The Relationship Between Latent Tuberculosis Infection and Acute Myocardial Infarction

Moises A. Huaman,[1,2] Eduardo Ticona,[3,4] Gustavo Miranda,[5] Richard J. Kryscio,[6] Raquel Mugruza,[3] Ernesto Aranda,[5,7] Paola L. Rondan,[3] David Henson,[2] Cesar Ticona,[3] Timothy R. Sterling,[8] Carl J. Fichtenbaum,[1] and Beth A. Garvy[2,9]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of Cincinnati College of Medicine, Ohio; [2]Department of Medicine, Division of Infectious Diseases, University of Kentucky College of Medicine, Lexington; [3]Department of Infectious Diseases and Tropical Medicine, Hospital Nacional Dos de Mayo, [4]Department of Internal Medicine, Universidad Nacional Mayor de San Marcos, and [5]Department of Cardiology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru; [6]Departments of Biostatistics and Statistics, University of Kentucky Colleges of Public Health and Arts & Sciences, Lexington; [7]Department of Internal Medicine, Division of Infectious Diseases, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [8]Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee; and [9]Department of Microbiology, Immunology and Molecular Genetics, University of Kentucky College of Medicine, Lexington

Background. Tuberculosis has been associated with an increased risk of cardiovascular disease (CVD), including acute myocardial infarction (AMI). We investigated whether latent tuberculosis infection (LTBI) is associated with AMI.

Methods. We conducted a case-control study in 2 large national public hospital networks in Lima, Peru, between July 2015 and March 2017. Case patients were patients with a first time diagnosis of type 1 (spontaneous) AMI. Controls were patients without a history of AMI. We excluded patients with known human immunodeficiency virus infection, tuberculosis disease, or prior LTBI treatment. We used the QuantiFERON-TB Gold In-Tube assay to identify LTBI. We used logistic regression modeling to estimate the odds ratio (OR) of LTBI in AMI case patients versus non-AMI controls.

Results. We enrolled 105 AMI case patients and 110 non-AMI controls during the study period. Overall, the median age was 62 years (interquartile range, 56–70 years); 69% of patients were male; 64% had hypertension, 40% dyslipidemia, and 39% diabetes mellitus; 30% used tobacco; and 24% were obese. AMI case patients were more likely than controls to be male (80% vs 59%; $P < .01$) and tobacco users (41% vs 20%; $P < .01$). LTBI was more frequent in AMI case patients than in controls (64% vs 49% [$P = .03$]; OR, 1.86; 95% confidence interval [CI], 1.08–3.22). After adjustment for age, sex, hypertension, dyslipidemia, diabetes mellitus, tobacco use, obesity, and family history of coronary artery disease, LTBI remained independently associated with AMI (adjusted OR, 1.90; 95% CI, 1.05–3.45).

Conclusions. LTBI was independently associated with AMI. Our results suggest a potentially important role of LTBI in CVD.

Keywords. tuberculosis; latent tuberculosis infection; cardiovascular disease; acute myocardial infarction.

It is estimated that approximately 1.7 billion persons worldwide have latent tuberculosis infection (LTBI) [1]. Persons considered at increased risk for progression to active tuberculosis disease—such as those living with human immunodeficiency virus (HIV), close tuberculosis contacts, transplant recipients, patients starting anti–tumor necrosis factor treatment, patients receiving dialysis, and patients with silicosis—may be screened and offered preventive therapy based on World Health Organization recommendations and/or local tuberculosis prevention guidelines [2, 3]. In settings with a low tuberculosis burden, additional risk groups may be considered for LTBI screening, including prisoners, immigrants from areas with high tuberculosis prevalence, healthcare workers,

homeless persons, and illicit drug users [2]. Nevertheless, the vast majority of LTBI cases remain undiagnosed and therefore untreated.

