Association Between Renal Failure and Foot Ulcer or Lower-Extremity Amputation in Patients With Diabetes

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OBJECTIVE — The objective of this study was to evaluate the association between foot ulcers (DFU) and lower-extremity amputation (LEA) and chronic kidney disease (CKD) in patients with diabetes.

RESEARCH DESIGN AND METHODS — This was a retrospective cohort study of individuals enrolled between 2002 and 2006 who were aged ≥35 years, had a history of diabetes, and were cared for in general practice. The physicians participated in The Health Information Network of the U.K.

RESULTS — The presence of DFU or LEA and estimated glomerular filtration rate (eGFR) were evaluated in 90,617 individuals with a median time of observation of 2.4 years. Of these individuals 378 had an LEA and 2,619 had a DFU. CKD (eGFR <60 ml/min per 1.73 m^2) was noted in 23,350 (26%) individuals in our cohort. For the development of DFU compared with our reference group (group 1 [eGFR ≥60 ml/min per 1.73 m^2]), the hazard ratio (HR) for group 2 (eGFR ≥30 and <60 ml/min per 1.73 m^2) was 1.85 (95% CI 1.71–2.01) and for group 3 (eGFR <30 ml/min per 1.73 m^2) was 3.92 (3.23–4.75) (all $P < 0.001$). For LEA, the HR for group 2 was 2.08 (1.68–2.58) and for group 3 was 7.71 (5.29–11.26) (all $P < 0.001$).

CONCLUSIONS — In this observational study, there is a strong association between stage of CKD and DFU or LEA that is probably not just related to the presence of peripheral arterial disease. Individuals with even moderate CKD (eGFR <60 ml/min per 1.73 m^2) have an increased risk for DFU and LEA.

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Diabetic foot ulcer (DFU) and lower-extremity amputation (LEA) are severe complications of older individuals who develop diabetes. LEA is often associated with a preexisting DFU. The annual incidence of DFU among those with diabetes is between 1.5 and 4%, and foot problems are the most frequent reason that individuals with diabetes are hospitalized (1). The health care costs associated with DFUs and LEAs are high. In 1995, U.S. Medicare claims for DFUs exceeded $1.4 billion (2). LEAs also have a profound effect on quality of life and are associated with increased health care costs and an increased risk of mortality (3–5). Nontraumatic LEAs are at least 15 times more prevalent in those with diabetes than in those with any other concomitant medical illness (3,6). In the U.S., nearly 80,000 LEAs are performed for diabetic patients each year (7). The rate of LEA, per the Centers for Disease Control and Prevention and other sources, is ~4–8 per 1,000 individuals hospitalized with diabetes, which contrasts with a rate of about 3 per 10,000 in the general population (7,8). Within 5 years of having an LEA about 60% of those with diabetes will die (5). As the number of individuals with diabetes increases, so probably will the number of individuals with an LEA.

Diabetes is a strong risk factor for chronic kidney disease (CKD). Surprisingly little has been published on the overall occurrence of DFU and LEA among those with CKD and diabetes. With respect to CKD and LEA, most studies have focused on end-stage renal disease (ESRD) and have often noted an association with peripheral arterial disease (PAD), thereby claiming a common atherosclerotic cause. For example, with respect to ESRD, regardless of the concomitant presence of diabetes, studies have shown various but markedly increased rates of LEA in that >5% and as many as 50% will have an amputation (9–11). Furthermore, the risk of LEA is at least two to six times greater among those with both diabetes and CKD than among those with diabetes alone (9,10). PAD is thought to be the mechanistic link between CKD and LEA (9–11). A recent study using data from the National Health and Nutrition Examination Survey demonstrated the importance of the relationship between CKD and PAD. Among those with a creatinine clearance of <60 ml/min per 1.73 m^2 who do not have ESRD, there was a 2.5 times increased risk of PAD compared with the risk for those without CKD (11). An analysis of participants in the Heart and Estrogen/Progestin Replacement Study also showed that women with CKD were between 1.63 and 3.24 times more likely to have PAD. In this study, the likelihood of PAD increased with decreasing creatinine clearance (12). Finally, although the onset of LEA has been associated with ESRD and CKD, studies have tended to associate the onset of LEA with clinically apparent PAD, but none have evaluated DFU among those with CKD or the onset of LEA among those with CKD but without clinically apparent PAD.

