The 25-Year Cumulative Incidence of Lower Extremity Amputations in People With Type 1 Diabetes

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OBJECTIVE—To examine the 25-year cumulative incidence of lower-extremity amputation (LEA) in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Cumulative incidence of LEA was ascertained in Wisconsin Epidemiologic Study of Diabetic Retinopathy participants (n = 943) using the Kaplan-Meier approach accounting for competing risk of death. Relationships of baseline characteristics with incidence of LEA were explored using a proportional hazards approach with discrete linear regression modeling.

RESULTS—The overall 25-year incidence of LEA was 10.1%. In multivariate analyses (results reported as odds ratio; 95% CI), being male (3.90; 2.29–6.65), heavy smoking (2.07; 1.11–3.85), having hypertension (3.36; 1.91–5.93), diabetic retinopathy (2.62; 1.13–6.09), neuropathy (1.68; 1.02–2.76), and higher HbA_{1c} (per 1% 1.40; 1.24–1.58) were independently associated with the incidence of LEA.

CONCLUSIONS—Our results show a high 25-year incidence of LEA and suggest that glycemic control and blood pressure control and preventing heavy smoking may result in reduction in its incidence.

Diabetes Care 34:649–651, 2011

Several studies have described the incidence of lower-extremity amputation (LEA) and its relationship to various risk factors such as glycemia and blood pressure (1–5), but few have studied cohorts of people with type 1 diabetes followed over a long period (1–4). Despite changes in care, the incidence of LEA remains high, at 0.15–0.36% per 10,000 people (2,3,5). In this study, we examine the 25-year cumulative incidence of LEA in a large cohort with type 1 diabetes participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

RESEARCH DESIGN AND METHODS

—Of the 1,210 people with type 1 diabetes identified in 1979 and 1980, 996 participated at the baseline examination, and 903, 816, 667, 567, and 520 participated at the 4-, 10-, 14-, 20-, and 25-year follow-ups, respectively (6). Of the 996 participants, 24 had baseline LEA and another 29 lacked follow-up data, leaving 943 for analysis in this report. Reasons for nonparticipation, comparisons of participants and nonparticipants, methods used to determine HbA_{1c} levels, gross proteinuria and history of smoking, medication use, and comorbidities and definitions are presented elsewhere (6,7).

Cumulative incidence of LEA was determined by history and included amputations of toes, feet, or legs. Traumatic amputations and amputations unrelated to diabetes were excluded. Cumulative incidence of LEA was defined based on the first amputation present at any follow-up examination in whom it was absent at baseline. Neuropathy was defined as self-reported history of loss of tactile and/or temperature sensitivity.

Cumulative 25-year incidence of LEA was determined using the Kaplan-Meier approach accounting for competing risk of death. Multivariate odds ratios (OR) and 95% CIs were calculated from discrete linear logistic hazard models. Age, sex, age at diabetes diagnosis, diabetes duration, HbA_{1c} levels, hypertension status, proteinuria, BMI, smoking status, heavy smoking, retinopathy severity, and history of cardiovascular disease and neuropathy at baseline were considered potential risk factors. In multivariate analyses, we considered only variables that were statistically significant in univariate analyses ($P < 0.10$). Time-dependent covariate analyses were also performed.

RESULTS

—Eighty-seven people had incident LEA. Of these, 53 (60.9%) had a toe or foot amputated, 13 (14.9%) had a leg amputated, and 21 (24.1%) had an amputation of a toe or foot followed by a leg. The 25-year overall cumulative incidence of LEA accounting for competing risk of death was 10.1% (95% CI 8.1–12.1); the 25-year cumulative incidence of major LEA (leg amputations) was 4.2% (95% CI 2.8–5.6). Cumulative incidence of LEA was related to baseline age ($P < 0.001$ for trend) and duration of diabetes ($P = 0.02$ for trend).

Male sex and other characteristics were univariately associated with the incidence of LEA (Table 1). In multivariate analyses (OR; 95% CI), male sex (3.90; 2.29–6.65), heavy smoking (2.07; 1.11–3.85), hypertension (3.36; 1.91–5.93), diabetic retinopathy (2.62; 1.13–6.09), history of peripheral neuropathy (1.68;

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Received 3 September 2010 and accepted 23 December 2010.
DOI: 10.2337/dc10-1712
Neither the National Institutes of Health nor the American Diabetes Association had any role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the article. The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Eye Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, or the National Institutes of Health.

