Diabetes Is the Strongest Risk Factor for Lower-Extremity Amputation in New Hemodialysis Patients

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OBJECTIVE — End-stage renal disease (ESRD) patients, especially those with diabetes, have an increased risk of nontraumatic lower-extremity amputation (LEA). The present study aims to examine the association of demographic and clinical variables with the risk of hospitalization for LEA among incident hemodialysis patients.

RESEARCH DESIGN AND METHODS — The study population consisted of incident hemodialysis patients from the study years 1996–1999 of the ESRD Core Indicator/Clinical Performance Measures (CPM) Project. Cox proportional hazard modeling was used to identify factors associated with LEA.

RESULTS — Four percent (116 of 3,272) of noncensored incident patients had an LEA during the 12-month follow-up period. Factors associated with LEA included diabetes as the cause of ESRD or preexisting comorbidity (hazard ratio 6.4, 95% CI 3.4–12.0), cardiovascular comorbidity (1.8, 1.2–2.8), hemodialysis inadequacy (urea reduction ratio [URR] <58.5% (1.9, 1.1–3.3), and lower serum albumin level (1.6, 1.1–2.3). Among patients with diabetes, hemodialysis inadequacy and cardiovascular comorbidity were risk factors for LEA (2.6, 1.4–4.8, and 1.7, 1.1–2.6, respectively).

CONCLUSIONS — These data suggest that diabetes is a potent risk factor for LEA in new hemodialysis patients. In ESRD patients with diabetes, a multipronged approach may reduce the rate of LEA. Potentially beneficial strategies include adherence to hemodialysis adequacy guidelines, aggressive treatment of cardiovascular comorbidities, and the utilization of LEA prevention strategies recommended for the general population of patients with diabetes.

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The incidence of lower-extremity amputation (LEA) is higher among end-stage renal disease (ESRD) patients than in the general U.S. population (1). In addition to the increased morbidity and diminished quality of life associated with an LEA, there is an increased risk of 1- and 2-year mortality following amputation (1). The identification of risk factors associated with LEA in incident ESRD patients can aid in the design of preventive efforts.

Patients with diabetes have a greatly elevated risk of developing ESRD (2), and the rate of LEA in U.S. ESRD patients with diabetes is ~10 times the rate of LEA in the general U.S. population of patients with diabetes (1). Therefore, the occurrence and prevention of LEA should be an important concern for the health care providers of ESRD patients with diabetes.

There is considerable evidence that diabetes is a risk factor for LEA in hemodialysis patients. For example, Eggers et al. (1) reported that the risk of LEA among all prevalent ESRD patients in the U.S. between 1991 and 1994 was associated with a primary diagnosis of diabetes or hypertension, increasing age, male sex, black race, and Native American race. In a nationwide sample of prevalent ESRD patients in 1993, O'Hare et al. (3) reported that risk factors for LEA in hemodialysis patients varied by the presence of diabetes. Among patients with diabetes, risk of LEA was associated with cardiac disease, previous hospitalization for lower-extremity ischemia, an increased time spent on dialysis, and male sex.

Both of the reports by Eggers et al. (1) and O'Hare et al. (3) included prevalent patients treated during the early to mid-1990s. The purpose of this report is to extend the descriptors of risk factors for LEA to a population of incident hemodialysis patients with and without diabetes from a more recent treatment era (i.e., 1995–1999) and to determine whether any of these risk factors may potentially be modifiable.

RESEARCH DESIGN AND METHODS

— Information for this study was obtained from the Centers for Medicare & Medicaid Services' (CMS's) ESRD Clinical Performance Measures (CPM) Project (known before 1999 as the ESRD Core Indicators Project) and from selected U.S. Renal Data System (USRDS) Standard Analytical Files (SAFs) for the years 1996–1999. Since 1994, the CMS ESRD Hemodialysis CPM Project has an-

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Abbreviations: BCG, bromcresol green; BCP, bromcresol purple; CMS, Centers for Medicare & Medicaid Services; CPM, Clinical Performance Measures; ESRD, end-stage renal disease; LEA, lower-extremity amputation; SAF, Standard Analytical File; URR, urea reduction ratio; USRDS, U.S. Renal Data System.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

nually collected data on a nationally representative random sample of ESRD patients stratified by ESRD Network (regional organizations contracted by CMS to perform quality oversight activities to assure the appropriateness of services and protection for dialysis patients). The ESRD Networks annually submit a listing of adult in-center hemodialysis patients who were alive and dialyzing on December 31 of the previous year. The national random sample is drawn from this universe of patients.

