Clinical Kidney Journal, 2019, 1–6

doi: 10.1093/ckj/sfz116
Original Article

ORIGINAL ARTICLE

Mortality after amputation in dialysis patients is high but not modified by diabetes status

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ABSTRACT

Background. Survival among dialysis patients with diabetes mellitus (DM) is inferior to survival of non-diabetic dialysis patients, probably due to the higher prevalence of diabetes-related comorbid conditions. One could hypothesize that these comorbid conditions also contribute to a decreased survival after amputation in diabetic patients compared with non-diabetic patients on dialysis.

Methods. Data were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis, a multicentre, prospective cohort study in which new patients with end-stage renal disease were monitored until transplantation or death. Amputation rates (incident cases) were calculated in patients with and without DM. The primary endpoint was all-cause survival after first amputation during dialysis therapy in diabetic patients compared with non-diabetic dialysis patients with an amputation. This was formally assessed using interaction analysis (Poisson regression).

Results. During follow-up (mean duration 2.9 years), 50 of the 413 diabetic patients had a new amputation (12.1%), compared with 20 of 1553 non-diabetic patients (1.2%). Amputation rates/1000 person-years were 47.9 [95% confidence interval (CI) 36.3–63.2] and 4.1 (95% CI 2.7–6.4), respectively, for diabetic patients and non-diabetic patients. Amputation increased mortality risk more than 4-fold in patients without diabetes [hazard ratio (HR) 4.6 (95% CI 2.8–7.6)] as well as in patients with diabetes [HR 4.6 (95% CI 3.3–6.4)]. No formal interaction between diabetes and amputation was found ($P = 0.12$).

Conclusions. Amputation in dialysis patients is associated with a 4-fold increased mortality risk; this mortality risk was similar for diabetes and non-diabetes patients. Importantly, the risk for amputation is 10-fold higher in DM compared with non-diabetic dialysis patients.

Keywords: amputation, diabetes mellitus, dialysis, mortality, survival

INTRODUCTION

Diabetes mellitus (DM) is the most common underlying cause of non-traumatic amputation. The main factors associated with diabetes-related amputation are sensory neuropathy, infection and ischaemia [1–5]. Another common cause of amputation is chronic kidney disease, with the highest risk in patients with end-stage renal disease (ESRD) [6]. Furthermore, several studies have shown an ~ 10-fold increased amputation risk in diabetic dialysis

Received: 13.6.2019; Editorial decision: 7.8.2019

patients compared with non-diabetic dialysis patients, although risk estimates showed a variation among different countries [7, 8].

Studies on survival after amputation in diabetic and non-diabetic patients with and without ESRD thus far have shown contrasting results. In some studies, diabetes was associated with an excess mortality after amputation [9, 10], whereas other studies showed similar or reduced mortality in diabetic patients compared with non-diabetic patients [7, 11–15]. Another study reported a time-dependent impact of diabetes on mortality, with a lower mortality in the first 2–3 years, but thereafter diabetic patients had a higher mortality compared with non-diabetic patients [16]. These contrasting results might be due to different study populations, different follow-up times and different statistical approaches.

The primary aim of this study was to compare the survival after amputation in diabetic dialysis patients with that of non-diabetic dialysis patients using a cohort study with long-term follow-up. The secondary aim of this study was to determine the incidence of a recurrent amputation in diabetic dialysis patients.

MATERIALS AND METHODS

Design

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective, multicentre cohort study in 38 dialysis centres throughout the Netherlands in which incident patients with ESRD were included at the time of initiation of dialysis treatment, from 1 January 1997 until 1 January 2007. Study visits took place at the start of dialysis, at 3 and 6 months and subsequently at 6-month intervals until the date of censoring (death, kidney transplantation or transfer to a non-participating dialysis centre) or the end of the follow-up on 1 January 2007. Data on demographic characteristics and comorbidities were collected at the time of entry into the study. Dialysis characteristics were collected 3 months after the start of RRT and at 6-month intervals thereafter. At the 3-month visit, patients were classified according to the treatment modality, that is, haemodialysis (HD) or peritoneal dialysis. The cause and type of renal disease were defined according to the criteria of the European Renal Association–European Dialysis and Transplantation Association [17]. For each patient, data on DM were collected, such as insulin dependency, patient-reported duration of DM and history of diabetic retinopathy for which laser therapy was performed. During each study visit, patients were asked if they had been operated on and/or admitted to the hospital. Surgical (operation) procedures on and dates were documented. Furthermore, hospital admissions and the reason for admission were registered.

