Diabetes Mellitus and Nontraumatic Lower Extremity Amputation in Black and White Americans


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Background: The comparative long-term risk of nontraumatic lower extremity amputation (LEA) in black and white Americans, 2 groups with strikingly different rates of diabetes mellitus, is not known.

Objective: To examine the 20-year incidence of LEA in relation to race and diabetes mellitus.

Methods: The 14,407 subjects in the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study were observed prospectively between 1971 and 1992. Prevalent diabetes mellitus was ascertained at the baseline examination, and incident diabetes mellitus, during follow-up. Lower extremity amputation was ascertained from hospital discharge records. Cox regression analysis was used to estimate associations between race, diabetes mellitus, and risk of first LEA.

Results: During the study period, 158 LEAs occurred among 108 subjects. While black subjects constituted 15.2% of the cohort, they represented 27.8% of the subjects with amputation (P = .002). The 20-year age-adjusted rate ratio of first LEAs for black subjects–white subjects was 2.14. Regression analyses confirmed the importance of diabetes mellitus as a key LEA risk factor. The association between prevalent diabetes mellitus and LEA risk was substantially higher (relative risk [RR], 7.19; 95% confidence interval [CI], 4.61-11.22) than that for incident diabetes mellitus (RR, 3.15 [CI, 1.84-5.37]), highlighting the importance of diabetes mellitus duration on LEA risk. While preliminary analyses adjusted for age and diabetes indicated a significant association between race and LEA risk (RR, 1.93 [95% CI, 1.26-2.96]), the effect of race diminished (RR, 1.49 [95% CI, 0.95-2.34]) following adjustment for education, hypertension, and smoking.

Conclusions: Although black subjects experienced higher age- and diabetes mellitus–adjusted rates of amputation than their white counterparts, a combination of social and environmental factors may account for the apparent ethnic difference. More research into nonbiological factors associated with LEA may reduce the occurrence of these procedures in both black and white individuals.

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LOWER EXTREMITY amputation (LEA) is a costly and disabling complication of diabetes mellitus that results from the individual and combined pathophysiologic effects of peripheral arterial disease and peripheral neuropathy.1-5 Despite the high prevalence of type 2 diabetes mellitus in the United States and other industrialized nations, there are no long-term, broadly generalizable studies of incident LEAs in individuals with and without diabetes mellitus from the same population, nor are there population-based rates of LEA in black and white Americans, 2 groups with strikingly different rates of diabetes mellitus. We performed this study to characterize the long-term incidence of LEA in the United States in relation to race and diabetes mellitus. We hypothesized that black Americans would be at higher risk of LEA than white Americans, regardless of their diabetes mellitus status.

RESULTS

At baseline, 852 subjects reported having been told by a physician that they had diabetes mellitus, and 174 of these also had urine test results positive for glucose. Additionally, 221 subjects who did not report diabetes mellitus also had glucose in their urine at baseline. Thus, 1073 subjects (7.4% of the NHEFS cohort) were considered to be prevalent cases of diabetes mellitus.

Following the baseline interview, 1167 subjects developed diabetes mellitus and were considered to be incident cases. Thus, 2240 subjects (15.5% of the cohort) had either prevalent or incident diabetes mellitus during the study. Of the 14,407 subjects in the cohort, 108 (0.7%) had at least 1 LEA during follow-up, and a total of 158 amputations were performed on these individuals.

The crude black subject–white subject rate ratio for all LEAs during
SUBJECTS AND METHODS

STUDY DESIGN
The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHESFS) involved a cohort of 14,407 subjects aged between 25 and 74 years at baseline examination between 1971 and 1975. The cohort consisted of 12,036 white and 2199 black subjects as well as 172 subjects of other races. The baseline interview included questions on medical conditions previously diagnosed by a physician, smoking history, and education. The baseline medical examination included measurements of height, weight, systolic and diastolic blood pressure, subscapular and triceps skinfold thicknesses, and a urine glucose test (semiquantitative). Body mass index (BMI, calculated as weight in kilograms divided by the height in meters squared) was calculated from subjects’ baseline height and weight and was used as a measure of relative weight. The ratio of the subscapular and triceps skinfolds was used as an indicator of fat distribution. Subjects were classified as hypertensive at baseline if they reported taking medications for high blood pressure or had a systolic blood pressure of 160 mm Hg or higher and/or a diastolic blood pressure of 95 mm Hg or higher. Follow-up interviews were conducted from 1982 to 1984, in 1987, and in 1992. The 1982 to 1984 interview was conducted at the subject’s residence. The 1987 and 1992 interviews were conducted by telephone.

