The Association of Chronic Kidney Disease and Dialysis Treatment with Foot Ulceration and Major Amputation

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This study was presented at the Diabetic Foot Study Group meeting, Sitges, September 2013, and at the Dutch Organisation of Diabetes Research (NVDO), November 2013.

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Abstract

Objective: To investigate the risk of chronic kidney disease (CKD) stage 4-5 and dialysis treatment on incidence of foot ulceration and major lower extremity amputation, in comparison to CKD stage 3.

Methods: In this retrospective study, all individuals who visited our hospital between 2006 and 2012 because of CKD 3 to 5 or dialysis treatment were included. Medical records were reviewed for incidence of foot ulceration and major amputation. The time from CKD 3, CKD 4-5 and dialysis treatment until incidence of first foot ulceration and first lower extremity amputation was calculated and analyzed by Kaplan Meier curves and multivariate Cox proportional hazards model. Diabetes mellitus, peripheral arterial disease, peripheral neuropathy and foot deformities were included for potential confounding.

Results: A total of 669 individuals were included: 539 in CKD 3, 540 in CKD 4-5, and 259 in dialysis treatment (individuals could progress from one group to the next). Unadjusted foot ulcer incidence rates / 1000 patients / year were 12 (CKD 3), 47 (CKD 4-5) and 104 (dialysis); $p<.001$. In multivariate analyses, the hazard ratio for incidence of foot ulceration in CKD 4-5 was 4.0 (95%CI 2.6-6.3), and in dialysis treatment 7.6 (95%CI 4.8-12.1) when compared to CKD 3. Hazard ratios for incidence of major amputation were 9.5 (95%CI 2.1-43.0) and 15 (95%CI 3.3-71.0) respectively.

Conclusions: CKD 4-5 and dialysis treatment are independent risk factors for incidence of foot ulceration and major amputation when compared to CKD 3. Maximum effort is needed in daily clinical practice to prevent foot ulcers and their devastating consequences in all individuals with CKD 4-5 or dialysis treatment.

Introduction

Individuals with chronic kidney disease (CKD) are at high risk of foot ulceration and major lower extremity amputation [1-3]. The highest risk has been found for individuals on dialysis treatment with diabetes mellitus [1-4]. However, this has only been investigated in patients with diabetes mellitus and end-stage renal disease (i.e. CKD stage 4 and 5). It is not clear if this high risk is also present in patients without diabetes mellitus, and if individuals with CKD 4-5 without dialysis treatment are at higher risk for foot ulceration and major amputation compared to individuals in earlier stages of CKD.

Most research concerning incidence of foot ulceration focuses on patients with diabetes, as diabetic foot ulceration is one of the major complications of diabetes [1-3,5]. However, patients with CKD without diabetes have comparable prevalence rates of risk factors compared to patients with diabetes without CKD [1-3]. As less than half of the patients with CKD have diabetes [2,3], the risk of CKD 4-5 and dialysis treatment for foot ulceration and major amputation warrants further investigation in a population reflective of daily clinical practice, i.e. inclusive of patients with and without diabetes.

Given the association between renal function and foot ulceration in patients with diabetes, and the increase in foot ulcers that is already seen in the period before dialysis treatment [8], it can be hypothesized that CKD 4-5 without dialysis treatment is also an independent risk factor for foot ulceration and major amputation. If such an increased risk is found, preventive measures should be part of daily clinical practice for all individuals progressing from CKD 3 to CKD 4-5.

The aim of this study is study to investigate the risk of both CKD 4-5 and dialysis treatment for incidence of FU and LEA, in comparison to CKD 3, and with respect to other relevant risk factors.

Materials and methods

This retrospective study was conducted in the department of nephrology, Ziekenhuisgroep Twente (Hospital Group Twente), the Netherlands. The research deemed exempt from review of an ethics committee and patient consent due to the retrospective character and the use of existing medical files only. The research activities of this study were consistent with the principles of the Declaration of Helsinki.

