Clinical aspects of the relation between diabetes mellitus and kidney disease: From hyperfiltration to dialysis

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CHAPTER 6

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 is inferior to survival of non-diabetic dialysis patients, probably due to higher prevalence of diabetes related co-morbid conditions. One could hypothesize that these co-morbid conditions also contribute to a decreased survival after amputation in diabetic patients compared to non-diabetic patients on dialysis.

Methods

Data were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which new patients with end stage renal disease (ESRD) were monitored until transplantation or death. Amputation rates (incident cases) were calculated in patients with and without diabetes mellitus. The primary endpoint was all cause survival after a first amputation during dialysis therapy in diabetic patients compared to 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 413 diabetic patients had a new amputation (12.1 %), compared to 20 of 1553 non-diabetic patients (1.2 %). Amputation rates/ 1000 person years were 47.9 (95% 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 fourfold, 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). No formal interaction between diabetes and amputation was found (p=0.12).

Conclusions

Amputation in dialysis patients is associated with a with a fourfold increased mortality risk; this mortality risk was similar for diabetes and non-diabetes patients. Importantly, the risk for amputation is tenfold higher in diabetes mellitus compared to non-diabetic dialysis patients.

Introduction

Diabetes mellitus is the most common underlying cause of non-traumatic amputation. The main factors associated with diabetes-related amputation are sensory neuropathy, infection and ischemia[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 an ~10-fold increased amputation risk in diabetic dialysis patients compared to non-diabetic dialysis patients, although risk estimates show a variation among different countries[7, 8].

Studies on survival after amputation in diabetic and non-diabetic patients with and without End Stage Renal Disease (ESRD) thus far showed contrasting results. In some studies diabetes was associated with an excess mortality after amputation[9, 10], while other studies showed similar or reduced mortality in diabetic patients compared to 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, thereafter diabetic patients had a higher mortality compared to non-diabetic patients[16]. These contrasting results might be due to different study populations, different follow-up time and different statistical approaches.

The primary aim of the present study was to compare survival after amputation in diabetic dialysis patients to 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, multicenter 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 January 1, 1997 until January 1, 2007. Study visits took place at the start of dialysis, at 3 months, 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 at 1 January

2007. Data on demographic characteristics and co-morbidities 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, i.e. hemodialysis (HD) or peritoneal dialysis (PD). 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 diabetes mellitus were collected such as insulin-dependency, patient-reported duration of diabetes mellitus and history of diabetic retinopathy for which laser therapy was performed. During each study visit, patients were asked if they had been operated and/or admitted to the hospital. Surgical (operation) procedures and date were documented. Furthermore hospital admissions and reason for admission were registered.

Patient selection

Patients aged ≥18 years who started with dialysis as 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 three 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 while 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 diabetes mellitus. To study the effect of amputation on mortality and the also potential of effect modification by diabetes, we compared mortality rates in four groups: 1. patients without amputation and without diabetes mellitus (DM) (reference), 2. patients without amputation but with diabetes, 3. patients with amputation, without diabetes, 4.patients with both an amputation and diabetes.

Statistical analysis

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

Mortality rates were compared with Poisson regression, and incidence rate ratios were estimated including 95% confidence intervals. 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 (Armonk, NY: IBM Corp). Time dependent analyses were performed in 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 NECOSAD. Twenty five percent of patients had diabetes mellitus at baseline (Table 1). Sixty four percent of diabetic patients were treated with insulin injections therapy. Patients with diabetes were older (mean age 63, ± SD 13 years) compared to non-diabetics (59, ± SD 16). Fourty –six percent of diabetic patients had retinopathy for which laser coagulation was performed. Seventy- one percent of patients with diabetes had diabetes as primary renal disease.

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

Amputation

At baseline, 24 of 413 diabetic patients (5.8%) had an amputation compared to only 9 out of 1553 non-diabetic patients (0.5%) (Table 2). During follow up (mean duration 2.9, ± SD 2.3 years), 50 diabetic patients had a new amputation (12.1%), compared to 20 non-diabetic patients (1.2%). Amputation rates/ 1000 person years were respectively 47.9 (95% CI 36.3- 63.2) and 4.1 (95% CI 2.7-6.4) for diabetic patients and non-diabetic patients. The level of amputation was different in both groups; patients with diabetes had mainly minor amputations (5.1%), while patients without diabetes had mainly major extremity amputations amputations (0.6%). After a first amputation on dialysis therapy almost fifty percent of patients (24 out of 50) with diabetes had a second amputation compared to 20 % percent (5 out of 20) of patients without DM. The majority of patients (37/50 diabetic patients with an amputation) used insulin therapy.

