Tropical Medicine and International Health doi:10.1111/tmi.12120

VOLUME 18 NO 7 PP 822–829 JULY 2013

Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania

Daniel Faurholt-Jepsen[1], Nyagosya Range[2], George PrayGod[3], Kidola Jeremiah[3], Maria Faurholt-Jepsen[1], Martine G. Aabye[4], John Changalucha[3], Dirk L. Christensen[5], Harleen M. S. Grewal[6], Torben Martinussen[7], Henrik Krarup[8], Daniel R. Witte[9], Aase B. Andersen[10] and Henrik Friis[1]

1 *Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark*
2 *Muhimbili Research Centre, National Institute for Medical Research, Dar Es Salaam, Tanzania*
3 *Mwanza Research Centre, National Institute for Medical Research, Mwanza, Tanzania*
4 *Clinical Research Centre, University of Copenhagen, Hvidovre Hospital, Hvidovre, Denmark*
5 *Department of International Health, University of Copenhagen, Copenhagen, Denmark*
6 *The Gade Institute, University of Bergen, Bergen, Norway*
7 *Biostatistics and Mathematics, University of Copenhagen, Copenhagen, Denmark*
8 *Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark*
9 *Steno Diabetes Center, Gentofte, Denmark*
10 *Department of Infectious Diseases, Odense University Hospital, Odense, Denmark*

Abstract

OBJECTIVE Strong evidence suggests diabetes may be associated with tuberculosis (TB) and could influence TB treatment outcomes. We assessed the role of diabetes on sputum culture conversion and mortality among patients undergoing TB treatment.

METHODS A total of 1250 Tanzanian TB patients were followed prospectively during TB treatment with sputum culture after 2 and 5 months. Survival status was assessed at least 1 year after initiation of treatment. At baseline, all participants underwent testing for diabetes and HIV, and the serum concentration of the acute phase reactant alpha-1 glycoprotein (AGP) was determined.

RESULTS There were no differences between participants with and without diabetes regarding the proportion of positive cultures at 2 (3.8% *vs.* 5.8%) and 5 (1.3% *vs.* 0.9%) months ($P > 0.46$). However, among patients with a positive TB culture, relatively more patients with diabetes died before the 5-month follow-up. Within the initial 100 days of TB treatment, diabetes was associated with a fivefold increased risk of mortality (RR 5.09, 95% CI 2.36; 11.02, $P < 0.001$) among HIV uninfected, and a twofold increase among HIV co-infected patient (RR 2.33 95% CI 1.20; 4.53, $P = 0.012$), while diabetes was not associated with long-term mortality. Further adjustment with AGP did not change the estimates.

CONCLUSION Diabetes considerably increases risk of early mortality during TB treatment. The effect may not be explained by increased severity of TB, but could be due to impaired TB treatment response. Research is needed to clarify the mechanism and to assess whether glycaemic control improves survival.

keywords tuberculosis, diabetes, mortality, Africa, prospective cohort study

Introduction

The double burden of infectious and chronic diseases in low-income countries is becoming a global health problem. Due to the nutrition and lifestyle transition, that is, increased intake of refined sugar and fat in combination with physical inactivity (Kuhnlein & Receveur 1996; Torun *et al.* 2002; Yajnik 2004), even among the poor, those already burdened by infectious diseases are now also at risk of chronic metabolic diseases.

In 2011, around 366 million people had diabetes, of whom 4 million died of diabetes-related causes (Roglic & Unwin 2010; Whiting *et al.* 2011). By 2030, the number of people with diabetes is projected to reach 552 million (Whiting *et al.* 2011). The increase is mainly driven by changes in low- and middle-income countries, which also

harbour 95% of the global burden of TB. This is of particular concern, as there is evidence to suggest that diabetes increases the risk of TB (Jeon & Murray 2008; Young *et al.* 2009), which will further encumber already burdened TB control programmes.

Diabetes may also worsen the clinical manifestations and treatment outcomes of TB (Dooley & Chaisson 2009; Ruslami *et al.* 2010a; Baker *et al.* 2011). More specifically, a couple of studies have reported more severe manifestations of TB in people with diabetes (Wang *et al.* 2005, 2009; Restrepo *et al.* 2007; Faurholt-Jepsen *et al.* 2012) and prolonged time to TB culture conversion and cure (Güler *et al.* 2007; Dooley *et al.* 2009; Wang *et al.* 2009), which may cause more frequent recurrence of TB (Sasaki *et al.* 2003). Finally, although diabetes has been associated with increased mortality in retrospective studies (Patel *et al.* 1977; Oursler *et al.* 2002; Dooley *et al.* 2009; Wang *et al.* 2009), only one small study reports mortality data from a low-income country (Mboussa *et al.* 2003). An inherent limitation of the available studies is that TB to some extent causes stress hyperglycaemia (Başoğlu *et al.* 1999; Gearhart & Parbhoo 2006), which may affect the diagnosis of diabetes. Hence, the associations between diabetes and TB found in case–control studies, the associations between diabetes and severe clinical manifestations based on cross-sectional studies and between diabetes and poor treatment outcomes, could be affected by reverse causality.