Patients were eligible for inclusion in this study if they were alive on 31 December of the year before the study year (i.e., 31 December 1995 for study year 1996) and were at least 18 years of age. If a patient was selected for more than one ESRD CPM study year, data from only the first year's appearance in the project were utilized for this study.

The ESRD CPM Project collects demographic data and clinical information on selected process measures and intermediate outcomes associated with quality of dialytic care. Data collection forms are sent to ESRD facilities with one or more patients selected for the sample. Facility staff verifies patient characteristic information on the forms (sex, race, Hispanic ethnicity, date of birth, primary cause of ESRD, date of first dialysis, and previous amputations) and abstract clinical information from patient medical records.

Clinical information is collected for the following areas for the months of October through December of the year before the study year: dialysis adequacy, anemia management, vascular access (collected only for study year 1999 and not analyzed for this report), and serum albumin. Information collected includes patient height, pre- and postdialysis weight, pre- and postdialysis blood urea nitrogen, hematocrit, serum albumin, and the laboratory method used to obtain the serum albumin value (bromcresol green [BCG] or bromcresol purple [BCP]). All patient characteristics and clinical or laboratory information used in the analyses for this study were obtained from the ESRD CPM data.

Preexisting comorbidity information was obtained from the USRDS's MEDEVID SAF (SAF.MEDEVID), which includes information from CMS's Form 2728. Comorbidities were grouped into two classifications for subsequent analyses: cardiovascular comorbidities (cardiac arrest, congestive heart failure, cerebrovascular disease, cardiac dysrhythmia, pericarditis, peripheral vascular disease, ischemic heart disease, and myocardial infarction) and noncardiovascular comorbidities (alcohol dependence, cancer, drug dependence, HIV, AIDS, inability to ambulate, inability to transfer, chronic obstructive pulmonary disease, and tobacco use). Hypertension as a comorbidity was examined separately and was not included in the cardiovascular group of comorbidities. We did not include diabetes in the noncardiovascular comorbidities category to avoid duplication of risk factors.

A patient was classified as having diabetes if diabetes was reported as the cause of ESRD on the ESRD CPM data collection form or if "diabetes, primary or contributing" or "diabetes, currently on insulin" were reported as preexisting comorbidities on CMS's Form 2728.

Hospitalizations for LEAs during the 12-month follow-up period were obtained from the USRDS Hospitalization SAF (SAF.HOSP). Our definition of LEA included *International Classification of Diseases, Ninth Revision* (ICD-9) codes 84.11–84.19 (84.11, amputation of toe; 84.12, amputation through foot; 84.13, disarticulation of ankle; 84.14, amputation of ankle through malleoli of tibia and fibula; 84.15, other amputation below knee; 84.16, disarticulation of knee; 84.17, amputation above knee; 84.18, disarticulation of hip; and 84.19, abdominopelvic amputation).

Data analysis

Patients were included in the sample for analysis if they had been dialyzing <6 months before 31 December of the year before the study year and if they had data reported for at least one of the study months for hematocrit, paired pre- and postdialysis blood urea nitrogen values, and serum albumin. Racial analyses were restricted to black and white patients due to small numbers in other racial categories. Primary cause of ESRD was categorized as diabetes compared with other causes combined due to small numbers for other specific causes. Serum albumin values determined by the BCG laboratory method are systematically higher (generally, ~0.3 g/dl) than those reported by the BCP method (4). We took this difference into account in our analyses and in our reporting of findings.

Associations of hospitalization for LEA during the 12-month follow-up period with patient demographic characteristics and selected clinical data were tested by Student's *t* test, hierarchical ANOVA, χ^2 analyses, and univariate Cox proportional hazard modeling ($P < 0.05$ considered significant for each test).