The eGFR was used to determine the stage of CKD corresponding to the KDOQI staging scheme [9]. The eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation [10]. CKD 3 was defined as an eGFR between 59 and 30 without dialysis treatment for more than three months; CKD 4-5 was defined as an eGFR below 30 without dialysis treatment for more than three months; dialysis treatment was defined as either peritoneal dialysis or hemodialysis treatment.

All individuals who visited our hospital between September 2006 and September 2012 with CKD 3 to 5 or undergoing dialysis treatment were enrolled from the hospital broad electronic medical records system. Individuals were followed from their first visit until: termination of dialysis treatment, they moved to another hospital, the end of the study period (September 2012), or when death occurred. Individuals could progress from either CKD 3 to CKD 4-5, or from CKD 4-5 to dialysis treatment. Individuals progressing to the next group were censored from the analyses in their previous group at that moment. When a non-healed ulcer was present at the moment of progressing to the next group, they were excluded from the analysis in this new group. For example: When incidence of the ulcer occurred during CKD 4-5 and this ulcer did not heal before dialysis treatment started, then the individual was excluded from analysis in the dialysis treatment group.

Foot ulceration was defined as all non-traumatic interruptions of the epithelium, or traumatic interruptions with impaired wound healing, occurring below the malleoli. All foot ulcers were treated in a multidisciplinary team in line with the international guidelines [11]. Major amputation was defined as all amputations proximal to the ankle joint. Amputations that were the result of trauma, oncology, complex regional pain syndrome or congenital causes were excluded, leaving amputations resulting from ulceration, infection and/or ischemia.

Peripheral Arterial Disease (PAD) was defined as intermittent claudication, critical limb ischemia, surgical revascularization or amputation because of PAD; the Rutherford classification was not available. Peripheral neuropathy was defined as 'loss of protective sensation', when a failed monofilament or tuning fork test was present [11]. Foot deformity was defined as either hallux valgus deformity, hammer toe, claw toe, pes cavus, pes planus, prominent metatarsal heads, or dislocated metatarsophalangeal joints. Myocardial ischemia was defined as either a diagnosis of myocardial infarction or instable angina. Cerebrovascular accident (CVA) was defined as either a diagnosis of CVA or transient ischemic attack. Smoking status was defined based on presence of medical records with a status of smoking. Current smoking status and former smoking status were combined as a positive smoking history. If the smoking status was negative or not present, a negative smoking history was noted. Total cholesterol was obtained from laboratory results at the start of CKD 3, CKD 4-5 and dialysis treatment.

Characteristics from the three groups (CKD 3, CKD 4-5, dialysis treatment) were compared using ANOVA for continuous variables and Pearson's X^2 or Fisher's exact test for categorical variables. Unadjusted incidence foot ulcer incidence rates were calculated for number of events per 1000 patients / year. Time analyses were made for incidence of foot ulceration and major amputation in the three groups using Kaplan Meier curves and multivariate Cox regression models. For univariate analysis, the following confounders were used: Diabetes

mellitus, PAD, peripheral neuropathy, history of foot ulceration (i.e. before the first known date in that specific group), history of amputation (i.e. before the first known date in that specific group), foot deformity, history of myocardial infarction, hypertension, history of CVA, smoking, total cholesterol, age and sex. Confounders with univariate P-values <.15 were selected for inclusion in the multivariate analysis. The multivariate model was stepwise formed into a parsimonious Cox proportional hazards model. A P-value <.05 was considered statistically significant. All analyses were performed using SPSS (version 20.0; SPSS, Chicago, IL).

Results

Inclusion and sample size

A total of 2010 individuals visited our hospital during the study period with CKD 3 to 5. Due to the large number of individuals with CKD 3 (n=1889), we obtained a random selection with SPSS, blinded for outcomes. After randomization, 539 individuals remained in the group of CKD 3.

We included 669 individuals in our study: 539 individuals in the group of CKD 3, 540 in the group of CKD 4-5 (of which 411 individuals who progressed from CKD 3), and 259 in the group of dialysis treatment (of which 159 who progressed from CKD 3 and 99 who progressed from CKD 4-5).

