Diabetes mellitus and latent tuberculosis infection: baseline analysis of a large UK cohort

Charlotte Jackson*[1], Jo Southern[2], Ajit Lalvani[3], Francis Drobniewski[3], Chris J. Griffiths[4], Marc Lipman[1,5], Graham H. Bothamley[6], Jonathan J. Deeks[7], Ambreen Imran[2], Onn Min Kon[3,8], Sithembinkosi Mpofu[2], Vladyslav Nikolayevskyy[2,3,4], Melanie Rees-Roberts[3], Alice Sitch[7], Saranya Sridhar[3], Chuen-Yan Tsou[2], Hilary Whitworth[3,9], Ibrahim Abubakar[1,2]

[1] University College London, London, UK

[2] Public Health England, London, UK

[3] Imperial College London, London, UK

[4] Queen Mary University of London, London, UK

[5] Royal Free London NHS Foundation Trust, London, UK

[6] Homerton University Hospital NHS Foundation Trust, London, UK

[7] Institute for Applied Health Research, University of Birmingham, Birmingham, UK

[8] Imperial College Healthcare NHS Trust, London, UK

[9] London School of Hygiene and Tropical Medicine, London, UK

*Corresponding author: Dr Charlotte Jackson, Institute for Infection and Immunity, St George's, University of London, Jenner Wing, Level 2, Cranmer Terrace, London SW17 0RE. Email: cjackson@sgul.ac.uk

Running title: Diabetes and latent TB infection

Word counts:

Abstract: 99

Main text: 969

ABSTRACT

We conducted a cross-sectional analysis of baseline data from a UK cohort study which enrolled participants at risk of latent tuberculosis infection (LTBI, defined as a positive result for either of the two interferon gamma release assays (IGRAs)). Binomial regression with a log link was used to estimate crude and adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) for the relationship between diabetes mellitus (DM) and LTBI. Adjusted for age, sex, ethnicity, body mass index and the presence of other immunocompromising conditions, DM was associated with a 15% higher prevalence of LTBI (adjusted PR=1.15, 95% CI 1.02-1.30, p=0.025).

Key words: Tuberculosis; Clinical epidemiology

To the Editor:

Diabetes mellitus (DM) and tuberculosis (TB) are major global public health priorities (1, 2). Many studies have assessed the relationship between DM and active TB disease (3). Data on the effect of DM on the risk of latent TB infection (LTBI) are more limited. A recent systematic review identified one cohort study, with an adjusted risk ratio of 4.40 (95% CI 0.50-38.55), and 12 cross-sectional studies which generated a pooled adjusted odds ratio of 1.18 (95% CI 1.06-1.30) (4).

The PREDICT (Prognostic Evaluation of Diagnostic IGRAs Consortium) study was a prospective, multi-site UK cohort study aiming to evaluate the predictive values of interferon gamma release assays (IGRAs) for the development of active TB among recent entrants to the UK from high-burden countries and contacts of active TB cases ("contacts"). PREDICT was approved by the Brent Research Ethics Committee (reference 10/H0717/14) and is registered on clinicaltrials.gov (NCT01162265). In this study, we use baseline data from PREDICT to investigate the association between DM and LTBI.

Recruitment took place between January 2011 and July 2015. After giving informed consent, participants completed a questionnaire and provided blood samples for IGRAs. Participants with evidence of active TB were excluded. The main exposure of interest in this secondary analysis was a self-reported history of DM. Data were also collected on the method of DM control used. The outcome of interest was LTBI, defined as a positive result for either or both of the two commercially available IGRAs, Quantiferon-TB Gold In-Tube (QFT-GIT – Qiagen) and TSpot.*TB* (Oxford Immunotec, Abingdon, UK). Participants with no valid IGRA results were excluded from this analysis. Other covariates on which data were collected are described in the Supplement.

Binomial regression with a log link was used to estimate crude and adjusted prevalence ratios (PRs and aPRs) and 95% CIs for the relationship between DM and LTBI (5). Age and

sex were treated as *a priori* confounders. A causal diagram of the relationships between potential confounders and outcomes using directed acyclic graphs, interpreted using dagitty.net (6) (Figure S1), was used to identify the minimum set of other covariates required for adjustment. P values were derived from likelihood ratio tests. We assessed potential interactions between DM and age (3) and DM and ethnicity (7), as observed for active TB (3, 7). All analyses used a complete-case approach. We conducted sensitivity analyses: 1) adjusting for age as a continuous variable using fractional polynomials (8); 2) using Poisson regression with robust standard errors (9); 3) restricting analysis to contacts; 4) including only participants who had concordant results for the two IGRAs; 5) repeating the primary analysis additionally adjusting for country of birth. Further methodological details and the questionnaire are provided in the Supplement.

9157 participants were included in the analysis (Table 1, Table S1, Figure S2). 756 participants (8.3%) reported having diabetes, of whom 535 provided information about how they controlled the condition: 409 taking medication, 55 on insulin, 20 using both insulin and other medication(s) and 51 through monitoring and/or diet only.