Table 1. Baseline characteristics, patients with diabetes compared to patients without diabetes.

	Patients with diabetes (N=413)	**Patients without diabetes (N=1638)**
Age at start dialysis	63 (13)	59 (16)
Male gender (%)	55	64
Primary renal disease		
Diabetes Mellitus	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)	16 (11)	0
Retinopathy (% lasercoagulation)	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		
Systolic	153 (24)	148 (24)
Diastolic	79 (12)	84 (13)
Body Mass Index (kg/m2)	27 (5)	25 (4)
Laboratory values		
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 per 1.73 m2)	5.6 (3.5)	5.2 (3.6)

Continuous predictors are presented as means (SD); categorical variables are presented as %.

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HD, hemodialysis; rGFR, residual glomerular filtration rate.

Table 2. Data on amputations.

	Patients with diabetes (N=413)	Patients without diabetes (N=1638)
First amputation		
Baseline	24 (5.8 %)	9 (0.6 %)
During follow up	50 (12.1 %)	20 (1.2 %)
Level of amputation (during follow up)		
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, min-max)	511 (380)	671 (409)
Second amputation	24	5
Days to second ampuation (from first amputation) (mean, min-max)	88 (91)	139 (148)

Survival after amputation

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

Survival after amputation and diabetes status

Mortality was higher in patients with diabetes (HR 1.6 , 95 % CI 1.4-1.9) compared to non-diabetic patients adjusted for age, gender, amputation at baseline and dialysis modality. Amputation increased mortality risk more than fourfold, in patients without diabetes (HR 4.6, 95 % CI 2.8-7.6) as well as in patients with diabetes the (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 diabetes mellitus does not add further to this risk.

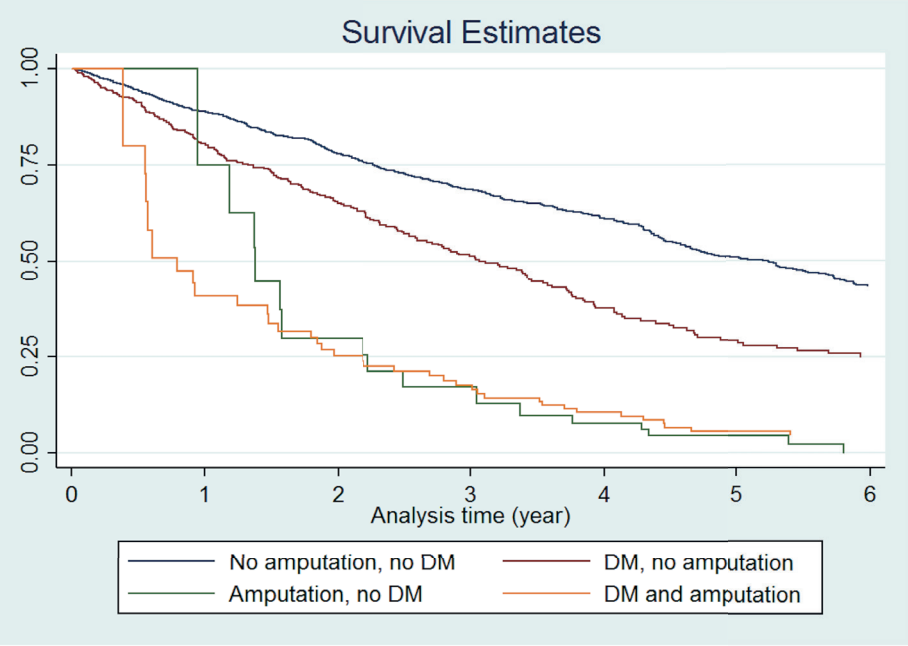

Figure 1. Survival without amputation and after amputation in diabetic and non-diabetic patients.