Characteristics of analysed groups

No clinically relevant differences were found between the groups (Table I). Of all individuals undergoing dialysis, 83.3 percent underwent hemodialysis, and 28.7 percent underwent peritoneal dialysis (data not in Table).

Foot ulceration

Two individuals in CKD 4-5 and eight individuals in dialysis treatment were excluded because of presence of a non-healed foot ulcer at the start of these groups. A statistically significant rise in unadjusted foot ulcer incidence rates was seen from CKD 3 to dialysis treatment, for all ulcers, and for ischemic, infected and deep ulcers as well (Table II). Higher unadjusted foot ulcer incidence rates were found within the three groups for individuals with diabetes, PAD, peripheral neuropathy, and foot deformity (Table II). Figure 1 represents the Kaplan Meier curve for incidence of foot ulceration. Log rank test showed significant differences between CKD 3, CKD 4-5 and dialysis treatment with a P-value <.001.

Table III represents the univariate and multivariate analysis for incidence of foot ulceration. Nine confounders met the criteria of a P-value <.15 in univariate analysis and were included in multivariate analysis. After fitting into a parsimonious model, diabetes mellitus, PAD, peripheral neuropathy and history of foot ulceration remained in the multivariate analysis. After multivariate analysis, a significant greater risk for foot ulceration was found for both CKD 4-5 and dialysis treatment when compared to CKD 3 (Hazard Ratio (HR) 4.0 (95% Confidence Interval (CI) 2.6-6.3) and 7.6 (95%CI 4.8-12.1) respectively). When dialysis treatment was directly compared to CKD 4-5, a significant greater risk was found (HR: 1.9 (95%CI 1.3-2.7)).

Major lower extremity amputation

Figure 2 represents the Kaplan Meier curve for major amputation. Log rank test showed significant differences between CKD 3, CKD 4-5 and dialysis treatment with a P-value <.001.

Table IV represents the univariate and multivariate analysis for major amputation. Nine confounders met the criteria of a P-value <.15 in univariate analysis and were included in multivariate analyses. A history of major amputation was excluded because the univariate

analysis could not be interpreted with a HR of 0.49 and a 95% CI from zero till endless. After fitting into a parsimonious model, PAD, peripheral neuropathy, history of foot ulceration and hypertension were left in the multivariate analysis. After multivariate analysis, a significant greater risk for major amputation was found for both CKD 4-5 and dialysis treatment when compared to CKD 3 (HR 9.5 (95%CI 2.1-43.0) and 15 (95%CI 3.3-71.0) respectively). When dialysis treatment was directly compared to CKD 4-5, no significant different risk was found (HR 1.6 (95%CI 0.7-3.7)).

Discussion

In this retrospective study, fourfold and almost eightfold increases in risks were found for incidence of foot ulceration in individuals with CKD 4-5 or dialysis treatment respectively, when compared to individuals with CKD 3. Similar high risks were found for major amputation. In multivariate analyses, this increased risk was found to be irrespective of known risk factors, most notably diabetes mellitus.

These findings are in line with previous studies showing a continuum risk for foot problems in individuals with chronic kidney disease, with the greatest risk for those on dialysis treatment [4,6-8]. In addition to these studies, we have shown that this risk is found in a population representative of daily clinical practice, including individuals with as well as without diabetes mellitus. Whereas the importance of preventive foot care is widely acknowledged for individuals with diabetes without CKD, this has so far received little attention for individuals with CKD without diabetes. Given the fourfold increase for foot ulceration in risk found for CKD 4-5 without dialysis treatment, preventive foot care should be made available for all individuals with CKD 4-5, not only for those with diabetes. In many countries, patients with CKD but without diabetes are not entitled to preventive foot care such

as podiatry. We believe this contributes to the development of preventable foot ulcers and amputation.

Patients with end-stage renal disease and foot ulcers have high rates of failure of foot salvage, resulting in high rates of amputation and mortality [12-15]. Early recognition of foot ulcers in these individuals is important to prevent these devastating consequences. Some promising results have been shown in studies investigating the effect of preventive programs in individuals on dialysis treatment [16-18]. However, these preventive programs should not only target individuals on dialysis treatment, but also those with CKD 4-5. The increased risk and high incidence rates found in our study indicate that maximum effort to prevent foot ulcers should be given to all individuals with CKD 4-5.

