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Original article

Diabetes mellitus and risk of all-cause mortality among patients with tuberculosis in the state of Georgia, 2009–2012

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ABSTRACT

Purpose: To estimate the association between diabetes mellitus (DM) and all-cause mortality during tuberculosis (TB) treatment.
Methods: From 2009 to 2012, a retrospective cohort study among reported TB cases in Georgia was conducted. Patients aged 16 years or older were classified by DM and human immunodeficiency virus (HIV) status at the time of TB diagnosis and followed during TB treatment to assess mortality. Hazard ratios were used to estimate the association between DM and death.
Results: Among 1325 patients with TB disease, 151 (11.4%) had DM, 147 (11.1%) were HIV-infected, and seven (0.5%) had both DM and HIV. Patients with TB-DM were more likely to have cavitary lung disease compared with those with TB alone (51.0% vs. 34.7%) and those with TB-HIV were more likely to have military/disseminated disease (12.9% vs. 3.4%) and resistance to rifampin or isoniazid (21.8% vs. 9.0%) compared with those without HIV infection ($P < .05$). In multivariable analysis, DM was not associated with death during TB treatment (hazard ratio, 1.22; 95% confidence interval, 0.70–2.12) or any death (adjusted odds ratio, 1.05; 95% confidence interval, 0.60–1.84).
Conclusions: Among TB patients in Georgia, the prevalence of comorbid DM and coinfection with HIV was nearly identical. In adjusted models, TB patients with DM did not have increased risk of all-cause mortality.

Introduction

The incidence of active tuberculosis (TB) disease in the United States has steadily declined during the past 2 decades from 26,673 reported TB cases (10.4 per 100,000) in 1992 to 9951 reported cases (3.2 cases per 100,000) in 2012 [1]. Mortality among patients with TB in the United States has also decreased. In 1992, the TB-related mortality rate was 0.7 per 100,000 and by 2011 had decreased to 0.2 per 100,000 [2]. Despite these decreases, subgroups of patients with TB remain at higher risk of death. Increased mortality has consistently been reported among those with multidrug-resistant TB [3–5], human immunodeficiency virus (HIV) coinfection [6,7], extrapulmonary TB [8,9], substance abuse [10,11], and concurrent chronic noncommunicable diseases [12,13]. Diabetes mellitus (DM), a noncommunicable disease with a rapidly expanding prevalence in the United States [14], has been estimated to increase the risk of active TB disease approximately 3-fold [15] and may impact TB-related mortality [16]. A 2011 meta-analysis estimated that mortality was more likely among patients with TB and DM (TB-DM) compared with those without DM (unadjusted risk ratio [RR], 1.89; 95% confidence interval [CI], 1.53–2.36) [17].

Although the prevalence of DM among newly diagnosed patients with TB in the United States is not well quantified, a few regional studies have reported DM prevalence between 14% and 28% among U.S. adults with TB [18–20]. The impact of DM on TB-related mortality is incompletely understood and prior studies have generally not assessed the effect of DM on TB mortality in the United States. The primary objectives of this study were: (1) to compare the demographic and clinical presentation characteristics of adult patients with TB and DM, TB and HIV, and TB without HIV or DM and (2) to estimate the association between DM and time until death during TB treatment. A secondary

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objective was to estimate the association between (1) DM and (2) HIV with any death (before or during TB treatment) among patients with TB.

Methods

Setting and participants

All TB cases reported between January 2009 and September 2012 in the state of Georgia, US, were included in this retrospective cohort study. In Georgia, all health care providers and laboratories are required by law to report clinical and laboratory confirmed TB cases to the Georgia Department of Public Health department [21]. Eligible study patients included all patients with pulmonary or extrapulmonary TB (diagnosed by positive culture or a combination of compatible clinical symptoms, radiological findings, and/or response to empiric therapy) aged 16 years or older reported to the Georgia state registry during the study period. TB cases were followed during TB treatment until the date of therapy completion, death, loss to follow-up, or until March 2013, whichever occurred first.

Study measures and data collection

The Georgia Department of Public Health verified reported TB cases, monitored patients on directly observed therapy, and was responsible for systematic collection of all patient information. Standardized TB reporting forms documented TB diagnosis, patient demographic and clinical characteristics, and treatment outcomes. All data were entered into the State Electronic Notifiable Disease Surveillance System (SendSS), a secure web-based software tool.

The primary study outcome was time until death, measured among patients who died from any cause during TB treatment. Patients with a date of death (determined from SendSS) before TB treatment completion date were defined as a death during TB treatment. Time to death was calculated as the number of days between TB treatment start and death date. Patients who died before initiating TB treatment were defined as death before TB treatment. Any death included patients that died during TB treatment or before TB treatment initiation.