We hypothesized that the risk of DFU and LEA is associated with worsening CKD. To test this hypothesis we evaluated the association between DFU and LEA and CKD in a large population-based cohort of individuals with diabetes. CKD was determined using a priori defined cut

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points for estimated glomerular filtration rate (eGFR). We also evaluated whether associations between DFU and LEA and CKD occurred in the absence of clinically apparent PAD.

RESEARCH DESIGN AND METHODS

— We conducted a retrospective cohort study of individuals with diabetes who were treated in general medical practices that participate with The Health Information Network (THIN) data system. This study was reviewed by the Institutional Review Board of the University of Pennsylvania.

THIN was created in 2002 and includes data from 300 physician practices in England and Wales. THIN subjects are broadly representative of the U.K. population and are similar in age, sex, and geographic characteristics (13). THIN includes records on 4.78 million patients, of whom 2.26 million are currently active participants. The patient population in THIN is stable with only ~3% of patients being lost per year attributable to leaving a practice or death. The database for THIN, contains information on medical diagnoses (acute and chronic), as well as free text on these conditions. THIN also includes laboratory values, which are electronically captured, and some aspects of the physical examination, as well as hospitalizations, consultations, and prescription medications, which are electronically transferred to THIN. The ability to ascertain the diagnosis of diabetes has been previously investigated by National Health Service investigators and is excellent (14).

CKD: exposure, risk factors/confounders, and outcome definition

All subjects enrolled in this cohort had at least two database records for diabetes between January 2002 and January 2005 and were required to be at least 35 years of age by January 2002.

The primary exposure variable was eGFR. The eGFR was estimated using the Modification of Diet in Renal Disease equation (15). Our estimate did not include a mathematical expression for ethnicity/race, which is a common practice in the U.K. (15). This omission was also necessary because race/ethnicity is not recorded in THIN. We also explored via sensitivity analyses whether the inability to adjust for race/ethnicity would have had an affect on our results (see below).

CKD was defined on the basis of eGFR and categorized into three levels corresponding to the U.S. National Kidney Foundation staging scheme for CKD. These three categories were defined by the National Kidney Foundation cut points between stage II and stage III CKD as well as between stage III and stage IV ($\geq$60, $\geq$30 to $<$60, and $<$30 ml/min per 1.73 m^2, respectively) (15).

Outcomes were determined separately in each study subject for incident DFU and incident LEA on the basis of the computerized medical records. Therefore, DFUs in this study were chronic or severe enough to require a patient to seek medical care and may not represent all wounds on the feet of those with diabetes. For a DFU to be considered incident, the subject must have had no report of a DFU for at least 6 months before the database record of the eGFR. For a LEA to be considered incident, it needed to be first coded after the database record of the eGFR. If the subject had a prior LEA, a new one must have occurred on the contralateral leg or a previous LEA must have been converted from a minor to major (transtibial) amputation. Because of the potential for recording error, it was not possible to identify a new minor amputation on a foot with a previous minor amputation (e.g., the amputation of the fifth digit after a previous amputation of the first). If an observed DFU or LEA did not meet these criteria it was categorized as "history of."

In 2002, a series of performance programs were established and became mandatory by 2003. These required documentation and assessments by the general practitioner at least every 15 months of lower-limb pulses, neuropathy (usually recorded as a failure to perceive 10 g of monofilament pressure), A1C, cigarette use, and serum creatinine in those patients with diabetes. These assessments were used as confounders in our study. However, a confounder must be associated with the risk factor of interest (i.e., CKD) and the outcome (DFU or LEA). It should not be on the causal pathway between the risk factor and the outcome. Our confounders also included subject age at the time of entering our cohort, duration of diabetes as noted in the medical record, practice site, diagnosis of history of myocardial infarction (myocardial infarction or unstable angina), sex, and history of hypertension. A subject was assumed to have PAD if he or she had an absence of pulses of both lower extremities (screening test frequently used in U.K. clinical practice and epidemiological studies) or had a medical diagnosis consistent with lower-extremity atherosclerotic disease (16). It is possible that this diagnosis of PAD lacks validity and therefore could result in an underestimate of the true association between CKD and LEA/DFU.