Factors either significantly associated with hospitalization for LEA during the 12-month follow-up period or considered to be conceptually important were entered into separate multivariate Cox proportional hazard models for the following groups of noncensored patients: all incident patients, incident patients with diabetes, and nondiabetic incident patients. Patients were censored if they received a renal transplant, were switched to peritoneal dialysis, or were lost to follow-up. Additional separate analyses were conducted on these groups of patients after excluding patients with a preexisting amputation reported on the ESRD CPM data collection form. Both forward and backward stepwise techniques, using the likelihood ratio statistic, were utilized to obtain the final model. Predictors with a *P* value <0.05 were retained in the final adjusted models. Data analyses were conducted utilizing SPSS for Windows, version 10.0 (5), and SAS 8.02 (6).

RESULTS — There were 27,876 nonduplicate patients included in the ESRD CPM Project for study years 1996–1999. Twelve percent (3,460 of 27,876) of patients had dialyzed for <6 months. Of these, 188 patients were censored for the following reasons: 114 received a renal transplant, 50 switched to peritoneal dialysis, and 24 were lost to follow-up. Sixty-two patients had a preexisting amputation reported on the ESRD CPM data collection form.

Diabetes was the primary cause of ESRD or reported as a preexisting comorbidity on the CMS's Form 2728 in 1,751 (54%) of the 3,272 noncensored patients. There were 116 (4%) patients hospitalized for an LEA during the 12-month follow-up period. Six percent ($n = 104$) of incident patients with diabetes had an LEA compared with 1% ($n = 12$) of patients without diabetes ($P < 0.001$) (unadjusted odds ratio 7.9, 95% CI 4.3–14.4).

Table 1 shows the univariate associations between demographic and clinical characteristics and the incidence of LEA

Table 1—*Unadjusted associations of selected patient characteristics and clinical indicators with hospitalization for amputation during the 12-month follow-up period for incident adult hemodialysis patients, 1996–1999*

Characteristic	Amputation	No amputation	HR (95% CI)
Total	116 (4)	3,156 (96)	—
Sex			
Male	70 (4)	1,678 (96)	1.3 (0.91–1.9)
Female	46 (3)	1,466 (97)	Referent
Race			
Black	39 (4)	963 (96)	Referent
White	65 (3)	1,831 (97)	0.88 (0.59–1.3)
Ethnicity			
Hispanic	16 (6)	276 (95)	1.7 (0.96–2.8)
Non-Hispanic	75 (3)	2,160 (97)	Referent
Age quartile (years)			
18–52.4	20 (3)	792 (98)	Referent
52.5–64.9	30 (4)	782 (96)	1.5 (0.86–2.7)
65.0–73.6	35 (4)	779 (96)	1.8 (1.02–3.1)*
≥73.7	31 (4)	781 (96)	1.6 (0.89–2.7)
Diabetes status†			
Diabetes	104 (6)	1,647 (94)	7.4 (4.1–13.5)‡
No diabetes	12 (1)	1,457 (99)	Referent
Preexisting comorbidities			
Cardiovascular‡	84 (5)	1,627 (95)	2.4 (1.6–3.7)‡
Noncardiovascular	31 (2)	1,487 (98)	Referent
Noncardiovascular	23 (4)	610 (96)	1.03 (0.65–1.6)
No noncardiovascular	92 (4)	2,504 (97)	Referent
URR quartile (%)§			
<58.5	42 (6)	726 (95)	2.4 (1.4–4.2)§
58.5–65.0	28 (4)	753 (96)	1.6 (0.86–2.8)
65.1–70.6	23 (3)	742 (97)	1.3 (0.70–2.4)
≥70.7	18 (2)	758 (98)	Referent
Hematocrit quartile (%)			
<28.7	28 (4)	783 (97)	1.2 (0.68–2.0)
28.7–31.8	27 (3)	790 (97)	1.1 (0.64–1.9)
31.9–34.5	37 (5)	762 (95)	1.6 (0.95–2.6)
≥34.6	24 (3)	787 (97)	Referent
Serum albumin (BCG) quartile (g/dl)§‖			
<3.3	44 (5)	813 (95)	1.8 (1.1–3.0)*
3.3–3.59	34 (4)	769 (96)	1.5 (0.88–2.6)
3.6–3.86	16 (2)	797 (98)	0.69 (0.36–1.3)
≥3.87	22 (3)	751 (97)	Referent
Postdialysis BMI quartile (kg/m^2)			
<21.4	23 (4)	589 (96)	1.3 (0.70–2.4)
21.4–24.6	20 (3)	593 (97)	1.1 (0.59–2.1)
24.7–29.0	29 (5)	584 (95)	1.6 (0.90–2.9)
≥29.1	18 (3)	594 (97)	Referent