Based on studies in Mwanza, Tanzania, we have recently reported that diabetes was strongly associated with incident TB (Faurholt-Jepsen *et al.* 2011). However, in contrast to previous studies, in this case–control study, an attempt was made to adjust for the acute phase response to reduce the significance of stress hyperglycaemia. Based on follow-up data, we now present data on the role of diabetes on treatment outcome (i.e. sputum culture conversion and mortality) among patients undergoing TB treatment.

Methods

Subjects and study design

Newly diagnosed pulmonary TB patients from Mwanza, Tanzania, were invited to participate in the study during from April 2006 to October 2008. Patients below 15 years of age, pregnant or lactating women, patients terminally ill from TB or HIV (judged unlikely to survive >48 h), patients suffering from other severe diseases and non-residents of Mwanza City were excluded. The study was nested in the framework of two larger nutritional intervention studies (PrayGod *et al.* 2011, 2012).

All participants were followed up for treatment outcome at 2 and 5 months (i.e. culture conversion) and for survival status at least 1 year after TB treatment started. Trained research personnel used tracing information provided at recruitment to locate the participants. The survival information was collected using a structured questionnaire on survival status, including information on recurrence of TB within the first year after TB treatment. If the participant had experienced recurrence of TB, the information was confirmed using the patient records from the TB health facilities. Of those confirmed to be dead (all-cause mortality), data on date and place of death were obtained. Moreover, mortality information was ascertained using either a death certificate or any other official document. If the survival information could not be obtained, the date of last known contact was used. Diabetes and HIV testing were not repeated; thus, the baseline diagnosis was used at all time points.

Measurements

Sputum smear microscopy was performed at the recruiting health facility and at the Zonal TB Reference Laboratory at Bugando Medical Centre. Using the spot-morning-spot procedure (IUATLD 2000), the smears were graded according to the presence of acid fast bacilli (AFB) as either negative (no AFB) or positive: 1–9 in 100 fields, 1+ (10–99 AFB in 100 fields), 2+ (1–10 AFB pr. field in >50 fields) or 3+ (>10 pr. field in >20 fields). Additionally, early morning sputum samples were collected in a sterile universal bottle for culture of *Mycobacterium tuberculosis* on Lowenstein Jensen solid media and graded as either negative (no growth of colonies) or positive: 1–19 colonies, 1+ (20–100 colonies), 2+ (innumerable discrete colonies) or 3+ (confluent growth). A positive test result was defined as sputum positive pulmonary TB (PTB+), and the final TB diagnosis relied on culture status; microscopy results were only used if the culture result was missing. However, the diagnosis sputum smear negative pulmonary TB (PTB−) was used for patients with a negative sputum result, but with clinical suspicion of TB, patient history, lack of clinical improvement after treatment with a broad spectrum antibiotic and chest X-ray suggestive of TB based on the WHO guidelines available when the study was conducted (WHO).

Sputum for culture was collected again after 2 months from those with a baseline PTB+ diagnosis, and similarly, a retest was carried out after 5 months. The grading of the culture at 2 and 5 months was identical to the baseline procedure.

HIV diagnosis was based on two rapid tests: *Determine HIV* 1/2 (Inverness Medical Innovations, Inc., Delaware,

DE, USA) and *Capillus HIV-1/HIV-2* (Trinity Biotech Plc., Wicklow Ireland). Samples with discordant results on the two rapid tests were retested by 3rd generation Vironostika HIV Uniform II plus O (Biomeriux, Boxtel, the Netherlands) at the NIMR, Mwanza laboratories.

Fasting blood glucose (FBG) was determined on capillary whole blood using point-of-care diagnostic instruments (HemoCue Glucose System 201+, HemoCue, Sweden). As the FBG in TB participants might be affected by the infection (non-diabetes stress hyperglycaemia; Başoğlu *et al.* 1999; Gearhart & Parbhoo 2006), the indication for offering a standard 75 g 2-h oral glucose tolerance test (OGTT) was expanded from the commonly used FBG 5.6–6.0 mM to 5.1–11.0 mM. Final diabetes diagnosis was based on either a FBG > 6.0 mM or a 2 h blood glucose > 11.0 mM (WHO 2006). The diabetes diagnosis was obtained after the TB diagnostics, and thus, the TB diagnosis was independent from the diabetes status. Participants already known to have diabetes were only classified as such in the study if the diagnosis could be reproduced by our methods.