In the past, LTBI has been considered a state of mycobacterial dormancy. However, studies in recent years have shown that mycobacterial subpopulations may actively replicate during latency, leading to dynamic and widely diverse host immune responses that vary over time [4–6]. Compared with findings in healthy controls, LTBI has been associated with enhanced lymphocyte and monocyte immune activation [7–9]. Although immunologic responses against *Mycobacterium tuberculosis* in the host prevent the development of active tuberculosis disease, the potential negative consequences of the associated persistence of immune activation in LTBI are unknown.

Immune activation is a well-recognized driver of atherosclerosis and cardiovascular disease (CVD). Chronic infections such as HIV have been associated with sustained immune activation and increased risk of CVD [10, 11]. Recently, tuberculosis disease was associated with an increased risk of acute myocardial infarction (AMI), ischemic stroke, and peripheral artery disease [12–15]. No studies, to our knowledge, have explored

the relationship between LTBI and CVD. We aimed to assess whether LTBI is associated with AMI.

METHODS

Study Design and Participants

We conducted a case-control study of adult patients with and without history of recent type 1 (spontaneous) AMI. Case patients were recruited from inpatient cardiology and internal medicine units at Hospital Nacional Dos de Mayo (hospital 1) and Hospital Nacional Edgardo Rebagliati Martins (hospital 2) networks in Lima, Peru, between July 2015 and March 2017. Controls were recruited from the same inpatient units as well as outpatient medicine clinics in both hospital networks. Case patients were patients who had a first-time diagnosis of AMI within the past year. AMI was defined based on the third universal definition of myocardial infarction [16] and had to be documented by ≥1 cardiologist in the patient's medical record. Thus, AMI was defined as a rise and/or fall of cardiac biomarker values with ≥1 value 3 times the upper limit of normal and ≥1 of the following criteria: (1) symptoms of ischemia, (2) compatible electrocardiographic changes (new ST-T changes or new left bundle branch block, or pathologic Q waves), and (3) intracoronary thrombus demonstrated with percutaneous coronary angiography.

Patients with AMI events secondary to ischemic imbalance (type 2 AMI), AMI events resulting in sudden death when cardiac biomarker values were unavailable (type 3 AMI), AMI events related to percutaneous coronary angiography (type 4a AMI), coronary stent thrombosis (type 4b AMI), or coronary artery bypass graft (type 5 AMI) were excluded. Controls were persons ≥40 years old who did not have a current AMI or a history of AMI, nor a history of stroke, transient ischemic attack, or peripheral vascular disease. We restricted controls to patients ≥40 years old because AMI case patients were expected to be in this age group. Exclusion criteria for case patients and controls were history of HIV infection, history of tuberculosis disease, history of LTBI treatment, suspected active tuberculosis disease based on cough or subjective fever for ≥2 weeks, unexplained significant weight loss, or recent documentation of clinical and/or radiologic suspicion of tuberculosis disease in the patient's medical record.

Study personnel reviewed medical records, communicated with medical providers at the study sites to inquire about potential study candidates, and visited the inpatient wards and outpatient clinics an average of once or twice a week during the study period. Study participants provided clinical information, and a blood sample for QuantiFERON-TB Gold In-Tube (QFT) testing to identify LTBI.

Study Entry Questionnaire and Record Review

Study personnel administered the study questionnaire. Participants were asked about their age, sex, race, region of residence, and occupation; history of incarceration or known tuberculosis contact; history of hypertension, dyslipidemia, or diabetes; current tobacco use; obesity (defined as a body mass index ≥30 kg/m^2); known family history of coronary artery disease (CAD); history of cancer; history of immunosuppression; and history of end-stage renal disease requiring dialysis. Study personnel reviewed the medical records of study participants to confirm the accuracy of self-reported history of hypertension, diabetes mellitus, dyslipidemia, cancer, immunosuppression, and end-stage renal disease. In case of discrepancies between self-reported history and medical records, we used the medical record information to define these comorbid conditions. We also reviewed medical records to extract available height, weight, and fasting lipid profile results including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels (in milligrams per deciliter). For case patients, we also extracted information on the number of coronary vessels affected by CAD if percutaneous coronary angiography had been performed as part of the current AMI management by the time of record review.