Prevalence of a positive IGRA was 31.5% and 27.3% amongst those with and without DM, respectively (Table 1: unadjusted PR=1.15, 95% CI 1.03-1.29, p=0.012). Characteristics associated with a positive IGRA on univariate analysis included increasing age, male sex, being born outside the UK, being a contact, having had a previous TB diagnosis or previous contact with a TB patient, and immunosuppression (Table 1). IGRA positivity varied by ethnicity, being highest in the Black African ethnic group and lowest amongst Black Caribbean participants. There was no evidence that having a positive IGRA was associated with previous BCG vaccination, HIV status, BMI, smoking, or social risk factors (Table 1).

Table 1: Characteristics of participants with and without LTBI, and unadjusted prevalence ratios for the association with LTBI

		IGRA positive [n (%)]	IGRA negative [n (%)]	Prevalence ratio (95% CI)	p
Total		2534 (27.7)	6623 (72.3)		
Diabetes (n = 9157)	No	2296 (27.3)	6105 (72.7)	Referent	
	Yes	238 (31.5)	518 (68.5)	1.15 (1.03-1.29)	0.012
Sex (n = 9107)	Male	1406 (30.9)	3149 (69.1)	Referent	
	Female	1116 (24.5)	3436 (75.5)	0.79 (0.74-0.85)	<0.001
Age group (years) (n = 9152)	16-25	510 (22.6)	1747 (77.4)	Referent	
	26-35	887 (28.2)	2258 (71.8)	1.25 (1.14-1.37)	
	36-45	470 (33.1)	949 (66.9)	1.47 (1.32-1.63)	
	>45	666 (28.6)	1665 (71.4)	1.26 (1.14-1.40)	<0.001
Country of birth (n = 9131)	Non-UK	2279 (29.7)	5385 (70.3)	Referent	
	UK	245 (16.7)	1222 (83.3)	0.56 (0.50-0.63)	<0.001
Ethnicity (n = 8934)	Indian	1043 (27.8)	2716 (72.3)	Referent	
	White	233 (21.0)	879 (79.1)	0.76 (0.67-0.86)	
	Black African	403 (37.0)	687 (63.0)	1.33 (1.21-1.46)	
	Mixed	270 (30.9)	603 (69.1)	1.11 (1.00-1.25)	
	Pakistani	264 (30.1)	614 (69.9)	1.08 (0.97-1.21)	
	Bangladeshi	134 (19.3)	561 (80.7)	0.69 (0.59-0.82)	
	Black Caribbean	37 (16.8)	183 (83.2)	0.61 (0.45-0.82)	
	Black Other / Chinese / Other	78 (25.4)	229 (74.6)	0.92 (0.75-1.12)	<0.001
Type of participant (n = 9157)	Contact	1384 (29.6)	3286 (70.4)	Referent	
	New entrant	1150 (25.6)	3337 (74.4)	0.86 (0.81-0.92)	<0.001
Previous BCG vaccination (n = 7759)	No	394 (27.8)	1024 (72.2)	Referent	
	Yes	1724 (27.2)	4617 (72.8)	0.98 (0.89-1.07)	0.65
Previous TB diagnosis (n = 9012)	No	2321 (26.7)	6368 (73.3)	Referent	
	Yes	180 (55.7)	143 (44.3)	2.09 (1.88-2.31)	<0.001
Previous contact with TB case (n = 8833)	No	2080 (27.1)	5599 (72.9)	Referent	
	Yes	355 (30.8)	799 (69.2)	1.14 (1.03-1.25)	0.01
HIV positive (n = 8539)	No	2366 (27·9)	6121 (72·1)	Referent	
	Yes	14 (26·9)	38 (73·1)	0·97 (0·62-1·51)	0.88
Other immunosuppression[a] (n = 9150)	No	2483 (27.9)	6425 (72.1)	Referent	
	Yes	49 (20.3)	193 (79.8)	0.73 (0.56-0.93)	0.007

Smoking (n = 9125)	No	2038 (27.6)	5352 (72.4)	Referent	
	Yes	489 (28.2)	1246 (71.8)	1.02 (0.94-1.11)	0.61
BMI (kg/m^2) (n = 8589)	<18.5	113 (26.3)	317 (73.7)	Referent	
	18.5 – 25	1155 (27.3)	3069 (72.7)	1.04 (0.88-1.23)	
	≥25	1122 (28.5)	2813 (71.5)	1.09 (0.92-1.28)	0.38
Any social risk factor[b] (n = 9157)	No	2407 (27.6)	6328 (72.4)	Referent	
	Yes	127 (30.1)	295 (69.9)	1.09 (0.94-1.27)	0.26

[a] Other immunosuppressive factors considered were: history of using anti-TNF-α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunoileal bypass, chronic renal failure or haemodialysis, gastrectomy.

[b] Social risk factors considered were: current or past homelessness, imprisonment or problem drug use.