Statistical analysis

Data were double entered, and all statistical analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA). The chi-square-test was used to test for differences in the distribution of TB culture grading as well as sputum culture conversion stratified by diabetes status. We used Kaplan–Meier plot to present the time-to-death data. Cox proportional hazards analysis was used to assess predictors of mortality in a multivariate analysis (Table 3, model 1) including status of diabetes (diabetes *vs.* non-diabetes), TB culture status (PTB− *vs.* PTB+) and HIV (HIV infected *vs.* HIV uninfected) and further adjusted for body mass index, sex and age (centred on the median age, 34 years) (model 2). The proportional hazards assumption was uncertain with regard to the diabetes variable; the score process test (Lin *et al.* 1993) was significant with $P = 0.02$, thus rejecting the Cox model. We therefore allowed the effect of this variable to change after an initial period of 100 days, and this revised model was accepted.

Ethics statement

Ethical permission was obtained from the Medical Research Coordinating committee of the National Institute for Medical Research (NIMR) in Tanzania, and consultative approval was given by The Danish National Committee on Biomedical Research Ethics. Written and oral information was presented to all eligible participants by the health staff before written informed consent was obtained. Written consent was obtained from parents/legal guardians of any participants under 18 years of age. Counselling prior to HIV testing was compulsory, and post-test counselling was offered to all who tested HIV positive. Participants with diagnosed HIV and/or diabetes were referred to the respective clinics for care and management.

Results

Of the 1250 TB patients recruited for the nutritional intervention studies, 40.8% ($n = 510$) were women, mean (SD) age was 36.5 years (12.9), 50.6% ($n = 633$) were HIV co-infected, and 16.4% ($n = 197$) were diagnosed with diabetes as previously reported (Faurholt-Jepsen *et al.* 2011; PrayGod *et al.* 2011, 2012). Background characteristics are shown in Table 1.

Of 1102 (88.2%) patients with diabetes and TB culture data available, 735 (66.7%) had positive sputum cultures at baseline. Among these PTB+ patients, 5.5% and 1.0% continued to be culture positive after 2 and 5 months of TB treatment, respectively. There were no differences between participants with and without diabetes regarding the proportion and intensity of positive cultures at any

Table 1 Background characteristics of 1250 patients with pulmonary tuberculosis (TB)

Age, years [mean (SD)]	36.5 (12.9)
Female sex	510 (40.8)
Ethnic group	
Msukuma tribe	570 (45.6)
Other tribes	679 (54.4)
Marital status	
Single	308 (24.8)
Married/cohabiting	658 (53.1)
Separated/divorced/widow	274 (22.1)
Occupation	
Farmer/Fisherman	488 (39.1)
Businessman/Employed	450 (36.1)
Housewife	146 (11.7)
Unemployed	62 (5.0)
Other	101 (8.1)
Religion	
Christian	931 (74.5)
Muslim	268 (21.5)
Other	50 (4.0)
Alpha-1 glycoprotein, g/l [mean (SD)]	2.4 (0.9)
TB status	
Sputum negative pulmonary TB (PTB−)	427 (34.2)
Sputum positive pulmonary TB (PTB+)	823 (65.8)
HIV infected	633 (50.6)
Diabetes*	197 (16.4)

Data are *n* (%) unless otherwise indicated.
*Diabetes data were available for 1205 (96.4%) participants.

time point (Table 2). However, among those with a positive culture at baseline, 10 and 19 patients with or without diabetes, respectively, had died before the 5-months follow-up visit. Thus, if these deaths were due to treatment failure and considered culture positive at 5 months, then the proportion of TB patients with a positive culture at 5 months would have been higher among those with diabetes comorbidity (12.6% *vs.* 5.0%. $P = 0.01$). Participants with diabetes more often had missing culture data – due to either missing sample or contamination – at both 2 (26.9% *vs.* 18.9%, $P = 0.010$) and 5 months (28.4% *vs.* 20.7%, $P = 0.203$).

Complete survival data up to at least 12 months were available for 1239 (99.1%) participants and were included in the mortality analyses. Median (interquartile range) follow-up time was 647 (492–833) days, and 172 (13.9%) died within the study period. Half of the study participants died in hospital, the other half died at home. Of the 172 (13.9%) deaths, 39 (3.1%) occurred within the first 60 days, 64 (5.2%) within 100 and 138 (11.1%) within 365 days. Within the first 60 days, 10 of 39 (25.6%) patients reported that the deceased had unknown diabetes status. Among the 1205 with available diabetes data, the proportion of deaths involving a patient with diabetes was 41.4, 34.0, and 24.4% after 60, 100 and 365 days, respectively.