DEFINITION OF PREVALENT AND INCIDENT DIABETES MELLITUS
At baseline, subjects who responded yes to the question “Has a doctor ever told you that you have diabetes or sugar diabetes?” were categorized as having prevalent diabetes mellitus. Subjects who did not report diabetes mellitus but who had evidence of glucose in their urine at baseline were also considered to have prevalent diabetes mellitus. At each follow-up survey, data were used from subjects’ reports of physician-diagnosed diabetes mellitus, health care facility records, and death certificates to identify incident cases of diabetes mellitus (International Classification of Diseases, Ninth Revision [codes 250.xx]). The characteristics of subjects with diabetes in this cohort have been described previously. Fasting glucose was not measured at baseline or during follow-up, nor was an oral glucose tolerance test conducted.

ASCERTAINMENT OF LEA
At each of the 3 follow-up interviews, subjects or their proxies were asked whether the subject had stayed overnight in a hospital since the previous interview. The International Classification of Diseases, Ninth Revision procedure codes corresponding to these 3 sets of hospitalization data were used to identify subjects with nontraumatic LEAs (codes 84.10-84.19).

STATISTICAL ANALYSIS
Crude rates of amputation (per 1000 person-years) were calculated separately for black and white subjects, and the age-adjusted rate ratio was calculated using the age distribution of the 1970 US population as the standard. Because subjects with multiple amputations contribute more than 1 event to the numerator, rates were calculated in 2 ways (1) the total number of LEAs during follow-up and (2) the subjects’ first amputation during follow-up. The unpaired t test and χ² statistic were used to examine differences in baseline characteristics between subjects who had an LEA during follow-up and those who had none, and between subjects with 1 LEA and those with 2 or more. Using Cox proportional hazards regression, we modeled associations between race, diabetes mellitus, and risk of first LEA. These analyses were controlled for potentially confounding factors; those variables hypothesized to be associated with both the primary exposures of interest (race and diabetes mellitus) and also with the outcome (LEA). The proportional hazards regression procedure (PHREG) was used in the SAS statistical software system (SAS Institute, Cary, NC; release 6.11, 1996).

Since duration of diabetes mellitus increases the risk of macrovascular complications, our models included separate indicator variables for incident and prevalent diabetes mellitus. While these variables are imperfect proxies for diabetes mellitus duration, distinguishing between case types in this way has been used in previous studies of diabetic complications. We examined the interaction of race and both prevalent and incident diabetes mellitus by using cross-product terms (eg, race × prevalent diabetes) to determine if the risk of LEA associated with diabetes mellitus duration depended on race. White subjects without diabetes were considered the reference group.

Age, sex, smoking history (ever vs never), baseline hypertension, and BMI and subcapular and triceps skinfold values were considered potential confounders of the association with LEA of either race or diabetes mellitus. Socioeconomic status (SES) was also considered a potential confounder. While no single variable adequately represents the complexity of SES, previous studies of diabetes mellitus have used education as a proxy, and it is reasonable to speculate that this variable is also associated with LEA. Quadratic terms for continuous variables were examined to determine if these measures had nonlinear associations with LEA risk. We also tested for interaction between race and smoking, baseline hypertension, and education.

Regression analyses were restricted to black and white subjects 35 years or older at baseline (n = 10,778) because there were no LEAs in the youngest age group. Disarticulations of the knee and hip were not considered in multivariate analyses, since they are unlikely to be associated with diabetes mellitus. Subjects with missing data for the independent variables were excluded from multivariate analyses.

We entered age, race, and prevalent and incident diabetes mellitus into an initial model predicting LEA risk. Potential confounders were then entered to determine how they influenced preliminary associations, and interaction and quadratic terms were examined. The Wald χ² test was used to test the significance of individual β coefficients, and the likelihood ratio test was used to define the final model. We tested the proportionality assumption in 2 ways with a focus on race and diabetes mellitus. First, we plotted the log(−log[survival]) function against log time separately for strata of diabetes mellitus and race, and then we examined interactions of log(time) with race and diabetes mellitus status.
follow-up was 2.87, and was attenuated slightly to 2.78 following adjustment for age (Table 1). The crude and age-adjusted rate ratios for first LEAs were 2.38 and 2.14, respectively.

Amputations of toes and amputations below and above the knee were more common in younger adults and, conversely, LEAs below and above the knee were more frequent in older age groups.