Statistical analysis

Definition of person-time. Our analysis was based on person-year estimates. Person-time was estimated from the database date for the first eGFR after 2002 until either an outcome occurred (LEA and DFU separately), the study subject died, the study subject left the practice, or the last transaction date in the database.

Multivariable analysis: explanatory models. Descriptive statistics are presented by CKD categories and confounders. The unadjusted hazard ratio (HR) of the association between our CKD categories and DFU or LEA with 95% CI was determined using proportional hazards regression analysis. Individuals with ESRD were excluded from these analyses. All estimates were calculated for the full sample and separately for both those with and those without clinical history of PAD (i.e., interaction). The final multivariable models (adjusted models) were developed by using variables deemed clinically important for LEA and DFU and any variable that changed the effect estimate by $>$15%. Proportional hazards models were used, and the HRs are reported with 95% CIs. The fit of the models was assessed visually using Cox-Snell residuals and by graphic display.

Sensitivity analyses were conducted by reestimating the eGFR using the mathematical expression for African descent by assuming that all subjects were of African descent, by assuming that only those in the most severe CKD class (i.e., those with eGFR $<$30 ml/min per 1.73 m^2) were of African descent, and by repetitive random sampling of 1% of the population and reclassifying them as if they were of African descent (1% is the U.K. census estimate of African ethnicity). We also conducted analyses excluding anyone with a past history of DFU or LEA just in case those with a past history truly did not have a new DFU or LEA after our measured eGFR. All statistical analyses were performed using Stata 9.2 (Stata Corporation, College Station, TX).

RESULTS

— There were 125,933 individuals identified with diabetes be-

Table 1—*Fully adjusted HRs (95% CI) for the onset of a new foot ulcer or LEA*

Variable	Foot ulcer	LEA
Prior foot ulcer	7.85 (7.16–8.62)*	13.06 (10.55–16.18)*
Prior amputation	8.00 (6.74–9.49)*	31.03 (23.93–40.23)*
Smoking		
0 per day	Ref	Ref
1–15 per day	0.94 (0.84–1.05)	1.16 (0.88–1.53)
>15 per day	0.97 (0.85–1.11)	0.62 (0.40–0.96)
Age by category		
35–40 years	Ref	Ref
>40–50 years	1.18 (0.92–1.49)	1.41 (0.71–2.89)
>50–60 years	1.26 (1.02–1.56)	1.81 (0.98–3.36)
>60–70 years	1.56 (1.27–1.92)	2.12 (1.16–3.85)
>70 years	2.42 (1.98–2.96)*	2.80 (1.56–5.03)*
A1C by category		
≤7.0%	Ref	Ref
>7.0% and ≤9.0%	1.15 (1.05–1.26)	1.80 (1.38–2.35)
>9.0%	1.66 (1.50–1.83)*	2.77 (2.10–3.64)*
Sex (women Ref)	0.98 (0.91–1.06)	0.50 (0.40–0.62)*
History of lower-extremity PAD	3.80 (3.51–4.12)*	12.00 (9.74–14.77)*
Loss of neurosensation	2.17 (1.88–2.51)*	2.34 (1.62,3.38)*
History of hypertension	1.17 (1.08,1.27)*	1.42 (1.15–1.75)*
History of myocardial ischemia	1.46 (1.35–1.59)*	1.63 (1.31–2.02)*
Duration of diabetes (years)	1.03 (1.03–1.04)	1.04 (1.04–1.05)
Mean arterial pressure	0.99 (0.99–1.00)	1.00 (0.99–1.01)
ESRD	6.12 (3.54–10.55)*	15.66 (6.48–37.86)*

P value, compared with reference (Ref)or, if categories are presented, as test for trend, $*P \leq 0.001$.