QFT Testing

Testing for LTBI was performed using QFT, according to the manufacturer's specifications [17]. A research laboratory technician trained in the QFT assay performed the analyses.

Statistical Analysis

We summarized categorical variables using percentages, and numeric variables using median and interquartile ranges (IQRs). We used χ^2 and Mann-Whitney-Wilcoxon tests for comparisons of categorical and numeric variables, respectively. We used logistic regression modeling to estimate the odds ratio (OR) of having LTBI in AMI case patients versus non-AMI controls, with adjustment for covariates. ORs were reported with 95% confidence intervals (CIs). For the final logistic regression model, AMI was entered as the dependent variable. The main independent variable was LTBI. The final model was adjusted for known CVD risk factors, as follows: age, sex, hypertension, dyslipidemia, diabetes, obesity, tobacco use, and family history of CAD. Additional variables that were significantly associated with either AMI or LTBI in univariate analyses were entered into the final regression model. We analyzed all data using Stata software (version 12.0; StataCorp). All P values were 2 tailed. We considered $P < .05$ as the level of statistical significance.

Ethical Considerations

The study was approved by the ethical committees and institutional review boards of the University of Kentucky in Lexington, the University of Cincinnati in Cincinnati, Ohio, Hospital Nacional Dos de Mayo in Lima, Peru, and Hospital Nacional Edgardo Rebagliati Martins, also in Lima. All participants signed written informed consent forms.

RESULTS

We enrolled 105 AMI case patients and 110 non-AMI controls during the 21-month study period. Table 1 shows the demographic and clinical characteristics of the study population. No significant differences were found between AMI case patients and non-AMI controls in terms of age, Hispanic race/ethnicity, hypertension, dyslipidemia, diabetes mellitus, or obesity. There were significantly more men and tobacco users among AMI case patients. Overall, men were more likely than women to use tobacco (39% vs 11%; $P < .01$). For case patients, the median interval between AMI diagnosis and study enrollment was 9 days (IQR, 5–21 days).

Complete fasting lipid profile results were available for 66 (63%) of the AMI case patients and 47 (43%) of the controls. Among these participants (n = 113), HDL levels were lower in AMI case patients than in non-AMI controls (median [IQR]; 30.4 [26–36.5] vs 33.5 [29–43.5] mg/dL; $P = .01$). There were no significant differences between case patients and controls in levels of total cholesterol (135.6 [110.3–161] vs 145.1 [118.9–191] mg/dL; $P = .10$), LDL (83.4 [100.6–57.8] vs 75.9 [61.1–113.7] mg/dL; $P = .63$), or triglycerides (126.6 [97–166.8] vs 136.4 [88.9–185.5] mg/dL; $P = .53$). For case patients, the median interval between AMI diagnosis and lipid profile testing was 4 days (IQR, 1–10 days).

Of the 215 study participants, 120 (56%) had a positive QFT test results and therefore were classified as having LTBI. One participant (0.5%) in the control group had an indeterminate QFT result and therefore was excluded from further analyses. LTBI was more frequent among AMI case patients than among non-AMI controls (64% vs 49%; $P = .03$; OR, 1.86; 95% CI, 1.08–3.22). Of the 105 AMI case patients, 52 (50%) had available percutaneous coronary angiographic results at the time of study entry. The median number of coronary vessels with any degree of CAD was 2 (IQR, 2–3).

