All-cause mortality after diabetes-related amputation in Barbados: a prospective case-control study

Ian R Hambleton, PHD 1; Ramesh Jonnalagadda, MS 2; Christopher R Davis, MB 3; Henry S Fraser, FRCP 2; Nish Chaturvedi, MD 4; Anselm J Hennis, FRCP 1, 2

(1) Chronic Disease Research Centre, Tropical Medicine Research Institute, The University of the West Indies, Barbados.
(2) Faculty of Medical Sciences, The University of the West Indies, Barbados.
(3) Faculty of Medicine, University of Bristol, Bristol, UK.
(4) International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College, London, UK.

Author for correspondence:
Dr Ian Hambleton
ian.hambleton@uwichill.edu.bb


This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective—To determine the mortality rate after diabetes-related lower extremity amputation (LEA) in an African-descent Caribbean population.

Research design and methods—A prospective case-control study. We recruited cases (diabetes and LEA), and age-matched controls (diabetes no LEA) in 1999-2001. We followed these groups for five-years to assess mortality risk and causes.

Results—There were 205 amputations (123 minor, 82 major). One and five-year survival rates were 69% and 44% among cases, and 97% and 82% among controls (case-control difference, p<0.001). Mortality rates (per 1000 person years) were 273.9 (95% confidence interval 207.1 - 362.3) after a major amputation, 113.4 (85.2-150.9) after a minor amputation, and 36.4 (25.6-51.8) among controls. Sepsis and cardiac disease were the most common causes of death.

Conclusions—These mortality rates are the highest reported worldwide. Interventions to limit sepsis and complications from cardiac disease offer a huge potential for improving post-LEA survival in this vulnerable group.
The diabetic foot syndrome, including lower-extremity amputation (LEA) is a major contributor to morbidity and mortality from diabetes in developed countries (1). There are limited outcome data from the developing world (2). High levels of type-2 diabetes are reported in the Caribbean (3), and the incidence of diabetes-related LEA in Barbados ranks among the highest reported in the world (4).

RESEARCH DESIGN AND METHODS

The Barbados studies of amputation among people with diabetes have proceeded in three stages. An initial amputation incidence study recruited participants undergoing LEA in the 12-month period starting November 1999. We defined an amputation as minor if it involved the toes or foot, and major if it was through the tibia or femur. We further divided major amputations into below the knee amputations (BKA) or above the knee amputations (AKA). We then recruited one randomly selected population-based control for every case to initiate a case-control study of risk factors for diabetic LEA. Control subjects had diabetes, had never had an amputation, and were age-matched in 5-year age groups. We restricted analyses to participants who reported their race as Black (205 cases, 194 controls). Detailed methods, along with LEA incidence and risk factors have been published (4). Follow-up via telephone interviews continued to July 2007 to assess five-year survival. We confirmed all reported deaths using official records. For those who had died, we collected cause of death from death certificates to report all-cause mortality. The study received ethical approval and all participants (or their proxies) gave informed consent for baseline and follow-up studies.

Statistical methods—We calculated survival using the Kaplan-Meier function, stratifying by amputation status (AKA, BKA, minor amputation, controls). We calculated all-cause mortality rates per 1000 person-years using the same group stratification and adjusting for age using a Poisson regression model accounting for censored data. We compared these rates using mortality rate ratios from our regression model, with all analyses performed using Stata (Release 10, StataCorp, College Station, Texas, US).

RESULTS

There were 123 (60%) minor amputations, 47 (23%) BKAs and 35 (17%) AKAs. Cases and controls were similarly aged as a result of the study design (cases 70.5 (12.8) years, controls 69.3 (12.2) years, p=0.34). Cases with a minor amputation were younger than those with a major amputation (minor LEA 67.1 (13.2) years, major LEA 75.7 (10.3) years, p<0.001), and we control for this age difference by presenting age-adjusted mortality rates. Average diabetes duration for cases and controls was 17.8 (11.2) and 11.8 (9.8) years respectively (p<0.001), with no difference between those with minor and major LEAs (p=0.35). There were marginally more male cases than controls (44.9% vs. 34.5%, p=0.04). Cases were more likely to have poorer glycaemic control (GHb 11.1% vs. 9.1% in controls) (p<0.001).

In the 5-years after the index LEA, there were 145 deaths (112 amputees, 33 controls). The figure presents the survival
experience among cases and controls, and highlights the low survival after major amputation. Survival rates at 3-months, 6-months, 1-year and 5-years after an AKA were 51%, 49%, 34%, and 10%, and after a BKA were 68%, 64%, 60%, and 28%. Survival rates after a minor amputation were 92%, 86%, 81% and 59%. Overall survival rates among cases were 80%, 75%, 69%, and 44%, and among controls were 100%, 99%, 97%, and 82%.

Age-adjusted all-cause mortality rates per 1000 person-years were 432.0 (95% confidence interval 294.7-633.1) after an AKA, 205.9 (95% CI 142.8-296.8) after a BKA, 273.9 (95% CI 207.1 - 362.3) after a major amputation, 113.4 (95% CI 85.2-150.9) after minor amputation, and 36.4 (95% CI 25.6-51.8) among controls. All-cause mortality after any amputation was 162.6 per 1000 person-years (95% CI 132.1-200.1). Mortality after a major LEA was over seven times greater than in controls (rate ratio 7.59, 95% CI 4.97-11.58, p<0.001) and over twice that for minor LEAs (rate ratio 2.43, 95% CI 1.66-3.55, p<0.001). The minor LEA rate was over three times greater than for controls (rate ratio 3.12, 95% CI 2.01-4.86, p<0.001). Overall, mortality among cases was almost five times that of controls (rate ratio 4.68, 95% CI 3.17-6.90, p<0.001).

We could not ascertain cause of death in 5 out of 145 (3%) persons (3 major amputations, 2 controls). Among 181 recorded causes of death, the five principal causes were sepsis (49, 27%), cardiac disease (45, 25%), stroke (18, 10%), pneumonia (17, 9%), and renal problems (14, 8%). There were no statistically significant differences in the proportion of cases and controls dying from each cause (p>0.05 for each cause of death).

**DISCUSSION**

This study documents for the first time, mortality associated with diabetes related LEA in the Caribbean. Mortality rates were above those from other studied populations (2,5). In particular the all-cause mortality rate after BKA among another high risk group, American Indians in North America, was reported as 143.7 per 1000 person-years, compared to 205.9 per 1000 person-years following BKA in our population.

Cardiovascular disease is the principal cause of death following diabetic amputation in the developed world (5). In this population sepsis and cardiac disease contributed to a similar number of deaths, as they did in a single study from West Africa (6). This raises the possibility of a different hierarchy of post-amputation complications in the developing world. Such differences may be underpinned by healthcare access and social influences, including footwear choices (4,7).

Patient factors and healthcare system inadequacies may contribute to the burden of diabetes-related complications. Effective solutions to reduce the burden of amputation have been successfully implemented in other settings (8). Improvement is required in simple techniques for optimizing glycemic control, preventing and detecting foot complications, the management of wounds and ulcers, and post-amputation support services.

**ACKNOWLEDGEMENTS.**

This work was supported by a Collaborative Research Initiative Grant awarded by the Wellcome Trust.
REFERENCES
Figure