tween January 2002 and January 2005 in THIN who were at least 35 years of age and who had at least two visits. At the start of our period of observation, the average age was 62.9 years (95% CI 62.8–63.0) and the median age was 64.6 years (52.6–82.6). Women represented 53% (66,928) of our cohort. Our subjects, after a documented eGFR, were followed for about 200,675 person-years of time between January 2002 and July 2005. The average time of follow-up was 2.2 years, and the median time was 2.4 years. During this time, 378 individuals had an LEA and 2,619 individuals had a DFU. Before entry into our cohort 3,491 subjects had a diagnosis of DFU and 768 had an LEA. Of those in our cohort who needed an amputation, 70 (18%) had a previous minor or contralateral LEA and 126 (33%) had a previous DFU >6 months before their entry into our cohort. Of those in our cohort who developed a DFU, 569 (22%) had a previous DFU before 6 months prior to entry into our cohort and 138 (5%) had a previous LEA. CKD (eGFR <60 ml/min per 1.73 m^2) was noted in 23,350 (26%) of our cohort. PAD was noted in 10,449 (12%) subjects. In addition, several other factors were associated with the development of DFU or LEA, such as hyperglycemia, peripheral neuropathy, hypertension, and history of myocardial infarction (Table 1). eGFR could be determined in 90,617 individuals (72% of the total).

Development of a DFU was associated with progressive CKD and many of our other variables (Tables 1 and 2). Compared with our reference group (group 1 [eGFR ≥60 ml/min per 1.73 m^2]) the HR for group 2 (eGFR ≥30 and

Table 2—*HRs (95% CI) of foot ulcer and LEA for the full dataset and for foot ulcer and LEA*

A. Full dataset	Foot ulcer	Foot ulcer adjusted	LEA	LEA adjusted (includes an interaction term for PAD)
CKD (eGFR)				
≥60 ml/min per 1.73 m^2	Ref	Ref	Ref	Ref
≥30 to <60 ml/min per 1.73 m^2	1.85 (1.71–2.01)	1.51 (1.38–1.66)	2.08 (1.68–2.58)	2.28 (1.54–3.36)
<30 ml/min per 1.73 m^2	3.92 (3.23–4.75)	3.22 (2.60–4.00)	7.71 (5.29–1.26)	8.05 (4.23–7.01)
B. Foot ulcer	**Foot ulcer without PAD**	**Foot ulcer without PAD adjusted**	**Foot ulcer with PAD**	**Foot ulcer with PAD adjusted**
CKD (eGFR)				
≥60 ml/min per 1.73 m^2	Ref	Ref	Ref	Ref
≥30 to <60 ml/min per 1.73 m^2	1.68 (1.51–1.86)	1.41 (1.24,1.58)	1.44 (1.26,1.65)	1.38 (1.18–1.60)
<30 ml/min per 1.73 m^2	3.86 (3.00–4.98)	3.32 (2.55–4.33)	2.10 (1.56,2.84)	2.04 (1.49–2.79)
C. LEA	**LEA without PAD**	**LEA without PAD adjusted**	**LEA with PAD**	**LEA with PAD adjusted**
CKD (eGFR)				
≥60 ml/min per 1.73 m^2	Ref	Ref	Ref	Ref
≥30 to <60 ml/min per 1.73 m^2	1.82 (1.28–2.60)	2.05 (1.37–3.07)	1.31 (1.00–1.72)*	1.60 (1.19–2.16)
<30 ml/min per 1.73 m^2	6.96 (3.50–13.83)	7.80 (3.82–15.90)	2.90 (1.76,4.76)	3.33 (1.93–5.77)

Adjusted and unadjusted results are shown. Parts B and C include results in the presence or absence of peripheral arterial disease. Compared with reference (Ref) or as a test for trend, all *P* values <0.001 unless $*P = 0.05$.

<60 ml/min per 1.73 m^2) was 1.85 (95% CI 1.71–2.01) and for group 3 (eGFR <30 ml/min per 1.73 m^2) was 3.92 (3.23–4.75) (all P values < 0.001). The fully adjusted associations between DFU and CKD were 1.51 (1.38–1.66) for group 2 and 3.22 (2.60–4.00) for group 3, both versus group 1 (all $P < 0.001$). An interaction due to PAD was also present ($P_{interaction} = 0.08$ for group 2; $P_{interaction} = 0.003$ for group 3), and, as a consequence, our CKD effect estimates are reported for those with and without PAD (Table 2).

