Adjusted[b] RR (95% CI)
Age at start (per 10 year increment)			1.41 (1.15–1.72)
Peripheral vascular disease	2.92 (2.16–3.94)	2.31 (1.69–3.14)	1.88 (1.25–2.83)
Left ventricular hypertrophy	1.75 (1.29–2.38)	1.76 (1.30–2.39)	1.68 (1.18–2.40)
Heart failure	4.87 (3.21–7.38)	3.25 (2.10–5.03)	2.50 (1.32–4.59)
Coronary artery disease			
No disease	1	1	1
Non-invasively treated	2.09 (1.42–3.07)	1.63 (1.10–2.42)	1.32 (0.78–2.22)
Invasively treated	1.56 (1.05–2.30)	1.01 (0.67–1.52)	0.65 (0.37–1.14)
BMI (kg/m^2)			
Normal (20–30)	1	1	1
Underweight (<20)	1.67 (1.00–2.79)	1.56 (0.93–2.62)	1.59 (0.84–3.00)
Overweight (>30)	1.02 (0.66–1.55)	0.92 (0.60–1.40)	0.82 (0.49–1.36)
Female sex			1.29 (0.91–1.84)
Cerebrovascular disease	2.18 (1.51–2.30)	1.63 (1.11–2.38)	1.25 (0.76–2.05)
Systolic blood pressure (per 10 mmHg)	0.98 (0.93–1.04)	0.99 (0.94–1.05)	0.98 (0.89–1.08)
Diastolic blood pressure (per 10 mmHg)	0.85 (0.76–0.95)	1.00 (0.89–1.13)	1.02 (0.84–1.24)

[a]Age- and sex-adjusted

[b] Multivariate model of all variables

than two comorbidities had a 3.6-fold risk of death compared with patients without comorbidities (Table 3). With further adjustment for kidney transplantation this relative risk of death was 2.5 (95% CI 1.6–3.9). Median survival times were 7.0, 4.4 and 2.7 years with one, two and three or more comorbidities, respectively. Without any comorbidity, the median survival time was over 9 years (Fig. 1).

Within 5 years after the initiation of RRT, the risk of death was 39% for all patients with type 1 diabetes, while the risk was only 26% in those without comorbidities. Hereby, the population-attributable risk percentage 33 [(0.39−0.26)/0.39] indicated that one-third of the mortality among patients with type 1 diabetes on RRT could be attributed to comorbidities. Adjustment for age and sex did not change this estimate.

Interaction analysis No statistically significant interactions were observed between the explanatory variables, i.e. the comorbidities, blood pressure, BMI, sex and age at start of RRT.

Discussion

Our study showed that comorbidities are frequent among patients with type 1 diabetes at the time they start RRT and that these comorbidities correlate with a lower probability of survival. The study included all patients who entered RRT during 2000–2008 in Finland, and data on the most relevant comorbidities were available. Notably, all comorbidities were associated with an increased risk of death. After adjustment for confounders, peripheral vascular disease, left ventricular hypertrophy and heart failure remained independent predictors of death. Type 1 diabetes patients with one or more comorbidities had more than twofold risk of death compared with those without comorbidities, and the risk increased with growing number of comorbidities. Patients with comorbidities had a lower probability of receiving a kidney transplant, but this did not explain their increased risk of death. Furthermore, the patients with type 1 diabetes presented with more comorbidities compared with patients without diabetes, and this was particularly evident for peripheral vascular disease.

Table 3 Number of comorbidities and risk of death among patients with type 1 diabetes on RRT

Number of comorbidities	Unadjusted RR (95% CI)	*p* value	Adjusted[a] RR (95% CI)	*p* value
0	1		1	
1	1.96 (1.38–2.79)	<0.001	1.78 (1.25–2.54)	0.001
2	3.05 (2.05–4.53)	<0.001	2.40 (1.59–3.62)	<0.001
3 or more	5.18 (3.38–7.93)	<0.001	3.65 (2.33–5.70)	<0.001

[a]Age- and sex-adjusted

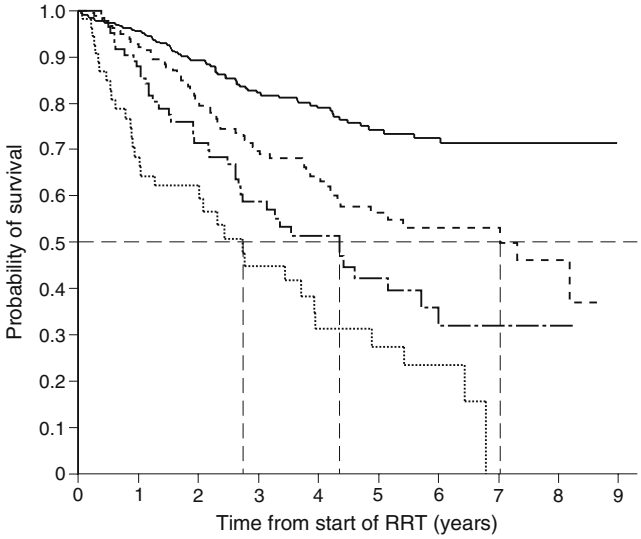

Fig. 1 Survival probability of patients with type 1 diabetes starting RRT according to number of comorbidities. Solid line, no comorbidities, lightly dashed line, median survival time; dashed line, one comorbidity; dotted/dashed line, two comorbidities; dotted line, three or more comorbidities

It is of note that, even after adjustment for comorbidities, type 1 diabetes patients still had worse survival than patients without diabetes, which means that comorbidities cannot alone explain the impaired survival. This emphasises the importance of studying this patient group with a high risk of death separately. Although our results are not unexpected and an everyday reality for the physicians who treat patients with diabetic renal disease, there are to our knowledge no previous studies that have specifically assessed the effect of comorbidities on survival in a patient population consisting exclusively of patients with type 1 diabetes. Data on a mix of patients with type 1 and type 2 diabetes are also limited.