Table 1—*Associations with incidence of LEA*

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex (male vs. female)	3.25	1.99–5.28	<0.001	3.90	2.29–6.65	<0.001
Age at diagnosis (years)						
10–19 vs. <10	0.71	0.41–1.22	0.21			
20–29 vs. <10	0.52	0.27–0.99	0.07			
Glycosylated hemoglobin A_{1c} (per 1%)	1.36	1.22–1.52	<0.001	1.40	1.24–1.58	<0.001
Glycosylated hemoglobin A_{1c} quartiles (%)						
9.5–10.5 vs. <9.5	1.63	0.88–3.03	0.12			
10.6–12.0 vs. <9.5	1.99	1.09–3.64	0.03			
12.1–19.5 vs. <9.5	4.61	2.49–8.54	<0.001			
Diabetic retinopathy	3.83	1.71–8.58	0.001	2.62	1.13–6.09	0.04
Diabetic retinopathy severity						
Mild vs. none	1.91	0.79–4.61	0.15			
Moderate vs. none	3.99	1.49–10.67	0.006			
PDR vs. none	13.53	5.73–31.93	<0.001			
Proteinuria	2.85	1.77–4.59	<0.001	1.34	0.74–2.41	0.34
Hypertension	3.21	2.03–5.06	<0.001	3.36	1.91–5.93	<0.001
Smoking history						
Past vs. never	1.77	0.98–3.20	0.06			
Current vs. never	2.01	1.23–3.90	0.006			
Pack years smoked						
<5 vs. none	1.44	0.73–2.84	0.30	1.26	0.58–2.72	0.56
5–14 vs. none	1.90	0.99–3.64	0.05	1.28	0.63–2.60	0.50
≥15 vs. none	2.52	1.43–4.46	0.01	2.07	1.11–3.85	0.02
Cardiovascular disease history*	0.93	0.27–3.17	0.91			
Neuropathy history	2.00	1.27–3.16	0.003	1.68	1.02–2.76	0.04
BMI (kg/m^2)						
25–30 vs. <25	1.13	0.70–1.83	0.61			
>30 vs. <25	0.45	0.14–1.46	0.18			

All models (univariate and multivariate) additionally control for age. Missing rows indicate that variable was not significant and thus not included in the final multivariate model. Smoking history was not entered in the model because of multicollinearity with pack years smoked variable. PDR, proliferative diabetic retinopathy. *Defined as having a history of angina, myocardial infarction, or stroke.

1.02–2.76), and higher HbA_{1c} level (per 1% 1.40; 1.24–1.58) were independently associated with 25-year incidence of LEA. Additionally, we performed time-dependent covariate analyses using data on all baseline variables at each follow-up visit. Our results showed that time-varying covariate associations of risk factors with LEA were consistent with association of baseline risk factors and LEA incidence.

CONCLUSIONS—The overall 25-year cumulative incidence of LEA, 10.1%, was high. Male sex, history of heavy smoking, higher HbA_{1c}, presence of hypertension, presence of retinopathy, and history of diabetic neuropathy were associated with LEA after controlling for age.

Our data confirm previous findings of a higher incidence of LEA in men (4,8), possibly related to higher prevalence of smoking in men. However, the association remained after controlling for smoking status (8). The lower incidence of LEA in women may be partially because of lower incidence of peripheral vascular disease in women (9). The lower occurrence of foot ulcers in women suggests that poorer self-care in men may also contribute to the finding of higher incidence of LEA in men (10).

Heavy smoking was related to incidence of LEA, which may be explained by the association of current and heavy smoking with development of atherosclerosis and peripheral arterial disease (9,11).

In the WESDR, people with hypertension and higher HbA_{1c} had increased risk of LEA. Similarly, in the United Kingdom Prospective Diabetes Study, duration and degree of hyperglycemia and increased systolic blood pressure were associated with increased risk of peripheral arterial disease, independently of other factors (12).

Other studies have found a relationship of retinopathy to LEA (13), suggesting that microvascular disease may be involved in the pathogenesis of LEA. History of neuropathy at baseline was independently associated with 62% increased odds of incident LEA. This may be because of decreased pain perception, impaired circulation and sensation, and, consequently, foot ulceration and infection in people with type 1 diabetes and neuropathy (9,14,15).

Longer diabetes duration, hyperglycemia, hyperlipidemia, and retinopathy have shown associations with LEA in people with type 2 diabetes (13). We previously compared 10-year cumulative incidence of LEA and associated risk factors in people with type 1 and 2 diabetes in our cohort. We found that while adjusting for diabetes duration, 10-year incidence of LEA was lower in people with type 1 diabetes than in people with type 2 diabetes. Differences in glycemic control did not explain this. It may be partially a result of poorer blood pressure control, higher frequency of atherosclerosis, and other factors not measured in our study in people with type 2 diabetes.

Our study has many strengths and some limitations. Despite the large proportion, the absolute number of LEAs was relatively small, reducing power to find some associations. Poorer survival in people with both histories of cardiovascular disease and LEA compared with those with cardiovascular disease without LEA suggests that selective mortality may have diminished the estimate of the effects of risk factors such as smoking or hypertension (K.S., unpublished data). Additionally, potential confounders, e.g., history of peripheral vascular disease and serum lipid levels, were not evaluated at baseline.

We found a high 25-year cumulative incidence of LEA in people with type 1 diabetes associated with three modifiable risk factors: hyperglycemia, hypertension, and heavy smoking. Glycemic and blood pressure control and preventing heavy smoking may result in its reduced incidence.

Acknowledgments—This work was supported by National Institutes of Health (Bethesda, MD)

Grants EY-016379 (to B.E.K.K. and R.K.) and DK-073217 (to R.K.) and by the American Diabetes Association (Alexandria, VA) Mentor-Based Postdoctoral Fellowship Award (to R.K.).

No potential conflicts of interest relevant to this article were reported.

K.S. researched data, contributed to discussion, wrote the article, and reviewed and edited the article. B.E.K.K. researched data, contributed to discussion, and reviewed and edited the article. K.E.L. and C.E.M. contributed to discussion and reviewed and edited the article. R.K. researched data, contributed to discussion, and reviewed and edited the article.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

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