Table 2 Tuberculosis culture grading and conversion among 735 tuberculosis (TB) patients with available baseline diabetes and TB culture data stratified by diabetes status

	Patients without diabetes ($n = 617$)	Patients with diabetes ($n = 118$)	P
Baseline TB culture grading, *n* (column%)			
+1 (incl. 1–19 colonies)	103 (16.7)	26 (22.0)	0.373
+2	87 (14.1)	15 (12.7)	
+3	427 (69.2)	77 (65.3)	
Follow-up TB culture grading, *n* (column%)			
2 months*			
Negative	436 (94.2)	76 (96.2)	0.465
Total positive TB culture (non-conversion)	27 (5.8)	3 (3.8)	
+1 (incl. 1–19 colonies)	25 (5.4)	1 (1.3)	
+2	0 (0.0)	0 (0.0)	
+3	2 (0.4)	2 (2.5)	
5 months†			
Negative	440 (99.1)	76 (98.7)	0.741
Total positive TB culture (non-conversion)	4 (0.9)	1 (1.3)	
+1 (incl. 1–19 colonies)	0 (0.0)	0 (0.0)	
+2	1 (0.2)	0 (0.0)	
+3	3 (0.7)	1 (1.3)	

Data are based on chi-square test, *n* (column%).
*Culture data available for 542 patients (73.7%) and 39 patients (5.3%) had died.
†Culture data available for 521 patients (70.9%) and 90 patients (12.2%) had died.

In univariate Cox proportional hazards analysis, diabetes did not seem to be associated with mortality (crude RR 1.35, 95% CI 0.91; 2.00, $P = 0.14$), but this was due to a time-dependant association (score process test, $P = 0.02$) with excess mortality risk exclusively within the initial 100 days of treatment (crude RR 2.70, 95% CI 1.53; 4.77, $P = 0.001$). After the initial 100 days, diabetes was not associated with excess mortality (RR 0.80, 95% CI 0.45; 1.43, $P = 0.45$). Furthermore, PTB– compared to PTB+ (crude RR 2.47, 95% CI 1.83; 3.33, $P < 0.001$) and HIV infected compared to HIV uninfected (crude RR 3.04, 95% CI 2.16; 4.29, $P < 0.001$) were associated with mortality.

The association between major morbidities (i.e. diabetes, TB, HIV) and risk of mortality was assessed in (i) a Kaplan–Meier survivor function (Figure 1, diabetes and HIV only), (ii) in a multivariate Cox proportional hazards analysis (Table 3, model 1), and (iii) in a multivariate analysis further adjusted for age (centred on the median, 34 years) and sex (Table 3, model 2). There was an interaction between diabetes and HIV (model 1: $P = 0.02$; model 2: $P = 0.07$), which was due to a higher diabetes-associated risk of mortality among HIV uninfected, and, similarly, the highest HIV-associated risk of mortality among non-diabetes participants. In the adjusted model (model 2), diabetes was associated with a fivefold increased risk of mortality (RR 5.09, 95% CI

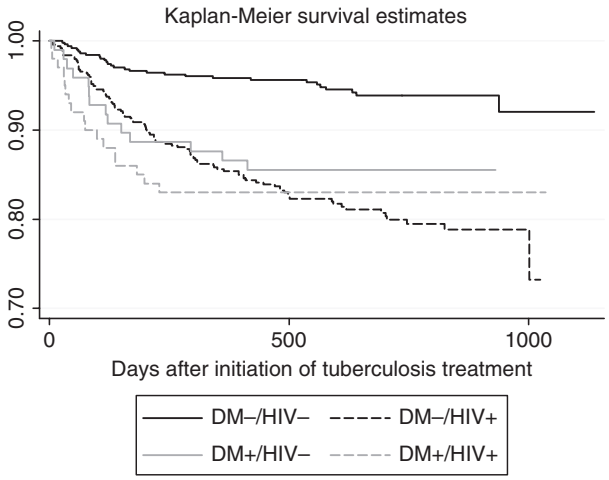

Figure 1 Mortality among 1239 pulmonary tuberculosis patients with and without diabetes and HIV. TB, tuberculosis; DM-, non-diabetes; DM+, diabetes; HIV-, HIV uninfected; HIV+, HIV infected.