Patient selection

Patients ≥18 years of age who started with dialysis as the initial renal replacement therapy were eligible for this study. Start of dialysis was considered as baseline and start of follow-up, except for analyses concerning treatment modality, in which case 3 months was considered as baseline; the reason is that after 3 months, most patients are considered to be on a 'definitive' dialysis mode. Informed consent was obtained before inclusion. This study was approved by the medical ethics committees of all participating centres.

Exposures and study outcomes

For all patients we extracted data on amputations; levels of amputations were categorized as toe(s), feet, below knee and above knee. Toe(s) and feet amputations were classified as minor amputation, whereas below knee and above knee were classified as major amputations. Second, amputations were classified as either prevalent (present at start follow up) or incident (during follow-up; ipsilateral amputation, contralateral amputation or both). We compared amputation rates between patients with and without DM. To study the effect of amputation on mortality and also the potential effect of modification by diabetes, we compared mortality rates in four groups: patients without amputation and without DM (reference), patients without amputation but with diabetes, patients with amputation without diabetes and patients with both amputation and diabetes.

Statistical analysis

Baseline variables were compared between diabetes and non-diabetes dialysis patients and expressed as a proportion or mean with standard deviation (SD). For time-to-event analysis, patients were censored at the time of the event under study (amputation or death), renal transplant or end of follow-up (1 January 2007). The amputation rate was calculated as the incidence rate and expressed as the number of amputations/100 person-years.

Mortality rates were compared with Poisson regression and incidence rate ratios were estimated including 95% confidence intervals (CIs). To estimate the effect of amputation on mortality, amputation was considered a time-dependent variable. The potential interaction between amputation and diabetes was assessed.

Effect estimates were adjusted for age, gender, dialysis modality, amputation at baseline, smoking, blood pressure, body mass index, myocardial infarction or stroke in multivariable models. Analyses were performed with SPSS statistical software, version 20.0 (IBM, Armonk, NY, USA). Time-dependent analyses were performed using Stata version 14.1 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics

Between January 1997 and January 2007, 2051 patients who started renal replacement therapy were included in the NECOSAD. Twenty-five percent of patients had DM at baseline (Table 1). Sixty-four percent of diabetic patients were treated with insulin injection therapy. Patients with diabetes were older (mean age 63 ± 13 years) compared with non-diabetics (59 ± 16 years). Forty-six percent of diabetic patients had retinopathy for which laser coagulation was performed. Seventy-one percent of patients with diabetes had diabetes as their primary renal disease.

HD was the dialysis modality in 68% of patients with DM and 63% of patients without DM. The prevalence of cardiovascular morbidity at baseline was higher compared with patients without DM. Peripheral artery disease was present in 19% of patients with DM compared with 10% in patients without DM.

Amputation

At baseline, 24 of 413 diabetic patients (5.8%) had an amputation compared with only 9 of 1553 non-diabetic patients (0.5%) (Table 2). During follow-up (mean duration 2.9 ± 2.3 years), 50 diabetic patients had a new amputation (12.1%) compared with 20 non-diabetic patients (1.2%). Amputation rates/1000 person-

Table 1. Baseline characteristics of patients with diabetes compared with patients without diabetes