The need for an amputation was associated with progressive CKD and many of our other variables (Tables 1 and 2). Compared with the reference group (group 1), the HR for group 2 was 2.08 (95% CI 1.68–2.58) and for group 3 was 7.71 (5.29–11.26) ($P < 0.001$). Our fully adjusted association between LEA and CKD was 2.18 (1.70–2.78) for group 2 and 7.09 (4.57–11.00) for group 3, respectively (all $P < 0.001$). These estimates were influenced primarily by an interaction due to PAD ($P_{interaction} = 0.07$ for group 2; $P_{interaction} = 0.04$ for group 3) (Table 2). All CKD effect estimates are therefore reported for those with and without PAD (Table 2).

As noted above, ~35,316 (28%) of those in THIN did not have the full data necessary for a calculation of eGFR. There were many attributes that were similar between those in our cohort and those who did not have data allowing an estimate of eGFR. For example, for our main confounders, the mean age was 63.9 years and ~51% were women. When their full medical record and not just data obtained after 2002 was evaluated, 5% had evidence of a foot ulcer at some time in their medical record versus 4% for our cohort and 1% had a record of an amputation versus 1% for our cohort, 26% used insulin versus 23% of our cohort, and 0.9% had a history of ESRD versus 0.8% of our cohort.

We conducted several sensitivity analyses. The Modification of Diet in Renal Disease estimation includes a term for African ethnicity (15). This term increases the eGFR estimate by ~20%. This variable is frequently not recommended for use in the calculation of eGFR in the U.K. (15). About 1% of the U.K. population is African. We were not able to measure ethnicity, but we did create sensitivity analysis to evaluate whether our inability to measure African ethnicity might have affected our results. First, we randomly assumed that 1–5% of our population might be African. This did not appreciably affect our point estimates as reported in Table 2. Next we assumed that all of the individuals in the worst CKD category were African. This had minimal effect on the estimation of our point estimates. For example, this resulted in point estimates of 2.08 (95% CI 1.68–2.56) and 7.18 (4.37–11.78) for CKD and LEA, respectively. Finally, we conducted an "unmeasured confounders" sensitivity analysis and were not able to eliminate the association of CKD with DFU or LEA using previously demonstrated effect estimates for race/ethnicity.

CONCLUSIONS — Several authors have noted a relationship between ESRD and LEA. Within one of the largest studied cohorts of diabetic subjects who have eGFR measurements, we have shown a strong association, not just with ESRD, but between the severity of CKD and the onset of both DFU and LEA among those with diabetes. Whereas this association is greatest for those with the most severe CKD, even those with less severe CKD were approximately two times more likely to develop a foot ulcer or undergo an LEA than those with minimal to no impairment (Table 2). This association was present among those without clinically apparent PAD. To confirm the appropriateness of our database and analysis, we were also able to show, as expected, an association between DFU or LEA and hyperglycemia, PAD, peripheral neuropathy, hypertension, history of myocardial infarction, age, previous history of DFU, previous history of LEA, and ESRD.

Traditionally, the complications of diabetes have been divided into those due to microvascular disease and those due to macrovascular disease. Microvascular complications include retinopathy, nephropathy, and peripheral neuropathy. Macrovascular diseases include coronary heart disease, stroke, and PAD/claudication. Exactly where DFUs and LEA fit into this scheme is not always clear. Many of these diabetic individuals have neuropathy and/or PAD. This might imply that these are both macro- and microvascular illnesses.

In our study we were able to explore DFU and LEA in individuals with or without clinically apparent PAD. We were able to show a relationship between these outcomes and progressive CKD. Although there may be many potential mechanisms used to explain the onset of CKD, DFU, and LEA in those with diabetes, it is fascinating to note that structurally in many ways the onset of CKD many be similar to the onset of DFU and/or LEA. As a consequence of hyperglycemia different cell types, such as mesangial cells, which have some phenotypic properties similar to those of fibroblasts, and podocytes, are damaged (17). These cells are damaged from hyperglycemia, but the damage is also physically attributable to the trauma induced by hypertension (18). Unlike renal cells, the cells of the dermis may be replenished from neighboring cells, transient amplifying cells local to the wound, and bone marrow–derived cells. One might hypothesize that the onset and progression of CKD might serve as an early marker (not actually a risk factor) because severe damage occurs first in the kidney (cells most sensitive to hyperglycemia that cannot replenish) and then later in the skin, which can replenish, resulting in the onset of DFU and ultimately LEA.