Data are *n* (%), unless noted otherwise. Percentages may not add up to 100% due to rounding. *Significant difference between the groups, $P < 0.05$. †Diabetes status: patients were categorized as having diabetes if diabetes was reported as the cause of ESRD on the ESRD CPM data collection form or if "diabetes, primary or contributing" or "diabetes, currently on insulin" was reported as a preexisting comorbidity on the CMS Form 2728. ‡Significant difference between the groups, $P < 0.001$. §Significant difference between the groups, $P < 0.01$. ‖BCG indicates the BCG laboratory method.

for incident hemodialysis patients. Patients with diabetes were seven times more likely to have an LEA compared with nondiabetic patients combined (hazard ratio [HR] 7.4, 95% CI 4.1–13.5). Patients with the lowest quartile of mean urea reduction ratio (URR) over the 3-month study period (URR <58.5%) were more likely to have an LEA (2.4, 1.4–4.2). Patients with cardiovascular comorbidities were more likely to have an LEA than patients with no cardiovascular comorbidities (2.4, 1.6–3.7). Patients with the lowest quartile of mean serum albumin (<3.3 g/dl, BCG) were more likely to have an LEA (1.8, 1.1–3.0). There were no significant differences among new hemodialysis patients in hospitalization for LEA during the 12-month follow-up period by sex, race, Hispanic ethnicity, noncardiovascular comorbidities, hematocrit, or postdialysis BMI.

The results of the final multivariate Cox proportional hazard models for hospitalization for LEA during the 12-month follow-up period for noncensored, all incident adult hemodialysis patients and stratified by diabetes status are shown in Table 2. Factors associated with increased risk for hospitalization for LEA included diabetes (HR 6.4, 95% CI 3.4–12.0), patients with preexisting cardiovascular comorbidities (1.8, 1.2–2.8), patients with mean URR <58.5% (1.9, 1.1–3.3), and patients with mean serum albumin <3.5 or 3.2 g/dl (for BCG and BCP, respectively) (1.6, 1.1–2.3). Sex, race, Hispanic ethnicity, age, hematocrit, history of hypertension, and noncardiovascular comorbidities were not significantly associated with risk of hospitalization for LEA during the 12-month follow-up period for these patients.

Among patients with diabetes, factors for increased risk of hospitalization for LEA included cardiovascular comorbidities (HR 1.7, 95% CI 1.1–2.6) and mean URR <58.5% (2.6, 1.4–4.8). Among patients without diabetes, younger patients and patients with mean serum albumin ≥3.5 or 3.2 g/dl (for BCG and BCP, respectively) were less likely to be hospitalized for LEA. Separate analyses of these groups of patients, after excluding patients with preexisting amputations, yielded similar results (data not shown).

CONCLUSIONS — The main results of our study are *1*) diabetes is the strongest risk factor for LEA in incident ESRD patients; *2*) the high risk of LEA, 6% among diabetic patients and 1% among nondiabetic patients, is present during the first half year of ESRD therapy and is comparable with that observed among prevalent ESRD patients; and *3*) inadequate hemodialysis (measured by URR <58.5%) is a risk factor for LEA among new ESRD patients and appears to interact with diabetes. In patients with diabetes,

Table 2—*Final adjusted multivariate Cox proportional hazard model predicting hospitalization for amputation during the 12-month follow-up period for incident adult hemodialysis patients, 1996–1999*