Although black subjects made up only 15.2% of the NHEFS cohort, they accounted for 27.8% of subjects with LEAs (P < .002; Table 2). Lower extremity amputations occurred more frequently in individuals with prevalent or incident diabetes mellitus than in subjects with no diabetes (P < .001 for both prevalent and incident cases). Subjects with LEAs were significantly older at baseline than those without (61.1 vs 48.8 years [P < .001]), and men underwent more amputations than women (P = .02). Baseline BMI was higher in subjects with LEAs than in those without (27.9 vs 25.6 kg/m² [P < .001]), as was the occurrence of baseline hypertension (60.4% vs 27.4% [P < .001]). There was no difference in smoking history between the 2 groups (61.0% vs 56.9%), but subjects with LEAs were significantly more likely than those without to have discontinued high school before graduation (74.1% vs 44.4%; P < .001).

Thirty-seven subjects (34.2% of all amputees) had 2 or more LEAs, and 10 (9.7%) had 3 or more. The most striking differences between subjects with 1 vs those with multiple LEAs were race and diabetes mellitus: 53% of black subjects with LEAs had 2 or more, compared with only 26% of their white counterparts (P = .008). Fifty-seven percent of subjects with multiple LEAs had diabetes mellitus at baseline, compared with only 28% of subjects with 1 LEA (P = .004; data not shown).

Figure 1 shows that black subjects were significantly more likely than their white counterparts to be included in 1 of the 2 diabetes mellitus categories (prevalent, 10.6% vs 6.8% [P < .001]; incident, 11.9% vs 7.4% [P < .001]). Figure 2 shows that, in subjects with diabetes mellitus, more LEAs occurred among black subjects than white; the difference, however, is significant only for incident diabetes mellitus (3.4% vs 1.4% [P = .02]). There was no race difference in the proportion of individuals without diabetes who had LEAs.

The final regression model was based on data from 101 subjects with LEAs and 9700 censored subjects, representing 91% of all black and white subjects 35 years or older. Results of our initial and final models of analy
sis of risk factors for first LEAs are presented in Table 3. The initial model, which examined only the effects of age, race, and diabetes mellitus, indicated significant associations between these factors and the risk of first LEA. While black subjects had nearly twice the diabetes mellitus– and age-adjusted risk of LEA compared with white subjects (relative risk [RR], 1.93 [95% confidence interval (CI), 1.26-2.90]), the magnitude of risk associated with diabetes mellitus was much larger; subjects with prevalent and incident diabetes mellitus had RRs of 7.97 and 3.46, respectively, indicating an effect of diabetes mellitus duration on LEA risk independent of age and race. There were no significant interactions between race and diabetes mellitus in this model. The final model was parsimonious, including variables for age, race, prevalent and incident diabetes mellitus, hypertension, smoking, and education. Relative to subjects who remained without diabetes throughout the study, those with prevalent diabetes mellitus had more than 7 times the risk of LEA, and one of few with black and white subjects and subjects with and without diabetes drawn from the same population. Our preliminary analyses showed that between 1971 and 1992, the age-adjusted rate of all LEAs was 2.8 times higher in black than white subjects, and that the age-adjusted rate of the first LEA was 2.1 times higher in black than white subjects.

To our knowledge, this is the longest prospective study of the combined effects of race and diabetes mellitus on the risk of LEA, and one of few with black and white subjects with and without diabetes drawn from the same population. Our preliminary analyses showed that between 1971 and 1992, the age-adjusted rate of all LEAs was 2.8 times higher in black than white subjects, and that the age-adjusted rate of the first LEA was 2.1 times higher in black than white subjects. The NHEFS offers a better design and population than prior studies of LEA. Previous investigations of LEA have been based on data from subjects with diabetes alone, without a comparison group without diabetes.5,24 These studies also had shorter follow-up periods,1,5,24 were not longitudinal1,23 or were not adjusted for potential con-