In the setting of a DFU, local trauma (e.g., walking, poor-fitting shoes, plantar contact with hard objects, and others) is often thought to initiate foot ulcers (19). Interestingly, in a recent secondary analysis of a randomized clinical trial of footwear, which looked only at one form of trauma that was due to daily weight bearing, the authors noted that by itself this form of trauma was not directly associated with DFUs (19,20). There may be many explanations for this result. Our preceding hypothesis might help to explain this finding and to explain why trauma does not cause wounds in everyone with diabetes; i.e., before trauma results in a clinically significant wound, an individual's ability to repair must first be altered. This explanation does not diminish the importance of trauma as the likely cause of the initial insult that results in a DFU or LEA, but it may be that CKD, neuropathy, PAD, and many other complications of diabetes are on the same causal pathway related to the progressive inability to repair. Statistically, if this is true, then in our study we underestimated the magnitude of the associations that we report by adjusting our models for PAD, neuropathy, and so on. As an alternative explanation, circulating factors that directly affect wound repair and ultimately are responsible for LEA and DFU, may exist as a consequence of progressive CKD.

There are a number of important potential limitations to our study. With respect to selection bias we did not have eGFR measurements for all subjects in

THIN, so perhaps the general practitioners preferentially measured creatinine in those with more severe renal disease who were most likely to develop a DFU or undergo an LEA. This is unlikely because this association is not well known. In addition, the completion of the required examinations is a performance criterion of the general practitioners, which is linked to their pay (www.nhsemployers.org/pay-conditions/index.cfm) (21). A recently published audit revealed that 96% complied (21). Our study began in 2002, before mandatory compliance and eGFR measurements were available for ~72% of subjects. After 2003 about 92% of subjects had eGFR measurements. It is also possible that general practitioners failed to diagnose or record our outcomes. If this were true then our results would have been biased to the null unless the general practitioners a priori decided that an association between eGFR, a value requiring calculation, and our outcomes existed. There could also be concerns that data are not always collected in the record for THIN. It is important to realize that per agreement with the company that organizes THIN, the record for THIN is the general practitioner's only medical record. We could have mis-specified the degree of CKD because we did not know the subjects' ethnicity/race. Ethnicity/race is an unmeasured confounder in our study. We were able to conduct several sensitivity analyses and found that our inability to determine race/ethnicity was not likely to have influenced our measurement of eGFR. Further, Abbott et al. (22) did note various rates of foot complications and PAD and DFU in ethnic groups. However, these authors concluded that variable rates of PAD and neuropathy at least partially explained the different rates of LEA and DFU in these ethnic groups. We did adjust for PAD and neuropathy in our study too. It is possible that important assessments such as PAD and neuropathy were measured with error. However, as in other studies they were measured by general practitioners in their practices, thereby making these assessments generalizable to other general practice settings and even to other studies such as that of Abbott et al. Because we know of no reason that the accuracy of their measurement would have been influenced by the general practitioner's knowledge of eGFR (a calculated blood test), this error is probably "nondifferential," meaning that any bias due to this error should have resulted in an underestimate in the association between CKD and LEA or DFU.

In summary, we have demonstrated a strong association between CKD and DFU or LEA among a population-based sample of individuals with diabetes who are cared for by general practitioners in the U.K. It is important to note that demonstrating an association is not the same as showing causation, which often requires an experimental design such as a randomized clinical trial and the demonstration of a common mechanism that causes CKD and failure of the skin to heal. On the basis of our study, it is likely that CKD and DFU or LEA among those with diabetes are associated more tightly then was recognized previously. Clinically, our findings are important in that we have shown an association between even individuals with moderate CKD (eGFR <60 ml/min per $1.73m^2$) and an increased risk for the onset of DFU and ultimately amputation.

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