Table 3 Relative risk for death during tuberculosis treatment among 1239 patients with pulmonary tuberculosis (TB)

	Model 1*			Model 2†			Model 3‡		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Diabetes (<100 days)§									
HIV negative	5.48	2.56; 11.72	<0.001	5.09	2.36; 11.02	<0.001	4.95	2.28; 10.76	<0.001
HIV positive	1.95	1.01; 3.76	0.048	2.33	1.20; 4.53	0.012	2.18	1.11; 4.41	0.024
Diabetes (>100 days)§									
HIV negative	1.60	0.74; 3.45	0.229	1.37	0.62; 3.06	0.435	1.41	0.64; 3.13	0.396
HIV positive	0.59	0.29; 1.11	0.100	0.63	0.32; 1.25	0.187	0.62	0.31; 1.24	0.180
HIV									
Non-diabetes	3.14	2.06; 4.79	<0.001	4.86	2.93; 8.05	<0.001	4.86	2.93; 8.06	<0.001
Diabetes	1.12	0.55; 2.27	0.762	2.23	1.01; 4.90	0.046	2.14	0.97; 4.76	0.061
Tuberculosis culture status									
Culture positive (PTB+)	Ref.	–; –	–	–	–; –	–	Ref.	–; –	–
Culture negative (PTB−)	1.88	1.36; 2.58	<0.001	2.02	1.44; 2.82	<0.001	1.91	1.33; 2.77	0.001

*Multivariate Cox proportional hazards analysis with diabetes, HIV and culture negative pulmonary tuberculosis as predictors (Interaction: HIV–diabetes, $P = 0.02$).
†Multivariate Cox proportional hazards analysis further adjusted for age, sex and body mass index (Interactions: HIV–diabetes $P = 0.07$, HIV-age $P < 0.001$). The model is centred on the median age (34 years).
‡Multivariate Cox proportional hazards analysis further adjusted for alpha-1 glycoprotein (Interactions: HIV–diabetes $P = 0.06$, HIV-age $P < 0.001$). The model is centred on the median age (34 years).
§The diabetes risk is time dependent; the score process test was significant with $P = 0.02$. Diabetes data were available for 1195 (96.4%) participants.

2.36; 11.02, $P < 0.001$) among HIV uninfected and within the initial 100 days of treatment. Diabetes was also associated with mortality in HIV infected individuals during the first 100 days, but not later. PTB− was associated with a twofold increased mortality risk compared to PTB+. Due to an interaction between age and HIV ($P < 0.001$), the model was centred on the median age (34 years). Thus, the HIV-associated mortality risk of RR 2.23 (95% CI 1.01; 4.90, $P = 0.046$) and 4.86 (95% CI 2.93; 8.05, $P < 0.001$) among participants with and without diabetes, respectively, reflects the risk for participants aged 34 years. Further, adjustment with AGP did not affect the estimates (model 3).

The analysis used in model 2 also revealed that men had a 53% higher mortality risk compared to women (RR 1.53, 95% CI 1.09; 2.16, $P = 0.015$). The role of the nutritional intervention was tested in a stratified analysis, but had no effect on the risk of mortality or any of the other covariates and was therefore not included in the final model. Also, treatment with ART known to cause metabolic changes (Carr *et al.* 1999) did not alter the estimates of the Cox regression (data not shown).

Discussion

We have recently reported that diabetes is strongly associated with risk of pulmonary TB in Tanzania, and here, we show that diabetes is highly associated with mortality during the first 100 days of TB treatment. The main methodological issue in this and other studies on the role of diabetes in relation to risk of TB, severity of manifestations, treatment outcomes and survival is that often diabetes status is assessed after development and diagnosis of TB disease. The acute phase response caused by serious infections comprises hyperglycaemia (Başoğlu *et al.* 1999; Gearhart & Parbhoo 2006). It is therefore possible that some of the pulmonary TB patients with blood glucose values suggestive of diabetes (Alberti *et al.* 1998) have non-diabetes stress-induced hyperglycaemia rather than diabetes. Therefore, estimates of the associations between diabetes and risk of TB, severity of TB, treatment outcomes and mortality may be affected by reverse causality, that is, that pulmonary TB causes non-diabetes stress hyperglycaemia misclassified as diabetes. Recently, a systematic review reported decreasing levels of hyperglycaemia during TB treatment (Jeon *et al.* 2010), indicating the existence of stress hyperglycaemia at the start of TB treatment. Therefore, we measured serum concentrations of the acute phase reactant AGP and adjusted the survival analysis for elevated levels to see whether the diabetes-associated mortality was simply due to a higher inflammatory response. However, this adjustment had no effect on any of the mortality estimates.