Table 1. Characteristics of Study Population Stratified by Study Group (n = 215)

Characteristic	Total (n = 215)	Case Patients (n = 105)	Controls (n = 110)	P Value[b]
Age, median (IQR), y	62 (56–70)	63 (55–70)	62 (56–68)	.71
Male sex	149 (69)	84 (80)	65 (59)	<.01[c]
Race/ethnicity				.66
Hispanic	206 (96)	100 (95)	106 (96)	
White	3 (1)	2 (2)	1 (1)	
African American	1 (1)	0	1 (1)	
Asian	5 (2)	3 (3)	2 (2)	
Region of residence				.58
Lima	163 (76)	76 (72)	87 (79)	
Coast other than Lima	27 (13)	16 (15)	11 (10)	
Highlands	12 (6)	7 (7)	5 (5)	
Amazons	13 (6)	6 (6)	7 (6)	
Hypertension	138 (64)	73 (70)	65 (59)	.11
Diabetes mellitus	84 (39)	34 (32)	50 (46)	.05
Dyslipidemia	86 (40)	44 (42)	42 (38)	.58
End-stage renal disease	6 (3)	3 (3)	3 (3)	.95
History of cancer	11 (5)	5 (5)	6 (5)	.83
History of immunosuppression	1 (1)	0	1 (1)	.33
Tobacco use	65 (30)	43 (41)	22 (20)	<.01[c]
BMI, median (IQR), kg/m^2	26.3 (19.7–29.7)	26.7 (24.7–30.5)	25.8 (23.5–29.1)	.06
Obesity (BMI ≥30 kg/m^2)	50 (23)	27 (26)	23 (21)	.42
Family history of CAD				.21
No	123 (57)	59 (56)	64 (58)	
Yes	83 (39)	39 (37)	44 (40)	
Unknown	9 (4)	7 (7)	2 (2)	
History of incarceration	10 (5)	6 (6)	4 (4)	.47
History of any tuberculosis contact	53 (25)	24 (23)	29 (26)	.55
History of LTBI	4 (2)	1 (1)	3 (3)	.34
Healthcare worker	19 (9)	9 (9)	10 (9)	.89

Abbreviations: BMI, body mass index; CAD, coronary artery disease; IQR, interquartile range; LTBI, latent tuberculosis infection.

[a]Data represent No. (%) of study participants unless otherwise specified.

[b]The χ^2 test for was used for categorical variables, and the Mann-Whitney test for numeric variables.

[c]$P < .05$ (statistically significant difference).

There were no significant differences in demographic or clinical characteristics between participants with or without LTBI (Table 2). The rates of LTBI did not differ significantly between hospitals 1 and 2 (53% vs 60%; $P = .34$). Because controls were recruited from inpatient wards (75%) and outpatient clinics (25%), we estimated LTBI rates for both subgroups and found no significant differences (49% vs 46%; $P = .79$). Complete fasting lipid profile results were available in 65 (54%) of participants with LTBI and 47 (50%) of those without LTBI. There were no significant differences in total cholesterol, HDL, LDL, or triglyceride levels by LTBI status.

In multivariable analysis, AMI was associated with increased odds of LTBI after adjustment for age, sex, hypertension, dyslipidemia, diabetes mellitus, current tobacco use, obesity, and family history of CAD (adjusted OR, 1.90; 95% CI, 1.05–3.45). This final model fit the data well (Hosmer-Lemeshow goodness-of-fit test, $P = .24$). The complete results of the final logistic regression model are shown in Table 3. In models that assessed for potential effect modification of sex and tobacco use, we found no significant interaction between sex and LTBI ($P = .12$), nor between tobacco use and LTBI ($P = .62$).

DISCUSSION

We demonstrated in this case-control study that recent AMI was independently associated with an approximately 2-fold increased odds of LTBI, after adjustment for established CVD risk factors and other potential confounders. As expected, known CVD risk factors such as male sex and tobacco use were also associated with AMI. To our knowledge, this is the first study to assess the relationship between LTBI and CVD.