Baseline characteristics	Patients with diabetes ($n = 413$)	Patients without diabetes ($n = 1638$)
Age at start of dialysis (years), mean (SD)	63 (13)	59 (16)
Gender (male), %	55	64
Primary renal disease, *n* (%)		
DM	295 (71)	0
Glomerulonephritis	7 (2)	245 (15)
Renal vascular disease	46 (11)	309 (19)
All other	65 (16)	1084 (66)
Treatment modality (% HD)	68	63
Comorbidity, %		
Cerebrovascular accident	13	6
Myocardial infarction	18	10
Severity of DM		
Peripheral artery disease without amputation, %	19	10
Duration of DM (years), mean (SD)	16 (11)	0
Retinopathy (laser coagulation), %	46	0
Insulin dependency, %	64	0
Medication, %		
Antihypertensive agents	85	70
Lipid-lowering medication	34	18
Smoking (currently or recently quit), %	20	29
Blood pressure (mmHg)		
Systolic	153 (24)	148 (24)
Diastolic	79 (12)	84 (13)
Body mass index (kg/m^2)	27 (5)	25 (4)
Laboratory values, mean (SD)		
Cholesterol (mmol/L)	4.9 (1.4)	5.1 (1.3)
Haemoglobin (g/dL)	11.1 (1.6)	11.2 (1.6)
Calcium (mmol/L)	2.3(0.26)	2.4 (0.25)
Phosphate (mmo/L)	1.8 (0.53)	1.8 (0.55)
rGFR (mL/min/1.73 m^2)	5.6 (3.5)	5.2 (3.6)

rGFR, residual glomerular filtration rate.

Table 2. Data on amputations

Amputation	Patients with diabetes ($n = 413$)	Patients without diabetes ($n = 1638$)
First amputation, *n* (%)		
Baseline	24 (5.8)	9 (0.5)
During follow-up	50 (12.1)	20 (1.2)
Level of amputation (during follow-up), *n* (%)		
Toe (minor)	21 (5.1)	6 (0.4)
Feet (minor)	8 (1.9)	1 (0.06)
Below knee (major)	16 (3.9)	9 (0.6)
Above knee (major)	5 (1.2)	4 (0.2)
Amputation rate/1000 person-years	47.9	4.1
Days to incident amputation, mean (SD)	511 (380)	671 (409)
Second amputation	24	5
Days to second amputation (from first amputation), mean (SD)	88 (91)	139 (148)

years were 47.9 (95% CI 36.3–63.2) and 4.1 (95% CI 2.7–6.4) for diabetic and non-diabetic patients, respectively. The level of amputation was different in both groups; patients with diabetes had mainly minor amputations (5.1%), whereas patients without diabetes had mainly major extremity amputations (0.6%). After the first amputation on dialysis therapy, almost 50% of patients (24 of 50) with diabetes had a second amputation compared with 20% (5 of 20) of patients without DM. The majority of patients (37/50 diabetic patients with an amputation) used insulin therapy.

Survival after amputation

In total, 911 patients (44%) died during follow-up. Fifty-four of 70 patients with a first amputation during dialysis therapy died (77.1%). Four patients with an amputation and DM received a renal transplant compared with no transplants in patients with an amputation without DM. Other reasons for censoring during follow-up (moving to an other centre, centre stopped participation, other and refusal) were similar in both groups.