Table 3. Poisson regression: effect of incident amputation and diabetes mellitus 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, amputation at baseline
b. Model adjusted for age, gender, amputation at baseline, dialysis modality, smoking, blood pressure, body mass index, myocardial infarction or stroke

In a subanalysis in patients with a major amputation we found no difference in mortality risk in diabetic patients compared with non-diabetic patients. The number of patients with a minor amputation without diabetes mellitus 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 diabetes mellitus is inferior to survival of non-diabetic dialysis patients[18-21], probably due to higher prevalence of diabetes related co-morbid conditions such as foot ulceration and infection, neuropathy, peripheral vascular disease and cardiovascular morbidity. These co-morbid conditions may also contribute to a higher incidence of amputation in diabetic dialysis patients. One could hypothesize that these co-morbid conditions also contribute to a decreased survival after amputation in dialysis patients with diabetes compared to non-diabetic patients. However results of this study showed that mortality after amputation in dialysis patients is high and diabetes mellitus does not further increase this mortality risk.

Hoffstad et al showed that mortality risk after lower extremity amputation in a large population with diabetes mellitus but without severe chronic kidney disease was threefold increased. They also showed that some of this risk excess can be explained by well-known complications of diabetes[22]. The study and also our results suggest that patients with an amputation have a poor prognosis, mostly independent of co-existing conditions such as diabetes, hypertension and presence of cardiovascular disease.

Furthermore the risk of a recurrent amputation in this study was high, especially in patients with diabetes mellitus. 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 the present study and these results 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 duration of diabetes mellitus, retinopathy for which laser coagulation therapy was performed and insulin dependency was available, which also reflects 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, 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 to 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 guideline in the renal clinic is essential[30]. Patients with ESRD are often dialyzed in a renal care unit separate from the diabetes care unit, in which regular foot screening and foot care education might be suboptimal. Implementation of monthly foot checks in renal care units was associated with reduction of major lower limb amputations in diabetic incident hemodialysis patients[31].

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Reference list

1. Pecoraro, R.E., G.E. Reiber, and E.M. Burgess, Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care, 1990. 13(5): p. 513-21.
2. Caputo, G.M., P.R. Cavanagh, J.S. Ulbrecht, G.W. Gibbons, and A.W. Karchmer, Assessment and management of foot disease in patients with diabetes. N Engl J Med, 1994. 331(13): p. 854-60.
3. Lipsky, B.A., A.R. Berendt, P.B. Cornia, J.C. Pile, E.J. Peters, D.G. Armstrong, et al., 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis, 2012. 54(12): p. e132-73.
4. Lavery, L.A., D.G. Armstrong, R.P. Wunderlich, J. Tredwell, and A.J. Boulton, Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care, 2003. 26(5): p. 1435-8.
5. Armstrong, D.G., A.J.M. Boulton, and S.A. Bus, Diabetic Foot Ulcers and Their Recurrence. N Engl J Med, 2017. 376(24): p. 2367-2375.
6. Lavery, L.A., N.A. Hunt, A. Ndip, D.C. Lavery, W. Van Houtum, and A.J. Boulton, Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care, 2010. 33(11): p. 2365-9.
7. Eggers, P.W., D. Gohdes, and J. Pugh, Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. Kidney Int, 1999. 56(4): p. 1524-33.
8. Combe, C., J.M. Albert, J.L. Bragg-Gresham, V.E. Andreucci, A. Disney, S. Fukuhara, et al., The burden of amputation among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis, 2009. 54(4): p. 680-92.
9. Heikkinen, M., J. Saarinen, V.P. Suominen, J. Virkkunen, and J. Salenius, Lower limb amputations: differences between the genders and long-term survival. Prosthet Orthot Int, 2007. 31(3): p. 277-86.
10. Kulkarni, J., S. Pande, and J. Morris, Survival rates in dysvascular lower limb amputees. Int J Surg, 2006. 4(4): p. 217-21.
11. Aulivola, B., C.N. Hile, A.D. Hamdan, M.G. Sheahan, J.R. Veraldi, J.J. Skillman, et al., Major lower extremity amputation: outcome of a modern series. Arch Surg, 2004. 139(4): p. 395-9; discussion 399.
12. Subramaniam, B., F. Pomposelli, D. Talmor, and K.W. Park, Perioperative and long-term morbidity and mortality after above-knee and below-knee amputations in diabetics and nondiabetics. Anesth Analg, 2005. 100(5): p. 1241-7, table of contents.
13. Wrobel, J.S., J.A. Mayfield, and G.E. Reiber, Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. Diabetes Care, 2001. 24(5): p. 860-4.
14. Pohjolainen, T. and H. Alaranta, Ten-year survival of Finnish lower limb amputees. Prosthet Orthot Int, 1998. 22(1): p. 10-16.
15. Dillingham, T.R., L.E. Pezzin, and A.D. Shore, Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. Arch Phys Med Rehabil, 2005. 86(3): p. 480-6.