The primary exposures of interest in this study were DM and HIV status. Medical records were reviewed to determine DM status. All patients were asked if they had ever been diagnosed with DM, patients who self-reported having DM were categorized as DM patients. Patients were not systematically screened for DM but had blood chemistry tests (including glucose) performed at the time of TB diagnosis and treatment initiation. Standard state TB protocols included offering all TB patients HIV screening with an enzyme-linked immunosorbent assay test; positive enzyme-linked immunosorbent assay was confirmed by Western blot. Patients with missing HIV results were classified as HIV negative.

Additional patient covariates of interest measured by interview in the cohort included demographic information, sociobehavioral characteristics, comorbidities, and clinical features. Multidrug-resistant TB was defined as resistance to both rifampin and isoniazid. Occupation, country of birth, history of homelessness, incarceration history, alcohol use in the past year, and drug use (injection or noninjection) were self-reported during patient interviews conducted by health care providers. End-stage renal disease (ESRD) was determined from medical records and patient medical records. Sputum acid fast bacilli (AFB) smear status, AFB culture for *Mycobacterium tuberculosis*, history of TB, tuberculin skin test result, chest radiograph findings (e.g., presence of lung cavity or miliary TB), and TB drug susceptibility information was abstracted SendSS.

Data analyses

Data analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). The association between patient characteristics with TB-DM, TB-HIV, and TB only was analyzed using bivariate analyses. We used χ^2 tests to calculate values of P for categorical variables, analysis of variance procedures to compare differences in normally distributed continuous variables (means), and Kruskal-Wallis test for comparison of nonnormally distributed variables (medians). A two-sided value of P less than .05 was considered statistically significant throughout the analyses. Cox proportional hazards regression models were used to estimate the hazard rate ratios and 95% CIs for time to mortality during TB treatment. Patients were censored at the time of treatment completion or last documented clinical visit date if death did not occur on or before either date of completion or last visit date. Proportional hazard assumptions were assessed graphically (log negative log curves), with goodness-of-fit tests (Schoenfeld residuals), and using time-dependent models [22]. Logistic regression models were used to estimate the odds ratio and 95% CI for the outcomes (1) death before TB treatment initiation and (2) any death (before or during TB treatment). Separate regression models and covariate selection strategies were created for estimates of the two primary exposures: (1) DM status and (2) HIV status. Selected covariates, considered to be known confounders were included in Cox and logistic regression models based on bivariate associations or biologic plausibility with the primary exposures and outcomes, previous literature, or directed acyclic graph theory [23]. Statistical interaction was assessed between the primary exposures of interest and all covariates included in the final Cox model.

Ethical approval

The study was approved by the Institutional Review Boards of Emory University and Georgia Department of Health.

Results

A total of 1428 patients with TB were reported to the state of Georgia during the study period. After excluding patients younger than 16 years ($n = 103$), 1325 were included in baseline analyses. A total of 1238 (93.4%) were included in longitudinal analyses, after excluding patients who died before TB treatment initiation ($n = 34$) or who had no TB treatment follow-up information ($n = 53$).

Among the 1325 patients with TB included in the study, 151 (11.4%) had DM, 147 patients had HIV (11.1%), and seven (0.5%) patients had both DM and HIV. Most patients were male (66.5%) and U.S. born (54.6%); the most common race/ethnicity was non-Hispanic black (48.2%) and the median age was 45 years (Table 1). Compared with patients with TB only (no DM or HIV), TB-DM patients had higher prevalence of ESRD (6.6% vs. 1.6%) but were less likely to be diagnosed in a correctional facility (2.0% vs. 9.4%) ($P < .01$). Patients with TB and HIV were more likely to report heavy alcohol use (25.2% vs. 14.5%), drug use (28.0% vs. 7.7%), and recent homelessness (29.2% vs. 7.1%) than TB only patients ($P < .01$) (Table 1).

Clinical TB characteristics at baseline differed among TB-DM patients, TB-HIV patients, and TB only patients (Table 1). TB-DM patients were more likely to have cavitary lung disease at time of TB diagnosis (51%) compared with patients with TB-HIV (19.9%) and TB only (34.7%) ($P < .01$). Patients with TB-DM were more likely to be sputum AFB smear positive (52.5%) compared with patients with TB-HIV coinfection (43.7%) and those with TB only (41.4%) ($P = .06$). Overall, extrapulmonary TB was common (28.8%) but more frequent among those patients with TB-HIV coinfection (38.1%)