**Table 3. Regression Coefficients, Relative Risks, and 95% Confidence Intervals for Associations in NHEFS Subjects Between Risk Factors and Lower Extremity Amputation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.06</td>
<td>1.06</td>
<td>1.04-1.08</td>
</tr>
<tr>
<td>Race</td>
<td>0.65</td>
<td>1.93</td>
<td>1.26-2.96</td>
</tr>
<tr>
<td>Prevalent diabetes mellitus</td>
<td>2.07</td>
<td>7.97</td>
<td>5.17-12.29</td>
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<tr>
<td>Incident diabetes mellitus</td>
<td>1.24</td>
<td>3.46</td>
<td>2.06-5.82</td>
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<tr>
<td><strong>Final model</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.05</td>
<td>1.05</td>
<td>1.03-1.08</td>
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<tr>
<td>Race</td>
<td>0.40</td>
<td>1.49</td>
<td>0.95-2.34</td>
</tr>
<tr>
<td>Prevalent diabetes mellitus</td>
<td>1.97</td>
<td>7.19</td>
<td>4.61-11.22</td>
</tr>
<tr>
<td>Incident diabetes mellitus</td>
<td>1.14</td>
<td>3.15</td>
<td>1.84-5.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.71</td>
<td>2.04</td>
<td>1.35-3.09</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>0.70</td>
<td>2.02</td>
<td>1.34-3.05</td>
</tr>
<tr>
<td>Education &lt; 12 y</td>
<td>0.76</td>
<td>2.14</td>
<td>1.32-3.49</td>
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</table>

*NHEFS indicates National Health and Nutrition Examination Survey, Epidemiologic Follow-up Study.

**COMMENT**

Education increased the RR of LEA among white subjects by 2.5 (95% CI, 1.5-4.4), independently of age, diabetes mellitus, smoking, and hypertension.

To our knowledge, this is the longest prospective study of the combined effects of race and diabetes mellitus on the risk of LEA, and one of few with black and white subjects with and without diabetes drawn from the same population. Our preliminary analyses showed that between 1971 and 1992, the age-adjusted rate of all LEAs was 2.8 times higher in black than white subjects, and that the age-adjusted rate of the first LEA was 2.1 times higher in black than white subjects.

The NHEFS offers a better design and population than prior studies of LEA. Previous investigations of LEA have been based on data from subjects with diabetes alone, without a comparison group without diabetes.5,24 These studies also had shorter follow-up periods,1,5,24 were not longitudinal1,23 or were not adjusted for potential con-

**Figure 1.** Percentage distribution by race and diabetes mellitus status of subjects in the National Health and Nutrition Examination Survey I, Epidemiologic Follow-up Study, 1971-1992 (NHEFS). There were significantly more prevalent and incident cases of diabetes among black than white subjects (P < .001 [x²]).

**Figure 2.** Percentage distribution by race and diabetes mellitus status of subjects with lower extremity amputation at follow-up in the National Health and Nutrition Examination Survey I, Epidemiologic Follow-up Study, 1971-1992. More black than white subjects with incident cases of diabetes had amputations (P = .02 [x²]).
RESULTS FROM multivariate analyses indicated that race per se may play a limited role in the cause of first LEAs when education, smoking, and hypertension are also considered. We showed that following adjustment for these factors, a significant age- and diabetes mellitus–adjusted association between being black and risk of LEA was diminished below conventional significance. However, the relatively small number of black subjects with LEA makes interpretation of this finding difficult. There may be unexplained factors that made black subjects more susceptible to diabetic complications leading to LEA. Alternatively, better adjustment in this study for SES or environmental factors might have diminished the LEA risk associated with race. Further studies are needed to address these questions.

Black individuals with diabetes mellitus may have worse glycemic control than their white counterparts, and may therefore be at increased risk of complications leading to LEA. Recent data from the Third National Health and Nutrition Examination Survey (NHANES III) support this hypothesis, showing that black subjects with impaired fasting glucose and undiagnosed and diagnosed diabetes mellitus had higher mean glycosylated hemoglobin levels than white subjects. Along the same lines, diabetes mellitus may be identified later among black than among white subjects, thereby increasing the prevalence of undiagnosed diabetes mellitus and raising the possibility that vascular and nerve damage and plantar ulcers may already be present at, or develop shortly after, diabetes mellitus diagnosis in black patients. This may reduce or eliminate the period of secondary prevention in this group. Greater rates of undiagnosed diabetes mellitus among black compared with white subjects were demonstrated in NHANES III.

Another explanation for our findings is that care for diabetes mellitus, diabetic neuropathy, and peripheral arterial disease may be worse among black subjects than white, leading to higher rates of amputation. A recent study showed that of individuals with diabetes mellitus, black subjects were more likely than white subjects to smoke and have uncontrolled hypertension, and less likely to have health insurance or a private health care provider. Another study showed that older black subjects were more likely than older white subjects to have LEA, and less likely to undergo lower extremity revascularization and angioplasty, 2 limb-sparing surgical procedures. Racial differences in glycemic control among diabetic subjects, duration of diabetes mellitus prior to diagnosis, prevalence of undiagnosed diabetes mellitus, and access to appropriate health care may all contribute to the higher rates of LEA among black Americans. However, these factors are more strongly related to social rather than biological phenomena. Consistent with the latter hypothesis is the recent finding of an inverse association between SES and all-cause mortality among individuals with diabetes in the Whitehall Study and the WHO Multinational Study of Vascular Disease in Diabetes.