Tuberculosis disease has been associated with an increased risk of acute coronary syndrome, ischemic stroke, and peripheral artery disease in large population-based retrospective

Table 2. Characteristics of Study Population With Valid QuantiFERON-TB Gold Test Results, Stratified by Latent Tuberculosis Infection Status (n = 214)

Characteristic	Study Participants, No. (%)[a]			
	Total (n = 214)[b]	LTBI (n = 120)	No LTBI (n = 94)	P Value[c]
Age, median (IQR), y	62 (56–70)	63 (57–68)	61 (55–72)	.26
Male sex	148 (69)	86 (72)	62 (66)	.37
Race/ethnicity				.25
Hispanic	205 (96)	115 (96)	90 (96)	
White	3 (1)	3 (3)	0	
African American	1 (1)	0	1 (1)	
Asian	5 (2)	2 (2)	3 (3)	
Region of residence				.41
Lima	162 (76)	90 (75)	72 (77)	
Coast other than Lima	27 (13)	18 (15)	9 (10)	
Highlands	12 (6)	7 (6)	5 (5)	
Amazons	13 (6)	5 (4)	8 (9)	
Hypertension	138 (65)	76 (63)	62 (66)	.69
Diabetes mellitus	83 (39)	45 (38)	38 (40)	.66
Dyslipidemia	85 (40)	49 (41)	36 (38)	.71
End-stage renal disease	6 (3)	4 (3)	2 (2)	.60
History of cancer	11 (5)	6 (5)	5 (5)	.93
History of immunosuppression	1 (1)	0	1 (1)	.26
Tobacco use	65 (30)	41 (34)	24 (26)	.17
BMI, median (IQR), kg/m^2	26.3 (23.9–29.8)	26.9 (24.7–29.4)	25.5 (23.5–30.4)	.13
Obesity (BMI ≥30 kg/m^2)	50 (23)	25 (21)	25 (27)	.38
Family history of CAD				.70
No	123 (58)	68 (57)	55 (59)	
Yes	82 (38)	48 (40)	34 (36)	
Unknown	9 (4)	4 (3)	5 (5)	
History of incarceration	10 (5)	4 (3)	6 (6)	.29
History of any tuberculosis contact	52 (24)	30 (25)	22 (23)	.79
History of LTBI	4 (2)	3 (3)	1 (1)	.44
Healthcare worker	19 (9)	10 (8)	9 (10)	.75

Abbreviations: BMI, body mass index; CAD, coronary artery disease; IQR, interquartile range; LTBI, latent tuberculosis infection.

[a]Data represent No. (%) of study participants unless otherwise specified.

[b]One of the 215 study participants had an indeterminate quantiFERON-TB test result; therefore, 214 participants were included in this analysis.

[c]The χ^2 test was used for categorical variables, and the Mann-Whitney test for numeric variables.

Table 3. Results of Logistic Regression Model for Study Group (Acute Myocardial Infarction [AMI] vs no AMI) as the Dependent Variable

Variable	Adjusted OR (95% CI)
LTBI	1.90 (1.05–3.45)[a]
Male sex	2.55 (1.28–5.06)[a]
Age, per 1-y increase	0.99 (.96–1.02)
History of hypertension	1.7 (.89–3.24)
History of diabetes mellitus	0.61 (.33–1.15)
Current tobacco use	2.04 (1.04–3.98)[a]
History of dyslipidemia	1.26 (.67–2.37)
Family history of CAD	
Present	0.96 (.52–1.77)
Unknown	3.87 (.67–22.27)
Obesity	1.28 (.63–2.61)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; LTBI, latent tuberculosis infection; OR, odds ratio.

[a]$P < .05$ (statistically significant difference).

cohort studies. In Taiwan, the adjusted risk of AMI and unstable angina was 1.4 times higher in persons with tuberculosis disease than in those without tuberculosis disease [12]. Similarly, the adjusted risks of ischemic stroke and peripheral artery disease were 1.5 and 3.9 times higher, respectively, in patients with tuberculosis disease than in controls without tuberculosis disease [13, 15]. Of note, the reference population for these studies did not differentiate between persons with and those without LTBI. We recently reported an almost 2-fold increased risk of AMI in persons with history of tuberculosis disease, compared with propensity-matched persons without a history of tuberculosis disease in the United States [14]. Persons with known LTBI-related claims were excluded from the aforementioned study; however, it is unlikely that all persons with LTBI would have been removed from the reference group, because LTBI testing is not universal. Whether LTBI and tuberculosis disease affect CVD risk similarly or in an incremental, stepwise fashion could be explored in future studies.

