Excess mortality among people with podoconiosis: secondary analysis of two Ethiopian cohorts

Hannah Masraf a,*, Temesgen Azemerawb, Meseret Mollac, Christopher Iain Jonesd, Stephen Bremnerd, Moses Ngarie, James A. Berkleye,f, Esther Kivayae,G, Greg Feganf,g, Abreham Tamiruh, Abebe Kelemeworkh, Trudie Lange,f, Melanie J. Newporta, and Gail Daveya,c

aCentre for Global Health Research, Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton BN1 9PX, UK; bDabat Research Centre, University of Gondar, Gondar, Ethiopia; cSchool of Public Health, Addis Ababa University, PO Box 9086, Addis Ababa, Ethiopia; dDepartment of Primary Care and Public Health, Brighton and Sussex Medical School, University of Sussex, Brighton BN1 9PX, UK; eKEMRI/Wellcome Trust Research Programme, Kilifi, Kenya; fCentre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK; gSwansea University Medical School, Swansea, UK; hInternational Orthodox Christian Charities Podoconiosis Project, Debre Markos, Ethiopia

*Corresponding author: Tel: 07701086485; E-mail: h.masraf1@uni.bsms.ac.uk

Received 30 June 2020; revised 18 August 2020; editorial decision 10 November 2020; accepted 10 November 2020

Background: While morbidity attributable to podoconiosis is relatively well studied, its pattern of mortality has not been established.

Methods: We compared the age-standardised mortality ratios (SMRs) of two datasets from northern Ethiopia: podoconiosis patients enrolled in a 1-y trial and a Health and Demographic Surveillance System cohort.

Results: The annual crude mortality rate per 1000 population for podoconiosis patients was 28.7 (95% confidence interval [CI] 17.3 to 44.8; n=663) while that of the general population was 2.8 (95% CI 2.3 to 3.4; n=44,095). The overall SMR for the study period was 6.0 (95% CI 3.6 to 9.4).

Conclusions: Podoconiosis patients experience elevated mortality compared with the general population and further research is required to understand the reasons.

Keywords: Ethiopia, mortality, non-filarial elephantiasis, podoconiosis

Introduction

Many of the neglected tropical diseases (NTDs) listed for elimination, including soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis (LF), onchocerciasis and trachoma, are thought of as disabling rather than the direct causes of excess mortality. Disability-adjusted life years (DALYs) estimates for these diseases are predominantly influenced by years lived with disability rather than years of life lost, although this may reflect the absence of data on mortality rather than data on the absence of disability.1

Podoconiosis, a non-infectious, geochemical NTD characterised by lymphoedema, is associated with severe social, economic, physical and mental health consequences.2 Acute dermatolymphangioadenitis (ADLA) attacks, similar to those in LF patients, occur at least monthly among untreated patients.3 Stigma results in the inability to marry, divorce among those already married, exclusion from school and ostracism in the community. Disability causes a productivity loss of 45% of working days per year on average, and depression is common.2 No information on mortality has yet been reported, although anecdotal evidence suggests increased mortality related to acute attacks.

We compared mortality in a group of podoconiosis patients enrolled in a clinical trial with that in a local general population cohort. Podoconiosis patient data were obtained from the completed Gojjam Lymphoedema Best Practice Trial (GoLBeT).4 In brief, this trial tested the effectiveness of a simple lymphoedema self-care package in reducing the incidence of ADLA among podoconiosis patient participants who were followed up over a 12-month period. This took place in the Aneded woreda (district) of Amhara region, 278 km northwest of Ethiopia’s capital Addis Ababa and 260 km from Bahir Dar, Amhara’s regional capital. GoLBeT mortality rates were standardised against those of the Dabat Health and Demographic Surveillance System (HDSS), a...
vital event registration system in the Dabat district of Amhara, 821 km northwest of Addis Ababa.5

Methods

The GoLBeT dataset and the Dabat HDSS were retrospectively analysed using data from a 17-month period (28 February 2015–30 July 2016) to ensure comparability. The Dabat HDSS was selected as the reference population, representing the Amhara region’s general population, as it shares sociodemographic characteristics with the GoLBeT and, like Aneded, Dabat’s economy relies on subsistence farming.

Demographic data including age, sex, and family-reported date of death were used in this analysis. Data from outside of the 17-month study period and people with incomplete demographic data and <18 y of age were excluded, thus aligning this with the GoLBeT inclusion, exclusion and withdrawal criteria.

Data analysis was performed with SPSS version 25.0 (IBM, Armonk, NY, USA). The age distributions of both populations were descriptively analysed and compared using a two-tailed Mann-Whitney U test. The crude and age-standardised mortality rates were calculated and expressed per 1000 population, using the Poisson distribution. SMRs were calculated using indirect standardisation. CIs for the SMRs were obtained using family-reported dates of death, which could have introduced recall bias. The number of deaths in the GoLBeT dataset is 28.66 (95% CI 17.25 to 44.75) per 1000 population, while that of the general population was 2.79 (95% CI 2.27 to 3.39) per 1000 population. The crude mortality rate ratio (MRR) was 10.26 (95% CI 3.00 to 35.05), indicating overall excess mortality among podoconiosis patients compared with the general population. When adjusting for age, the annual mortality rate for the GoLBeT population was 22.45 (95% CI 12.56 to 37.02) per 1000 population. Age-adjusted SMRs further suggest higher mortality rates among all ages of adult podoconiosis patients (Table 1). The overall SMR for the study period was 5.99 (95% CI 3.61 to 9.36). The SMR for those ≤60 y of age was 12.42 (95% CI 6.79 to 20.84) and the SMR for those >60 y was 2.45 (95% CI 0.79 to 5.70).