If elevated LEA risk were related more to black race than to social factors, one would not expect to find an association between SES and LEA risk among white subjects. However, the significant association between SES and LEA among white subjects and the lower race-associated risk among their black counterparts following adjustment for education, smoking, and hypertension suggest not only that race per se may play a limited role in the cause of LEA, but also that social factors act to increase LEA risk regardless of race.

Our results are consistent with findings from previous studies of LEA to the extent that we found significant associations between increased risk of LEA and diabetes mellitus, smoking, and hypertension. Our results indicate that the risk of LEA was 7 and 3 times higher among individuals with prevalent and incident diabetes mellitus, respectively, compared with those without diabetes. The graded risks associated with these case types suggest an effect of duration of diabetes mellitus on LEA risk, and are consistent with previous findings.

While rates of all LEAs are important from a public health and resource use perspective, the rate of first LEA is more related to cause. In our investigation, age-adjusted rates of all and of first LEAs indicated that black subjects experienced higher rates of LEA than white, a finding that is consistent with a previous study. However, it should be emphasized that in this and other studies that used hospital records to ascertain LEA, it is often not possible to determine if the “first” LEA ascertained during the study period is actually the first LEA for that individual.

In our study, 54 (50%) of 108 subjects with LEA had diabetes mellitus listed as a discharge diagnosis. This finding is consistent with results from the National Hospital Discharge Survey, which found that 51% of all patients with LEAs had diabetes mellitus as a discharge diagnosis. It is consistent also with data from the Centers for Disease Control and Prevention, which showed that 45% of LEAs were performed on people with diabetes mellitus listed on a medical record. However, in the NHESF, diabetes mellitus may have been present in a larger proportion of LEAs than we report. Two of the 54 subjects with LEAs who did not have diabetes mellitus on their discharge records reported diabetes mellitus at baseline, and 6 reported diabetes mellitus during follow-up. Although these subjects were classified as having diabetes mellitus in our analyses, the discrepancy between self-reported diabetes mellitus and diabetes mellitus listed on discharge records following LEA highlights underreporting of diabetes mellitus–related LEAs.
on these records. Such underreporting results in an underestimation of the contribution of diabetes mellitus to the occurrence of LEA.

This study has several limitations, mostly related to the data available in the NHESFs. Since fasting glucose levels were not available, we relied on subject reports of physician-diagnosed diabetes mellitus, hospital discharge records, and death certificates. It is known that self-reporting underestimates true prevalence of diabetes mellitus by 30% to 50% and that hospital records underreport diabetes mellitus by as much as 40%. Diabetes mellitus is also underreported on death certificates.17-30 It was not possible to determine the extent of misclassification resulting from undiagnosed and unreported diabetes mellitus. However, since diabetes mellitus was more frequently undiagnosed in black subjects than in white subjects, and since blacks were at higher risk of LEAs, any misclassification that occurred would likely have resulted in an underestimation of the association between race and LEA. Underreporting and misclassification of diabetes mellitus may help explain why the magnitude of the association between diabetes mellitus and LEA was lower here than in a previous study4 in which the rate ratio was reported to be as high as 15. However, in the Most and Sinnock4 study, ascertainment of diabetes mellitus was limited to information gathered from the same hospital discharge records from which the LEA data were obtained. In our study, diabetes mellitus diagnoses from hospital discharge records were supplemented by a urine glucose test at baseline and by subject reports throughout the follow-up period. More extensive diabetes mellitus ascertainment and diabetes mellitus ascertainment independent of the hospital visit during which the LEA occurred may also help explain the difference in rates between studies.

In summary, this study showed that during 20 years of follow-up, the age-adjusted rate of LEA among black Americans was 2.8 times that of their white counterparts, and that diabetes mellitus and its duration were strong predictors of LEA risk. Hypertension, smoking, and low educational level were also strongly predictive of LEA risk. These factors appear to diminish the biological link between race and LEA. Decreasing the occurrence of diabetes mellitus by addressing risk factors such as obesity as well as reductions in hypertension and smoking are strategies that may have a substantial impact on the future occurrence of LEA among both black and white adults.

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