If TB patients with more severe disease, accompanied by an acute phase response that leads to stress hyperglycaemia, are incorrectly diagnosed with diabetes, this leads to an overestimation of the true association between diabetes and mortality. In this situation, adjustment for elevated AGP is intended to reduce the significance of this reverse causality. If diabetes disease leads to more severe TB, which is accompanied by an acute phase response and cause mortality, then adjustment for elevated AGP is expected to remove or reduce the estimate of a true causal association between diabetes and mortality. However, after the adjustments, we still found that a diagnosis of diabetes was associated with increased risk of dying. This suggests that the association found is neither due to reverse causality nor more advanced TB disease. Thus, the current data do not explain why diabetes comorbidity was a major risk factor for mortality within the early phase of treatment and why diabetes was not a long-term risk factor.

We recently reported that diabetes had little, and possibly no clinical relevant, impact on the clinical presentation of TB, when the patients were enrolled in the study (Faurholt-Jepsen *et al.* 2012). Despite few baseline effects, our findings reflect that diabetes has a negative effect on treatment outcome. Also, our analyses suggest that treatment failure attributable to diabetes might mediate an effect of diabetes on mortality. In fact, several studies have reported that pulmonary TB patients with diabetes had more advanced TB disease than patients without diabetes and that diabetes was associated with delayed sputum conversion and reduced cure rate (Wang *et al.* 2005, 2009; Alisjahbana *et al.* 2007; Restrepo *et al.* 2007). Indeed, the latter could be explained by an effect of diabetes on absorption and metabolism of TB drugs, as a study from Indonesia found lower plasma levels of rifampicin in TB patients with diabetes during the continuation phase of treatment (Nijland *et al.* 2006). The effect on absorption could possibly be mediated through increased body weight and differences in hepatic induction. However, the study found no indication of a diabetes-associated rifampicin difference during the initial phase of TB treatment (Ruslami *et al.* 2010b). In our study, those with a diagnosis of diabetes had only slightly elevated serum acute phase reactants and neutrophil counts (Faurholt-Jepsen *et al.* 2012), but due to the high early mortality rate before the 2-month follow-up among patients with diabetes, it is possible that there was a larger proportion of non-converters in this group. From a study in Maryland, USA, it was reported that diabetes delayed time to conversion from 39 to 49 days, but with similar conversion rates after 60 days (Dooley *et al.* 2009). Also, in an Indonesian study, diabetes was associated with a positive culture at the end of treatment (Alisjahbana *et al.* 2007). As we did not follow sputum conversion during the intensive phase (<60 days), we cannot exclude the possibility that the apparent effect of diabetes on mortality was explained by early impairment of the treatment effect. Besides, while one of six patients was diagnosed with diabetes at baseline, almost half of the deaths occurring during the first 60 days involved a patient with diabetes. Thus, it is possible that death among those with diabetes was due to treatment failure. Furthermore, the diabetes status of 10 patients dying in this period was unknown, and we can only speculate whether diabetes was involved in these deaths.

There are divergent data on the role of diabetes on TB mortality, and few data are available from low-income countries (Baker *et al.* 2011), which harbour the largest burden of TB. Two studies from Indonesia and Saudi Arabia found no differences in mortality risk among TB patients with or without diabetes (Singla *et al.* 2006; Alisjahbana *et al.* 2007), whereas three smaller, retrospective studies, two from the USA and one from Taiwan, reported increased mortality risk among patients with diabetes (Oursler *et al.* 2002; Dooley *et al.* 2009; Wang *et al.* 2009). The study from Indonesia (Alisjahbana *et al.* 2007), a lower-middle-income country, was the only available prospective study and used similar methods, but based their diabetes diagnosis solely on FBG and excluded all patients with impaired fasting glycaemia. However, the study had very little mortality, and this was not associated with diabetes (Alisjahbana *et al.* 2007). As in our study, they did not find baseline differences on bacteriological examination between patients with or without diabetes, but diabetes comorbidity was associated with a higher treatment failure (not cured) at the end of treatment. Despite more severe TB among those with diabetes, only two deaths were reported from the study at the end of treatment, both of which had diabetes comorbidity.