The age-adjusted SMRs provided very strong evidence for differences in mortality between populations in the 31–40, 41–50 and 51–60 y groups and no strong evidence for differences in the 18–30, 61–70 or ≥71 y age groups. This suggests that podoconiosis contributes to mortality, directly or indirectly. We found no evidence for trends in mortality by either disease stage or income, but numbers in the GoLBeT dataset were small. Podoconiosis patients may suffer sepsis secondary to adenolymphangitis or podoconiosis could interact with underlying comorbidities. Of the podoconiosis patients studied, the most common perimortem signs and symptoms included a feeling of weakness (31.6%), generalised swelling (26.3%), jaundice (15.8%) and difficulty breathing/shortness of breath (15.8%). Some of these signs are indicative of sepsis and/or organ damage, but without autopsy data this cannot be confirmed. The high prevalence of mental health disorders and poverty among patients might also be implicated in mortality.

Our study had a number of limitations. Both populations used family-reported dates of death, which could have introduced recall bias. The number of deaths in the GoLBeT dataset was small, making further mortality modelling adjustments inappropriate. Confounding may have been introduced due to

| Age group (years) | Annual mortality rate per 1000 population (95% CI) | GoLBeT | SMR (95% CI) |
|------------------|-----------------------------------------------|-------|-------------|
| 18–30            | 0.86 (0.56 to 1.25)                            | 14.29 (0.36 to 79.59) | 16.69 (0.42 to 93.00) |
| 31–40            | 1.21 (0.68 to 2.00)                            | 26.79 (5.52 to 78.28) | 22.11 (4.56 to 64.62) |
| 41–50            | 2.42 (1.46 to 3.78)                            | 25.16 (6.86 to 64.42) | 10.38 (2.83 to 26.57) |
| 51–60            | 3.33 (2.00 to 5.19)                            | 36.59 (13.43 to 79.63) | 10.99 (4.03 to 23.93) |
| 61–70            | 7.52 (4.95 to 10.94)                           | 18.35 (2.22 to 66.28) | 2.44 (0.30 to 8.81) |
| ≥71              | 24.99 (19.45 to 31.63)                         | 61.22 (12.62 to 178.92) | 2.46 (0.51 to 7.16) |

Table 1. A summary of the age-adjusted annual mortality data and the associated SMRs for the GoLBeT and Dabat HDSS datasets
differences in mortality between the datasets unrelated to podoconiosis.

Conclusions
This study provides evidence that podoconiosis patients experience greater mortality than the general population in northern Ethiopia. If such an observation is confirmed in future studies, this will have important implications for our understanding of the global DALYs burden of podoconiosis, its impact on the health of individuals and the benefits on mortality of scaling up morbidity management programmes.

Supplementary data
Supplementary data are available at Transactions online.

Authors' contributions: The secondary analyses protocol was developed by HM, CJ, SB and GD. GoLBeT data were obtained by MM with the aid of a team supervised by AT and AK. Dabat DHSS data were obtained by a team supervised by TA. The trial was monitored by EK. GF supervised randomisation. MN, MM and JB managed the data. Statistical analyses were undertaken by HM, CJ and SB. HM wrote the first draft of the article, which was commented on by all authors. GD is the guarantor of the study.

Acknowledgements: We acknowledge the huge contributions of Dr Henok Negussie and Prof Fikre Enquoselassie to the GoLBeT study. Both died before these analyses were performed.

Funding: The GoLBeT study was funded via the Joint Global Health Trials Initiative by the Wellcome Trust, the UK Medical Research Council and UK AID (MRK007211/1, WT099946/MA). This UK funded award is part of the European and Developing Countries Clinical Trials Partnership 2 programme supported by the European Union.

Competing interests: None declared.

Ethical approval: Ethical approval for GoLBeT was granted by the Institutional Review Board of the College of Health Sciences, Addis Ababa University (protocol 071/13/SPH); the National Ethical Review Committee of the Ethiopian Science and Technology Agency (approval 3-1/794/06); the Ethiopian Food, Medicine and Health Care Administration Authority (reference 02/6-1/05/39) and the Research Ethics and Governance Committee of Brighton & Sussex Medical School (approval 13/107/DAV). GoLBeT is registered in the International Standard Randomised Controlled Trials Number Register (ISRCTN76805210).

Data availability: The Dabat HDSS is available via licensed access in the INDEPTH Data repository at https://www.indepth-isshare.org/index.php/catalog/163 (reference ID INDEPTH.ET051.CMD2015.V1). Data from the GoLBeT are available to researchers under the terms of the GoLBeT Data Sharing Protocol on the public webpage of the GoLBeT (https://podo.org/research/golbet-trial).

References
1 Hotez PJ, Alvarado M, Basáñez M-G, et al. The Global Burden of Disease Study 2010: interpretation and implications for the neglected tropical diseases. PLoS Negl Trop Dis. 2014;8(7):e2865.
2 Deribe K, Tekola-Ayele F, Davey G. Podoconiosis: endemic non-filarial elephantiasis, vol. 1, 1st ed. Cham: Springer; 2016.
3 Bekele K, Deribe K, Amberbir T, et al. Burden assessment of podoconiosis in Wayu Tuka woreda, east Wollega zone, western Ethiopia: a community-based cross-sectional study. BMJ Open. 2016; 6(9):e012308.
4 Negussie H, Molla M, Ngari M, et al. Lymphoedema management to prevent acute dermatolymphangitis in podoconiosis in northern Ethiopia (GoLBeT): a pragmatic randomised controlled trial. Lancet Glob Health. 2018;6(7):e795–803.
5 INDEPTH Network. Dabat HDSS. Available from: http://www.indepth-network.org/member-centres/dabat-hdss [accessed 2 May 2020].