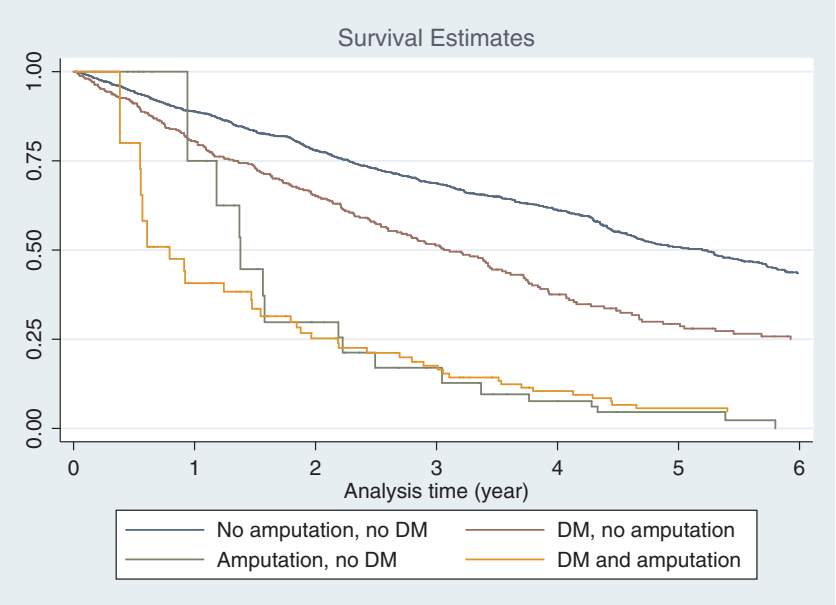

FIGURE 1: Survival without amputation and after amputation in diabetic and non-diabetic patients.

Table 3. Poisson regression: effect of incident amputation and DM on mortality in ESRD

Patient group	*n*	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Adjusted HR (95 % CI)[b]
1. Amputation−, DM−	1618	1.0 (reference)	1.0 (reference)	1.0 (reference)
2. Amputation−, DM+	363	1.7 (1.5–2.0)	1.6 (1.4–1.9)	1.6 (1.4–1.9)
3. Amputation+, DM−	20	5.9 (3.6–9.8)	4.6 (2.8–7.6)	4.6 (2.8–7.5)
4. Amputation+, DM+	50	3.9 (2.8–5.5)	4.6 (3.2–6.4)	5.0 (3.5–7.2)

[a]Model adjusted for age, gender and amputation at baseline.
[b]Model adjusted for age, gender, amputation at baseline, dialysis modality, smoking, blood pressure, body mass index, myocardial infarction or stroke.

Survival after amputation and diabetes status

Mortality was higher in patients with diabetes [HR 1.6 (95% CI 1.4–1.9)] compared with non-diabetic patients adjusted for age, gender, amputation at baseline and dialysis modality. Amputation increased mortality risk more than 4-fold in patients without diabetes [HR 4.6 (95% CI 2.8–7.6)] as well as in patients with diabetes [HR 4.6 (95% CI 3.3–6.4)] (Figure 1). Further adjustment for smoking, blood pressure, body mass index, myocardial infarction or stroke did not change these results substantially (Table 3). No formal interaction between diabetes and amputation was found ($P = 0.12$ from likelihood ratio test), meaning that mortality risk after amputation is high but coexisting DM does not add further to this risk.

In a subanalysis in patients with a major amputation, we found no difference in the mortality risk in diabetic patients compared with non-diabetic patients. The number of patients with a minor amputation without DM was too small to perform a subanalysis in patients with a minor amputation.

DISCUSSION

The results of this study demonstrate that the burden of non-traumatic amputation in dialysis patients remains high, especially in patients with diabetes, with an incidence rate of amputation of 4/100 person-years in diabetic patients compared with 0.4/100 person-years in non-diabetic patients. We also showed that amputation in this medically compromised patient group is associated with a clearly increased mortality risk; this mortality risk was similar for diabetic and non-diabetic patients.

Survival among dialysis patients with DM is inferior to survival of non-diabetic dialysis patients [18–21], probably due to the higher prevalence of diabetes-related comorbid conditions, including foot ulceration and infection, neuropathy, peripheral vascular disease and cardiovascular morbidity. These comorbid conditions may also contribute to a higher incidence of amputation in diabetic dialysis patients. One could hypothesize that these comorbid conditions also contribute to a decreased survival after amputation in dialysis patients with diabetes compared with non-diabetic patients. However, results of this study showed that mortality after amputation in dialysis patients is high and DM does not further increase this mortality risk.

Hoffstad *et al.* [22] showed that mortality risk after lower extremity amputation in a large population with DM but without severe chronic kidney disease was 3-fold increased. They also showed that some of this risk excess can be explained by well-known complications of diabetes. The study and also our results suggest that patients with an amputation have a poor prognosis,

mostly independent of coexisting conditions such as diabetes, hypertension and the presence of cardiovascular disease.