The retrospective design of our study is a limitation. All variables were obtained from medical files, of which completeness can not be guaranteed. Additionally, variables such as the Rutherford classification, use of aspirin and statines, and information on smoking cessation were not available for all patients. By reading all files, operation reports and letters to the general practitioners, maximum effort possible has been given to obtain all available information. Known confounders were controlled for in multivariate analyses, such as diabetes mellitus, peripheral arterial disease and a history of foot ulceration, but it can not be ruled out that other confounders may have played a role. The low incidence of major amputation in CKD 3, CKD 4-5 and dialysis treatment led to relatively broad 95% confidence intervals in our study, which limits firm statistical conclusions. Because of the small proportion of ethnic groups in our population, we did not have to correct for influences of ethnic groups in our analyses.

In conclusion, in this retrospective study we showed that CKD 4-5 and dialysis treatment are independent risk factors for incidence of foot ulceration and lower extremity amputation when

compared to CKD 3. Maximum effort is needed in daily clinical practice to prevent foot ulcers and their devastating consequences in all individuals with CKD 4-5 or dialysis treatment, with or without diabetes.

Disclosures

None.

Acknowledgements

The authors address special thanks to clinical epidemiologists Prof. J. van der Palen, PhD, and M. Brusse, PhD, (both from Medisch Spectrum Twente, Enschede, the Netherlands) for their assistance with the statistical analyses.

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Table I: Characteristics of individuals with CKD 3, CKD 4-5 or dialysis treatment

Characteristic	CKD 3	CKD 4-5	Dialysis treatment	P-value
N	539	540	259	
Male sex	58.1	56.3	60.6	.51
Mean age ± SD (years)	64.4 ± 11.7	64.8 ± 13.3	64.2 ± 13.9	.75
Diabetes mellitus	38.8	37.6	38.6	.92
Peripheral arterial disease	25.5	22.2	26.6	.32
Peripheral neuropathy	24.5	25.7	29.7	.28
History of foot ulceration	5.0	9.3	15.8	<.001 [a,b,c]
History of lower extremity amputation	0.4	0.7	2.3	.02 [b]
Foot deformity	13.4	12.4	13.9	.82
History of myocardial ischemia	34.7	31.9	28.2	.18
Hypertension	68.8	66.7	66.0	.65
History of CVA	26.0	25.9	25.5	.99
Smoking	41.2	41.3	38.2	.67
Mean total cholesterol ± SD (mmol / L)	5.2 ± 1.3	4.9 ± 1.4	4.1 ± 1.2	<.001 [a,b,c]

Note: Numbers are % or as indicated; [a] = CKD 3 vs CKD 4-5 significantly different with P-value < .05; [b] = CKD 3 vs. dialysis treatment significantly different with P-value < .05; [c] = CKD 4-5 vs. dialysis treatment significantly different with P-value < .05.

Table 2: Unadjusted foot ulcer incidence rates / 1000 patients / year

	CKD 3	CKD 4-5	Dialysis treatment	*P-value* [a]
All ulcers	12 (7-16)	47 (37-57)	104 (77-131)	*<.001*
Ischemic ulcers	3 (1-5)	15 (9-21)	46 (28-64)	*<.001*
Infected ulcers	6 (3-10)	15 (9-21)	27 (14-41)	*.007*
Deep ulcers (tendon/bone)	4 (1-6)	15 (9-21)	35 (19-50)	*.007*
Diabetes	23 (13-33)	91 (65-117)	219 (146-291)	*<.001*
No diabetes	5 (2-9)	25 (16-35)	57 (33-81)	*.007*
P-value [b]	*<.001*	*<.001*	*<.001*	
PAD	29 (15-43)	98 (62-134)	182 (109-255)	*.02*
No Pad	6 (3-10)	35 (24-45)	80 (52-107)	*<.001*
P-value [b]	*<.001*	*<.001*	*.002*	
Peripheral neuropathy	26 (12-41)	94 (61-128)	171 (109-233)	*.02*
No peripheral neuropathy	8 (4-12)	34 (24-45)	74 (47-102)	*.002*
P-value [b]	*.002*	*<.001*	*.002*	
Foot deformity	36 (14-58)	90 (43-137)	220 (90-350)	*.03*
No foot deformity	9 (5-13)	42 (31-52)	93 (66-120)	*<.001*
P-value [b]	*.001*	*.02*	*.02*	