Complete covariate data were available for 8336 participants (91.0% of the included participants; Table S2 compares these 8336 participants with the 821 with incomplete data). Adjusting for sex, age group, ethnicity, immunosuppression and BMI, the aPR for the association between DM and LTBI was 1.15 (95% CI 1.02-1.30, p=0.025, Table S3). There was no evidence of interaction between DM and age group (p=0.22) and weak evidence of interaction between DM and ethnicity (p=0.055, Table S4). Sensitivity analyses produced similar results, although the aPR increased to 1.29 (95% CI 1.09-1.52, p=0.002) when analysis was restricted to contacts (Table S5).

Our results are likely to be generalisible to migrants and contacts in the UK (although there were some differences between participants included and excluded from the analysis [Tables S1 and S2]), but perhaps not to other settings with different distributions of risk factors including country of birth and ethnicity. We used both of the commercially available IGRAs, and conducted a sensitivity analysis restricted to participants with concordant results, providing additional certainty regarding the diagnosis of LTBI. Limitations of the study include the self-reported nature of DM status, although this was frequently supported

by reported use of insulin or oral hypoglycaemic agents. Any participants with undiagnosed DM would be misclassified; this would be non-differential with respect to IGRA status and could bias our estimates towards the null. It is also possible that DM (and other forms of immunosuppression) influences the response to IGRA (10).

This is a cross-sectional analysis so we cannot be certain whether DM onset preceded LTBI. However, the association persisted when analysis was restricted to contacts, who were considered likely to have acquired infection recently. Residual confounding (e.g. by socioeconomic status) could inflate our estimated aPRs. Reported HIV prevalence was low and may be an underestimate as it was based on self-report.

Consistent with a previous systematic review and meta-analysis (4), this study suggests that, after adjustment for age, sex, BMI, ethnicity and immunosuppression, DM is associated with a small increase in the prevalence of positive IGRA results, amongst individuals at high risk of LTBI. Prospective studies are needed to further investigate the temporal relationship between DM and both infection and disease onset.

ACKNOWLEDGEMENTS

We are grateful to all members of the PREDICT Study Group: Ibrahim Abubakar, David Adeboyeku, Nabeela Bari, Jack Barker, Helen Booth, Graham Bothamley, Felix Chua, Dean Creer, Mathina Darmalingam, Robert N. Davidson, Martin Dedicoat, Jonathan J Deeks, Francis Drobniewski, Anne Dunleavy, Jose Figueroa, Chris Griffiths, Pranab Haldar, Mimi Haseldean, Andrew Hayward, Norman Johnson, Onn Min Kon, Heinke Kunst, Ajit Lalvani, Marc Lipman, Stefan Losewicz, Joanne Lord, William Lynn, Bobby Mann, Heather Milburn, John Moore-Gillon, Geoff Packe, Anton Pozniak, Frances Sanderson, Jo Southern.

We also thank Beverley Marks the study administrator, laboratory staff who undertook tests, clinical and nursing colleagues who contributed to participant recruitment, and our study

steering committee (Prof Bertie Squire – chair, Dr Sani Aliyu, Dr Stuart Baugh, Aurora Dawson) and data monitoring committee (Dr Chapman – Chair, Dr Adrian Smith and Dr Jon Innes, Dr Jonathan Deeks). We are also grateful to Sue Dart as well as all the temples, mosques, offices and other congregate settings for their assistance.

CONTRIBUTORSHIP STATEMENT

IA conceived and oversaw design and conduct of this analysis. JS co-ordinated the study and contributed to study design. CG, ML, GHB and OMK contributed to study design and recruitment; AL, FD and JJD contributed to study design. CJ conducted statistical analysis with support from AS and JJD, and drafted the manuscript. AI and SM recruited participants. VN, MR-R, SS, C-YT and HW performed laboratory work supervised by AL and FD. All authors critically reviewed and contributed to the manuscript. IA is the chief investigator of the PREDICT study; FD and AL are co-PIs.

DECLARATION OF INTERESTS

CJ has undertaken paid consultancy work for Otsuka Pharmaceutical unrelated to the content of this paper.

AL has several issued patents underpinning immunodiagnostics for tuberculosis. The ESAT-6/CFP-10 interferon-gamma ELISpot was commercialised by an Oxford University spin-out company (Oxford Immunotec plc, Abingdon, UK) from which Oxford University and AL have royalty entitlements.

JS, FD, AI, OMK, SM, VN, MR-R, CJG, ML, GHB, JJD, AS, SS, C-YT, HW and IA declare no conflicts of interest.

FUNDING

This work was supported by the National Institute for Health Research [grant numbers NIHR HTA 08/68/01, NIHR SRF-2011-04-001, NIHR NF-SI-0616-10037 to IA]. FD was supported by the Imperial Biomedical Research Centre.

PREVIOUS PRESENTATION OF DATA

Interim results of this study were presented at the British Thoracic Society Winter Meeting, London, December 2013 (abstract number S57).

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