Infection may contribute to atherogenesis and acute cardiovascular events through different mechanisms [18]. Similar to what has been described in other chronic infections, such as HIV infection [10], persistent immune activation related to intermittent low level microbial replication is a possible driver of the association between LTBI and AMI [19]. Supporting this hypothesis, studies indicate that there is ongoing *M. tuberculosis* replication and metabolic activity during LTBI [4, 5]. Contrary to the former view of LTBI as a state of mycobacterial dormancy, LTBI is now recognized as a continuous spectrum of host-pathogen interactions in which replicating and metabolically quiescent mycobacterial populations coexist and are constrained by variable host immune responses within each granuloma [6, 20].

Study findings have also suggested that persons with LTBI may have elevated levels of immune activation markers and proinflammatory cytokines in peripheral blood. For instance,

a study in Norway showed that LTBI was associated with increased serum levels of interleukin 1β, 6, and 22 and tumor necrosis factor α [7]; however, this finding has not been replicated in other studies. In India, LTBI was associated with higher levels of monocyte/macrophage activation markers and chemotactic mediators, such as CD14, CXCL3, CCL2, and CCL8 [21]. We recently reported a subtle increase in plasma interferon γ levels in persons with LTBI in the United States, compared with controls without LTBI [9]. Furthermore, studies using RNA sequencing of peripheral blood cells have shown that persons with LTBI who progress to tuberculosis disease overexpress genes involved in interferon responses [22], indicating that this subset of high-risk patients with LTBI may have enhanced systemic immune activation several months before developing clinical tuberculosis disease.

Wergeland et al [23] showed a trend toward increased expression of the T-cell activation markers HLA-DR and CD38 in CD4$^+$ and CD8$^+$ T cells of patients with LTBI, compared with healthy controls; however, the observed differences were not statistically significant. In a study of HIV-infected patients, CD38 expression in CD4$^+$ and CD8$^+$ T cells was significantly elevated in LTBI/HIV coinfection, compared with HIV monoinfection [8]. Although these data suggest that immune activation is present in at least certain subsets of patients with LTBI, these studies have been limited by small sample sizes and lack of adjustment for potential confounders. There is a need for larger studies aimed at characterizing immune activation in LTBI and its potential role in CVD. In addition, the effect of LTBI treatment on immune activation requires further attention, because changes in T-cell responses to specific *M. tuberculosis* antigens occur through the course of LTBI treatment [24, 25].

Another potential contributory mechanism of LTBI to AMI is molecular mimicry between mycobacterial heat shock protein 65 and human heat shock protein antigens causing autoimmune responses and atherogenesis [26–28]. Another possible mechanistic link between tuberculosis and CVD may involve the accumulation of lipids within macrophages, an early step in the development of atherosclerosis. *M. tuberculosis* promotes intracellular accumulation of lipids and favors a foamy macrophage phenotype suitable for mycobacterial growth and persistence [29, 30]. In the guinea pig model, experimental infection with *M. tuberculosis* was associated with increased lung and tissue levels of oxidized LDL, and increased expression of the scavenger receptors CD36 and lectinlike oxidized LDL receptor 1 in the macrophage [31]. Remarkably, these receptors are closely involved in the pathogenesis of atherosclerosis and CVD [32, 33].

Whether the lipid changes induced by *M. tuberculosis* within the macrophage contribute to systemic atherogenesis in the vascular tissue could be explored in future studies. Of note, our group [9] previously reported no differences in circulating levels of total cholesterol, HDL, LDL, or triglycerides among persons

with and without LTBI. In this study, we found similar results; however, complete lipid profiles were available in only a subset of participants. Furthermore, lipid profile results among AMI case patients may have been affected by recent AMI diagnosis and treatment. Therefore, these results need to be interpreted with caution. Finally, it is also possible that the increased rate of LTBI among AMI case patients could be a surrogate marker of unfavorable sociodemographic conditions not measured in the current study. CVD and atherosclerosis risk factors are associated with low socioeconomic status and uninsured populations [34], similar to what happens in LTBI and tuberculosis disease.