Note: Values are: unadjusted foot ulcer incidence rate / 1000 patients / year (95% confidence interval); [a]: P-value of the difference between the three groups (CKD 3 – CKD 4-5 – Dialysis treatment); [b]: P-value of the difference between individuals with or without the risk factor within the group.

Table III: Hazard ratios for incidence foot ulceration in all individuals

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
CKD group (CKD 3 ref)				
CKD 4-5	3.8 (2.4 – 5.9)	<0.001	4.0 (2.6 – 6.3)	<.001
Dialysis treatment	8.0 (5.1 – 13)	<0.001	7.6 (4.8 – 12.1)	<.001
Diabetes mellitus	3.3 (2.4 – 4.6)	<0.001	2.8 (1.9 – 3.9)	<.001
Peripheral arterial disease	2.7 (1.9 – 3.6)	<0.001	2.2 (1.6 – 3.1)	<.001
Peripheral neuropathy	2.9 (2.1 – 3.9)	<0.001	1.6 (1.2 – 2.3)	.005
History of foot ulceration	4.3 (2.9 – 6.5)	<0.001	2.3 (1.5 – 3.5)	<.001
History of lower extremity amputation	5.2 (2.5 – 11.0)	<0.001		
Foot deformity	2.2 (1.5 – 3.2)	<0.001		
History of myocardial ischemia	1.5 (1.1 – 2.0)	0.02		
Hypertension	0.8 (0.6 – 1.2)	0.29		
History of CVA	0.8 (0.5 – 1.1)	0.19		
Smoking	0.9 (0.7 – 1.3)	0.67		
Total cholesterol	0.7 (0.6 – 0.8)	<0.001		
Age	1.0 (1.0 – 1.0)	0.13		
Sex (men as reference)	1.0 (0.8 – 1.4)	0.85		

Note: Variables with P-value <.15 in univariate analysis were included in the multivariate analysis. Multivariate analysis was step wised formed into a parsimonious model. HR = Hazard Ratio; CI = Confidence Interval.

Table IV: Hazard ratios for incidence lower extremity amputation in all individuals

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
CKD group (CKD 3 ref)				
CKD 4-5	10.0 (2.2 – 45.0)	0.003	9.5 (2.1 – 43.0)	.004
Dialysis treatment	22.0 (4.8 – 100.0)	<0.001	15.0 (5.3 – 71.0)	.001
Diabetes mellitus	2.3 (1.1 – 5.2)	<0.001		
Peripheral arterial disease	5.0 (2.3 – 11.0)	<0.001	3.8 (1.7 – 8.6)	.002
Peripheral neuropathy	6.1 (2.7 – 14.0)	<0.001	3.2 (1.3 – 7.4)	.008
History of foot ulceration	13.0 (5.9 – 28.0)	<0.001	6.8 (2.9 – 16.0)	<.001
Foot deformity	1.3 (0.4 – 3.7)	0.65		
History of myocardial ischemia	1.8 (0.8 – 3.9)	0.13		
Hypertension	0.4 (0.2 – 1.0)	0.04	0.3 (0.1 – 0.7)	.005
History of CVA	0.8 (0.3 – 2.0)	0.60		
Smoking	1.8 (0.8 – 3.8)	0.16		
Total cholesterol	0.6 (0.4 – 0.9)	0.02		
Age	1.0 (1.0 – 1.1)	0.19		
Sex (men as reference)	0.4 (0.2 – 1.0)	0.05		

Note: Variables with P-value <.15 in univariate analysis were included in the multivariate analysis. Multivariate analysis was step wised formed into a parsimonious model. HR = Hazard Ratio; CI = Confidence Interval.