16. Icks, A., M. Scheer, S. Morbach, J. Genz, B. Haastert, G. Giani, et al., Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: survival in a population-based 5-year cohort in Germany. Diabetes Care, 2011. 34(6): p. 1350-4.
17. Stel, V.S., P.C. van Dijk, J.G. van Manen, F.W. Dekker, D. Ansell, F. Conte, et al., Prevalence of co-morbidity in different European RRT populations and its effect on access to renal transplantation. Nephrol Dial Transplant, 2005. 20(12): p. 2803-11.
18. Liem, Y.S., J.B. Wong, M.G. Hunink, F.T. de Charro, and W.C. Winkelmayer, Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. Kidney Int, 2007. 71(2): p. 153-8.
19. Vonesh, E.F., J.J. Snyder, R.N. Foley, and A.J. Collins, The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. Kidney Int, 2004. 66(6): p. 2389-401.
20. Van Dijk, P.C., K.J. Jager, B. Stengel, C. Gronhagen-Riska, T.G. Feest, and J.D. Briggs, Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). Kidney Int, 2005. 67(4): p. 1489-99.
21. Schroijen, M.A., M.W. van de Luijtgaarden, M. Noordzij, P. Ravani, F. Jarraya, F. Collart, et al., Survival in dialysis patients is different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. Diabetologia, 2013. 56(9): p. 1949-57.
22. Hoffstad, O., N. Mitra, J. Walsh, and D.J. Margolis, Diabetes, lower-extremity amputation, and death. Diabetes Care, 2015. 38(10): p. 1852-7.
23. Borkosky, S.L. and T.S. Roukis, Incidence of re-amputation following partial first ray amputation associated with diabetes mellitus and peripheral sensory neuropathy: a systematic review. Diabet Foot Ankle, 2012. 3.
24. Kanade, R., R. van Deursen, J. Burton, V. Davies, K. Harding, and P. Price, Re-amputation occurrence in the diabetic population in South Wales, UK. Int Wound J, 2007. 4(4): p. 344-52.
25. Butler, C.R., M.L. Schwarze, R. Katz, S.M. Hailpern, W. Kreuter, Y.N. Hall, et al., Lower Extremity Amputation and Health Care Utilization in the Last Year of Life among Medicare Beneficiaries with ESRD. J Am Soc Nephrol, 2019.
26. Arneja, A.S., J. Tamiji, B.M. Hiebert, P.S. Tappia, and L. Galimova, Functional outcomes of patients with amputation receiving chronic dialysis for end-stage renal disease. Am J Phys Med Rehabil, 2015. 94(4): p. 257-68.
27. Wukich, D.K., J. Ahn, K.M. Raspovic, F.A. Gottschalk, J. La Fontaine, and L.A. Lavery, Comparison of Transtibial Amputations in Diabetic Patients With and Without End-Stage Renal Disease. Foot Ankle Int, 2017. 38(4): p. 388-396.
28. Osthus, T.B., N. von der Lippe, L. Ribu, T. Rustoen, T. Leivestad, T. Dammen, et al., Health-related quality of life and all-cause mortality in patients with diabetes on dialysis. BMC Nephrol, 2012. 13: p. 78.
29. Raspovic, K.M., J. Ahn, J. La Fontaine, L.A. Lavery, and D.K. Wukich, End-Stage Renal Disease Negatively Affects Physical Quality of Life in Patients With Diabetic Foot Complications. Int J Low Extrem Wounds, 2017. 16(2): p. 135-142.
30. Schaper, N.C., J.J. Van Netten, J. Apelqvist, B.A. Lipsky, K. Bakker, and F. International Working Group on the Diabetic, Prevention and management of foot problems in diabetes: A Summary Guidance for Daily Practice 2015, based on the IWGDF guidance documents. Diabetes Res Clin Pract, 2017. 124: p. 84-92.

31. Marn Pernat, A., V. Persic, L. Usvyat, L. Saunders, J. Rogus, F.W. Maddux, et al., Implementation of routine foot check in patients with diabetes on hemodialysis: associations with outcomes. BMJ Open Diabetes Res Care, 2016. 4(1): p. e000158.