Characteristic	All	Diabetes as the cause of ESRD	Other causes combined
Male sex	NS	NS	NS
White race (black race = referent)	NS	NS	
Increasing age (years)	NS	NS	1.09 (1.02–1.2) [<0.01]
Hispanic ethnicity (non-Hispanic = referent)	NS	NS	NS
Diabetes status*			
Diabetes (without diabetes = referent)	6.4 (3.4–12.0) [<0.001]	NE†	NE
Cardiovascular comorbidities	1.8 (1.2–2.8) [<0.01]	1.7 (1.1–2.6) [<0.05]	NS
Noncardiovascular comorbidities	NS	NS	NS
Hypertension as comorbidity	NS	NS	NS
Mean hematocrit (%)	NS	NS	NS
Mean serum albumin <3.5/3.2 g/dl (BCG/BCP)	1.6 (1.1–2.3) [<0.05]	NS	3.8 (1.1–12.5) [<0.05]
Mean URR quartile (%) (highest quartile of ≥70.7% = referent)			
1 (<58.5)	1.9 (1.1–3.3) [<0.05]	2.6 (1.4–4.8) [<0.01]	NS
2 (58.5–65.0)	1.3 (0.72–2.3) [0.3886]	1.7 (0.86–3.2) [0.1279]	
3 (65.1–70.6)	1.1 (0.59–2.0) [0.7779]	1.3 (0.62–2.6) [0.5208]	

Data are HR (95% CI) [*P* value], where applicable. *Diabetes status: patients were categorized as having diabetes if diabetes was reported as the cause of ESRD on the ESRD CPM data collection form or if "diabetes, primary or contributing" or "diabetes, currently on insulin" was reported as a preexisting comorbidity on the CMS Form 2728. NE, not entered into the model; NS, not significant.

LEA was associated with a URR <58.5% and with cardiovascular comorbidities. In contrast, in nondiabetic patients, first LEA was associated with increasing age and low serum albumin, but not URR or cardiovascular comorbidities.

Our finding that diabetes was the strongest risk factor for LEA in new hemodialysis patients supports previous findings in studies (1,3) of prevalent hemodialysis patients. This finding is consistent with earlier findings identifying an association between diabetes and risk of LEA in the general population. Diabetes was the strongest risk factor for LEA in patients from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (7). A study (8) of the 1997 Nationwide Inpatient Sample and the 1997 National Health Interview Survey showed that the rate of LEA in individuals with diabetes was 28 times the rate of LEA in those without diabetes.

We found that decreased hemodialysis adequacy is a stronger risk factor for LEA in patients with diabetes than in nondiabetic patients. There was a dose-dependent relationship between risk of LEA and URR. Hemodialysis inadequacy has not been previously reported to be associated with risk of LEA. Our findings may suggest a short clinical latency between low URR and its effect on LEA, as our study used a shorter follow-up period than previous studies. Because hemodialysis adequacy is a strong risk factor in patients with ESRD and is modifiable, it should be monitored closely by the health care providers of hemodialysis patients with diabetes.

We found cardiovascular comorbidity to be a risk factor for LEA in patients with diabetes, but not in nondiabetic patients. Our sample size and the large number of comorbidity categories precluded a more detailed analysis of cardiovascular comorbidities. Previous research suggests that the data collection instrument (CMS Form 2728) may have a higher sensitivity for detecting comorbid cardiovascular disease in ESRD patients with diabetes compared with those without diabetes (9), although it is unclear how this would affect our findings. Peripheral vascular disease and abnormal electrocardiogram readings are risk factors for LEA in patients with diabetes (10), so the relationship between specific cardiovascular comorbidities and LEA needs to be explored further in ESRD patients with diabetes.

We found an association between decreased serum albumin and LEA in all new hemodialysis patients, which supports previous findings (3,10). We found that male sex was not associated with LEA in new hemodialysis patients, perhaps because our study did not have adequate power to detect the weak association that has previously been found (1) in prevalent hemodialysis patients.

The observed relationship between hemodialysis inadequacy and risk of LEA may be due to the pathological effects of uremia. Uremia in chronic renal failure may increase the risk of infection (11), polyneuropathy (12), autonomic dysfunction (13), and peripheral vascular disease (14), all of which can be involved in the pathogenesis of LEA. Hemodialysis inadequacy has been found to be associated with mortality due to coronary artery disease, other cardiac disease, cerebrovascular disease, and infection and with all-cause mortality (15). The association between URR and mortality may be stronger in patients with diabetes than in those without diabetes (15,16), supporting our finding of a possible interaction between low URR and diabetes.