The remaining four studies were all retrospective, with the largest study reporting no effect of diabetes on mortality among TB inpatients (Singla *et al.* 2006). In one study from Maryland, USA, the overall reported mortality was 9% with the odds of death twice as high among TB patients with diabetes and with increasing risk after adjustment for HIV status (Dooley *et al.* 2009). The patients were considered to have diabetes, if they had a history of elevated random non-fasting samples or from medical records; thus, the diagnosis was not obtained during the study. Also from another TB population from Maryland the reported deaths were 21% with the risk of mortality being almost seven times higher among patients with diabetes (Oursler *et al.* 2002). However, there is no

indication of how the diabetes diagnosis was obtained, whether the patients were treated or suffered from insulin-dependent diabetes (type I). Also, it is surprising that the mortality in general was very high in the US studies, but the reason for this remains unclear. Finally, in a retrospective study from Taiwan with 217 in- and outpatients without HIV comorbidity, 11.1% were reported dead with the odds of dying being more than seven times higher among patients with diabetes comorbidity (Wang *et al.* 2009). The diabetes diagnosis was based on historical records or FBG suggestive of diabetes, whereas patients who did not have elevated FBG were chosen as controls. None of the previous studies have reported a time-dependent mortality risk among patients with diabetes comorbidity. If diabetes in general is associated with early TB mortality, timing of the diabetes diagnosis as well as subsequent treatment may be essential for survival. By splitting the data at 100 days, it seems as if this period is the most vulnerable for the TB patients. We also tested the data by splitting at 60 and 80 days, which similarly was accepted by the model (not shown), but we chose reporting the effect as we did to ensure future interventions based on data like ours would not end prematurely.

Ideally, patients with a test result compatible with diabetes should have a confirmatory diabetes test, after the acute phase response has faded. If confirmed, then lifestyle changes or medical intervention could be introduced. However, if indeed diabetes increases early mortality, then there is a need for diagnostic tools to distinguish between stress hyperglycaemia and diabetes and for studies to determine the effects of glycaemic control among diabetics during TB treatment.

In most low-income settings, people do not know whether they have diabetes or not. If diabetes (or hyperglycaemia) is associated with excess mortality, a routine glucose screening at the TB clinics may be necessary to identify those at increased risk of death due to diabetes. As we missed the blood glucose screening in 10 of 39 deaths in the first 60 days, it may be necessary to improve the timing and give the blood glucose test high priority immediately after TB diagnosis. In addition to the identification of patients at risk, it is equally important to improve the management of such patients; better supervision of TB treatment and more frequent routine visits during the initial treatment phase could be one approach, whereas a medical intervention to normalise the blood glucose levels should be tested under safe conditions. The use of intensive insulin therapy to control hyperglycaemia in severe illness has proven difficult to manage (Griesdale *et al.* 2009) and may not even be feasible in a resource poor setting.

Conclusion

Diabetes considerably increases the risk of dying during TB treatment, and this effect is not explained by greater severity of TB disease at the start of treatment. As there is evidence to suggest that diabetes also increases the risk of developing TB, the ongoing diabetes epidemic is a major threat to TB control programmes. While prevention of diabetes is crucial, it is also important to identify TB patients at risk of diabetes comorbidity to improve care and possibly reduce morbidity and mortality.

Acknowledgements

We thank all health service providers at the TB clinics and study participants involved in the study. The study was supported by the Danish Council for Independent Research, by Danida and by the University of Copenhagen. The funding bodies had no role in the study design, data collection, data analysis, data interpretation or decision to publish the findings.

References

Alberti KGMM, Zimmet PZ & Consultation WHO (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. *Diabetic Medicine* **15**, 539–553.

Alisjahbana B, Sahiratmadja E, Nelwan EJ *et al.* (2007) The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. *Clinical Infectious Diseases* **45**, 428–435.

Baker MA, Harries AD, Jeon CY *et al.* (2011) The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Medicine* **9**, 81.

Başoğlu OK, Bacakoğlu F, Cok G, Sayiner A & Ateş M (1999) The oral glucose tolerance test in patients with respiratory infections. *Monaldi Archives for Chest Disease* **54**, 307–310.

Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ & Cooper DA (1999) Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: acohort study. *The Lancet* **353**, 2093–2099.

Dooley KE & Chaisson RE (2009) Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious Diseases* **9**, 737–746.

Dooley KE, Tang T, Golub JE, Dorman SE & Cronin W (2009) Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *American Journal of Tropical Medicine and Hygiene* **80**, 634–639.

Faurholt-Jepsen D, Range N, PrayGod G *et al.* (2011) Diabetes is a risk factor for pulmonary tuberculosis: a case–control study from Mwanza, Tanzania. *PLoS ONE* **6**, e24215.

Faurholt-Jepsen D, Range N, PrayGod G *et al.* (2012) The role of diabetes on the clinical manifestations of pulmonary

tuberculosis. *Tropical Medicine & International Health* **17**, 877–883.

Gearhart MM & Parbhoo SK (2006) Hyperglycemia in the critically ill patient. *AACN Clinical Issues* **17**, 50–55.

Griesdale DEG, De Souza RJ, Van Dam RM *et al.* (2009) Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *Canadian Medical Association Journal* **180**, 821–827.