Furthermore, the risk of a recurrent amputation in this study was high, especially in patients with DM. Almost 50% of diabetic patients received a recurrent amputation during follow-up, which is in line with data from studies on diabetic patients without ESRD [23, 24]. The number of patients who received a recurrent amputation, however, was relatively small in this study, and these results provide further confirmation in independent cohorts with long-term follow-up.

There are some potential limitations that should be taken into account when interpreting the data. First, data on glycaemic control were not available. However, data on the duration of DM retinopathy for which laser coagulation therapy was performed and insulin dependency was available, which also reflects the severity of diabetes. As the patients in the NECOSAD cohort are treated to prevailing diabetes guidelines, it is unlikely that glycaemic control is structurally different from control in other dialysis-based cohorts. Similar reasoning applies to cardiovascular risk management. We thus consider our results generalizable to other dialysis-based cohorts.

Second, the severity of peripheral vascular disease and information about limb salvage therapy was not available. Third, by the design of the study, data on amputations were extracted from data on hospitalizations and surgery. Therefore we cannot exclude that some patients with a minor amputation without hospitalization were not included in this study. Another limitation of this study, due to inadequate sample size, is that we could not evaluate the number of patients in each subgroup of level of amputation, especially in the subgroup with minor amputations.

Although it is important to assess survival after amputation, from a patient's perspective it is also relevant to know what quality of life will remain after amputation. Only a few studies explored quality of life and/or functional outcomes after amputation on chronic dialysis therapy and reported a longer length of stay in hospital [25] and lower functional independence measure scores after limb amputation compared with patients without ESRD [26, 27]. Furthermore, quality of life is reduced [28, 29]. This shows that the combination of ESRD and amputation poses a high disease burden on patients.

In order to reduce the number of amputations in dialysis patients, further optimizing and/or implementing foot care according to the international guidelines in the renal clinic is essential [30]. Patients with ESRD are often dialysed in a renal care unit separate from the diabetes care unit, thus regular foot screening and foot care education might be suboptimal. Implementation of monthly foot checks in renal care units was associated with a reduction in major lower limb amputations in diabetic incident HD patients [31].

ACKNOWLEDGEMENTS

The nursing staff of the 38 different dialysis units, who collected most of the data, are gratefully acknowledged for their assistance. Moreover, the authors thank the staff of the NECOSAD trial office for assistance in the logistics of this study. The NECOSAD Study Group consisted of A.J. Apperloo, J.A. Bijlsma, M. Boekhout, W.H. Boer, P.J.M. van der Boog, H.R. Büller, M. van Buren, F.Th. de Charro, C.J. Doorenbos, M.A. van den Dorpel, A. van Es, W.J. Fagel, G.W. Feith, C.W.H. de Fijter, L.A.M. Frenken, J.A.C.A. van Geelen, P.G.G. Gerlag, W. Grave, J.P.M.C. Gorgels, R.M. Huisman, K.J. Jager, K. Jie, W.A.H. Koning-Mulder, M.I. Koolen, T.K. Kremer Hovinga, A.T.J. Lavrijssen, A.J. Luik, J. van der Meulen, K.J. Parlevliet, M.H.M. Raasveld, F.M. van der Sande, M.J.M. Schonck, M.M.J. Schuurmans, C.E.H. Siegert, C.A. Stegeman, P. Stevens, J.G.P. Thijssen, R.M. Valentijn, G. H. Vastenburg, C.A. Verburgh, H.H. Vincent and P.F. Vos.

FUNDING

The study was supported by grants from the Dutch Kidney Foundation and the Dutch National Health Insurance Board. Sponsors had no involvement in the research and/or preparation of the article.

AUTHORS' CONTRIBUTIONS

M.A.S., M.v.D. and O.M.D. were involved in the design of the study, analysis and interpretation of the data, drafting the manuscript and revision of the manuscript based on comments from co-authors. J.F.H. and F.W.D. were involved in the design of the study, interpretation of the data and revision of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

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