Several studies have, however, shown that comorbidities increase mortality among RRT patients [12–14], and a large European study reported that coronary artery disease, peripheral vascular disease and cerebrovascular disease all increase the risk of death by approximately 40% [9]. To our knowledge, only two small studies have estimated the effect of comorbidities on mortality in patients with diabetes on RRT, and no study has focused solely on patients with type 1 diabetes. Foley et al. found that cardiac failure, left ventricular hypertrophy and ischaemic heart disease associate with increased mortality among diabetes patients on RRT, but they did not study peripheral vascular disease [11]. A Croatian study reported coronary artery disease as one of the most important predictors of death among 44 patients with diabetes on haemodialysis [15].

Comorbidities have been shown to be more common among patients with diabetes than among other RRT patients [10, 16, 17]. A large study from New Zealand and Australia 1991–2005 reported prevalence of comorbidities separately for type 1 diabetes [16]. Of these RRT patients, 34% had coronary heart disease, 43% had peripheral vascular disease and 12% had cerebrovascular disease. The prevalence of cerebrovascular disease was almost the same (11%) in our study, whereas coronary artery disease (22%) and peripheral vascular disease (19%) were less common. As age at start of RRT was approximately the same, this factor does not explain the observed differences. All in all, data on the prevalence of comorbidities among patients with type 1 diabetes on RRT are scarce.

Of all comorbidities, heart failure increased the risk of death the most, with a relative risk of 2.5. In this registry-based study we did not have information about type or underlying cause of heart failure. Another strong independent risk factor for death was peripheral vascular disease. In patients with peripheral vascular disease, infections are a frequent problem. However, as we did not have any information about the presence of infections, it was impossible to determine how much they contributed to the risk of death, but it is possible that infections potentiated peripheral vascular disease as a risk factor. It is of note, however, that infection was not a more common cause of death among patients with than without peripheral vascular disease.

One-third of the patients had left ventricular hypertrophy, which was the most common comorbidity predicting survival. This emphasises the importance of early identification and treatment of factors that lead to left ventricular hypertrophy, such as hypertension. Almost all patients were prescribed blood-pressure-lowering drugs, but the majority of the patients had, nevertheless, hypertension prior to the start of RRT. It should be noted that blood pressure assessment was based on one single observation just before the start of RRT, and may therefore not represent long-term blood pressure levels. Fluid retention can cause elevation of the blood pressure and is frequently present at the start of RRT, and it is therefore not surprising that our study did not demonstrate a correlation between blood pressure and mortality.

A major strength of the present study was the total coverage of patients with type 1 diabetes entering RRT in Finland during the entire study period. The information on the outcome, mortality, was also complete. Selection bias was thus minimal. Furthermore, in most of the earlier studies it was not possible to distinguish between patients with type 1 and type 2 diabetes. The Finnish Registry for Kidney Diseases has exceptionally comprehensive data on comorbidities before the start of RRT and these data were collected systematically using the same form for all patients, a procedure that reduces information bias.

Our results cannot automatically be applied to other parts of the world. The Finnish population is genetically quite homogeneous (and almost entirely white) and the incidence of type 1 diabetes in Finland is one of the highest in the world [18]. Consequently, special emphasis has been directed towards treatment of type 1 diabetes. It can therefore be speculated that the concerted efforts of the healthcare system have led to the relatively good prognosis of patients with type 1 diabetes in Finland [19]. Another potential pitfall of our study is reporting bias towards more difficult cases, as the reporting of comorbidities to the Finnish Registry for Kidney Diseases is mainly based on existing information, and comorbidities are not examined for registry purposes. For example, the prevalence of coronary artery disease was surprisingly low compared with that in an earlier study [16]. This and high cardiovascular mortality may indicate underreporting of coronary artery disease in our study population. The likelihood of patients with undiagnosed coronary artery disease and the correlation between coronary artery disease and mortality highlights the importance of more intensive identification strategies. Information on comorbidities was collected only at the start of RRT and some patients might have developed coronary artery disease during follow-up. However, if some patients with comorbidities were misclassified as not having comorbidities, this would have diluted the association between comorbidities and mortality. Notably, the high cardiovascular death rate is probably partly a consequence of left ventricular hypertrophy and heart failure caused by diabetic cardiomyopathy independent of coronary artery disease.

Unexpectedly, little is known about the prevalence of comorbidities and how they influence mortality among patients with type 1 diabetes on RRT. It has been suggested that this group of patients differs in many respects from patients with type 2 diabetes, and should be analysed as a separate entity [16]. Our study shows that comorbidities are common among these patients, and that one-third of all deaths can be attributed to the comorbidities. Early identification and treatment of comorbidities appear essential in order to reduce the risk of premature death in this patient group. Left ventricular hypertrophy, peripheral vascular disease and heart failure usually develop slowly, and their treatment becomes more difficult as they progress. Therefore, efficient treatment should be started years before a patient develops ESRD.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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