Güler M, Ünsal E, Dursun B, AydIn Ö Capan N (2007) Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. *International Journal of Clinical Practice* **61**, 231–235.

IUATLD (2000) Technical Guide: Sputum Examination for Tuberculosis by Direct Microscopy in Low Income Countries, 5th edn. International Union Against Tuberculosis and Lung Disease (IUATLD), Paris.

Jeon CY & Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Medicine* **5**, e152.

Jeon CY, Harries AD, Baker MA *et al.* (2010) Bi-directional screening for tuberculosis and diabetes: a systematic review. *Tropical Medicine and International Health* **15**, 1300–1314.

Kuhnlein H & Receveur O (1996) Dietary change and traditional food systems of indigenous peoples. *Annual Review of Nutrition* **16**, 417–442.

Lin DY, Wei LJ & Ying Z (1993) Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* **80**, 557–572.

Mboussa J, Monabeka H, Kombo M, Yokolo D, Yoka-Mbio A & Yala F (2003) Evolution de la tuberculose pulmonaire chez les diabétiques. *Revue de Pneumologie Clinique* **59**, 39–44.

Nijland HMJ, Ruslami R, Stalenhoef JE *et al.* (2006) Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clinical Infectious Diseases* **43**, 848–854.

Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS & Chaisson RE (2002) Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. *Clinical Infectious Diseases* **34**, 752–759.

Patel J, De Souza C & Jigjini S (1977) Diabetes and tuberculosis. *Indian Journal of Tuberculosis* **24**, 155–158.

PrayGod G, Range N, Faurholt-Jepsen D *et al.* (2011) Daily multi-micronutrient supplementation during tuberculosis treatment increases weight and grip strength among HIV-uninfected but not HIV-infected patients in Mwanza, Tanzania. *The Journal of Nutrition* **141**, 685–691.

PrayGod G, Range N, Faurholt-Jepsen D *et al.* (2012) The effect of energy-protein supplementation on weight, body composition and handgrip strength among pulmonary tuberculosis HIV-co-infected patients: randomised controlled trial in Mwanza, Tanzania. *British Journal of Nutrition* **107**, 1–9.

Restrepo BI, Fisher-Hoch SP, Crespo JG *et al.* (2007) Type 2 diabetes and tuberculosis in a dynamic bi-national border population. *Epidemiology and Infection* **135**, 483–491.

Roglic G & Unwin N (2010) Mortality attributable to diabetes: estimates for the year 2010. *Diabetes Research and Clinical Practice* **87**, 15–19.

Ruslami R, Aarnoutse RE, Alisjahbana B, Van Der Ven AJAM & Van Crevel R (2010a) Implications of the global increase of diabetes for tuberculosis control and patient care. *Tropical Medicine and International Health* **15**, 1289–1299.

Ruslami R, Nijland HMJ, Adhiarta IGN *et al.* (2010b) Pharmacokinetics of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. *Antimicrobial Agents and Chemotherapy* **54**, 1068–1074.

Sasaki Y, Yamagishi F, Yagi T *et al.* (2003) A study on pulmonary tuberculosis retreatment cases. *Kekkaku* **78**, 723–732.

Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA & Osman MM (2006) Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *International Journal of Tuberculosis and Lung Disease* **10**, 74–79.

Torun B, Stein AD, Schroeder D *et al.* (2002) Rural-to-urban migration and cardiovascular disease risk factors in young Guatemalan adults. *International Journal of Epidemiology* **31**, 218–226.

Wang JY, Lee LN & Hsueh PR (2005) Factors changing the manifestation of pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* **9**, 777–783.

Wang CS, Yang CJ, Chen HC *et al.* (2009) Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiology and Infection* **137**, 203–210.

Whiting DR, Guariguata L, Weil C & Shaw J (2011) IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice* **94**, 311–321.

WHO(2006) Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. Geneva, Switzerland: http://www.who.int/diabetes/publications/en/ (Accessed 12 March 2009).

WHO. Treatment of Tuberculosis: guidelines for national programmes. http://www.who.int/tb/publications/tb_treatment-guidelines/en/index.html (Accessed 12 August 2012).

Yajnik CS (2004) Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *Journal of Nutrition* **134**, 205–210.

Young F, Critchley JA, Johnstone LK & Unwin NC (2009) A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization. *Globalization and Health* **5**, 9.

Corresponding Author Daniel Faurholt-Jepsen, Department of Nutrition, Exercise and Sports, University of Copenhagen, Rolighedsvej 30, 1958 Frederiksberg C, Denmark. Tel.: +45 26 74 12 42; E-mail: daniel@faurholt-jepsen.com