Another potential explanation for the inadequate dialysis in patients with LEAs is that these patients may be more likely to have a permanent venous catheter as a dialysis access. Permanent catheterization reduces delivered dialysis dose (17). Our sample size limited our ability to explore this possibility in our study population.

Our study was limited by the small numbers of incident hemodialysis patients compared with the prevalent hemodialysis population. This necessitated the categorization of comorbidities as cardiovascular or noncardiovascular. HbA_{1c} level is not a quality indicator being tracked by the ESRD CPM Project, thus

any association between glycemic control and LEA could not be examined.

Another limitation of our study was the definition of existing amputation, which (as defined on the ESRD CPM Project data collection instrument) did not include "toe(s), finger(s), or mid-foot (Symes)" amputations, but did include upper-limb amputations. Definition of LEA as an outcome also differs between our study and previous studies. Our study and that of Eggers et al. (1) defined LEA as a toe amputation or higher; the O'Hare study (3) included transmetatarsal amputation or higher. Some studies (18) suggest that toe amputations affect quality of life less than more proximal amputations. However, we feel that toe amputations are indeed clinically important because it has been shown (19) that toe amputation is a risk factor for future amputation.

Our findings are clinically relevant to LEA prevention efforts in ESRD patients with diabetes for several reasons. Our finding that dialysis inadequacy is a risk factor for LEA in new hemodialysis patients with diabetes has important implications for prevention. Inadequate dialysis, in contrast to the other risk factors described, is readily modifiable by changes in clinical practice. Further, clinically beneficial increases of dialysis dose increase quality-adjusted life expectancy and are cost-effective (20,21). Emphasis on aggressive treatment of cardiovascular risk factors, such as hypercholesterolemia, may also impact the frequency of LEAs for patients with diabetes.

How might this information on the high risk of LEA among incident hemodialysis patients be used to improve care? Hemodialysis adequacy and cardiovascular disease in ESRD patients with diabetes can be monitored by the ESRD Networks (dialysis facilities) and by health care providers outside the ESRD Networks. ESRD Networks provide feedback on quality of care to providers and treatment centers, based on Network monitoring activity and information from the ESRD CPM Project. This quality control system has been shown (22,23) to be an effective means of improving dialysis adequacy. It is interesting to speculate that similar improvement in the use of preventive measures, especially those already well described for patients with diabetes (24), can be undertaken without the implementation of an entirely new prevention program. Integration of LEA prevention programs into the weekly routine of in-center dialysis treatment could increase participation and compliance. Risk factors specific to ESRD patients, such as low URR or low serum albumin, can be addressed by new prevention programs and by the existing quality control system.

Our study focused on incident hemodialysis patients alone, so our results may highlight risk factors that should be addressed at the start of hemodialysis therapy. Previous studies used prevalent patients, although it should be noted that roughly one-half of the patients in the study of O'Hare et al. (3) were incident patients. They found that the risk of LEA increased with time spent on hemodialysis, which suggests that prevention efforts earlier in the course of renal failure might be more effective in preventing amputation.

Our study population is from the years 1995 through 1999, so comparison of our findings with earlier studies may reflect changes in treatment of U.S. ESRD patients that have occurred as a result of the ESRD Network quality control efforts. Our finding that sex was not a risk factor for LEA suggests that the national ESRD Health Care Quality Improvement Program may be helping to reduce disparities in access to hemodialysis treatment. Future studies will provide more insight into how the profile of LEA risk factors changes with further improvements in quality of care of ESRD patients.

In conclusion, we found that diabetes was the strongest risk factor for LEA in incident dialysis patients. Among patients with diabetes, inadequate hemodialysis dose was a strong risk factor for LEA. Improvement of hemodialysis adequacy can help to prevent LEAs in the new ESRD population, especially in patients with diabetes. Aggressive treatment and monitoring of cardiovascular disease in ESRD patients with diabetes may also help to prevent LEAs, and future research can focus on the relationship of specific cardiovascular diseases to risk of LEA in ESRD patients with diabetes. Risk factors elucidated by our study, previous studies, and future research should stimulate the design of efficient LEA prevention programs in this high-risk patient population.

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