Our study had limitations. First, the study groups were unbalanced with regard to important established CVD risk factors, such as male sex and current tobacco use. Although the association between LTBI and AMI remained present even after adjustment for these and other potential confounders, a residual confounding effect of such risk factors cannot be fully excluded. In addition, because most controls were recruited from general medicine units where diabetes mellitus is prevalent, this comorbid condition was common among controls. This may explain the low but nonsignificant OR of diabetes in AMI. Interestingly, diabetes has been associated with a small increased risk for LTBI [35]; therefore, the elevated prevalence of diabetes among controls could have biased the relationship of LTBI and AMI toward the null hypothesis. Future studies should balance a priori these important factors among comparison groups.

Second, LTBI was diagnosed using the QFT test, which measures the host immune response to *M. tuberculosis* antigens, and can produce false-positive and false-negative results. However, the QFT assay is more specific than the tuberculin skin test and is therefore particularly helpful in settings where BCG vaccination is common, such as Peru [36]. In addition, prior studies using the QFT test in Lima, Peru, estimated LTBI rates of 55% among household contacts of patients with tuberculosis [37] and 49% among diabetic patients attending outpatient clinics [38]. Thus, our LTBI rate of 49% in the control group falls within an expected range. Furthermore, our rate of indeterminate results (0.5%) was very similar to what has been reported in large population-based surveys, such as the US National Health and Nutrition Examination Survey (0.3%) [39], indicating good performance of the QFT test in our study setting.

Third, our cross-sectional study design did not allow for a temporal analysis of the relationship between LTBI and AMI. However, because the majority of case patients were recruited shortly after their first AMI event (median interval, 9 days), and considering the 6–12-week lag between *M. tuberculosis* infection and a positive QFT assay result, it is very likely that the diagnosis of LTBI preceded the diagnosis of AMI.

In conclusion, we found that LTBI was independently associated with AMI. Because LTBI is common in many settings, and because the occurrence of additional (established) CVD risk factors is on the rise worldwide, the potential contribution of LTBI in the CVD epidemic should be further explored. Our results have potential clinical and programmatic implications, because LTBI is a common condition that often remains unrecognized and untreated, particularly in settings with a high tuberculosis burden. Studies on the pathogenic mechanisms driving this association and the potential beneficial role of LTBI treatment are needed.

Notes

References

1. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med **2016**; 13:e1002152.
2. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: World Health Organization, **2015**.
3. World Health Organization. Implementing the end TB strategy: the essentials. Geneva, Switzerland: World Health Organization, **2015**.
4. Gill WP, Harik NS, Whiddon MR, Liao RP, Mittler JE, Sherman DR. A replication clock for *Mycobacterium tuberculosis*. Nat Med **2009**; 15:211–4.
5. Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol **2009**; 7:845–55.
6. Gideon HP, Phuah J, Myers AJ, et al. Variability in tuberculosis granuloma T cell responses exists, but a balance of pro- and anti-inflammatory cytokines is associated with sterilization. PLoS Pathog **2015**; 11:e1004603.
7. Cowan J, Pandey S, Filion LG, Angel JB, Kumar A, Cameron DW. Comparison of interferon-γ-, interleukin (IL)-17- and IL-22-expressing CD4 T cells, IL-22-expressing granulocytes and proinflammatory cytokines during latent and active tuberculosis infection. Clin Exp Immunol **2012**; 167:317–29.
8. Sullivan ZA, Wong EB, Ndung'u T, Kasprowicz VO, Bishai WR. Latent and active tuberculosis infection increase immune activation in individuals co-infected with HIV. EBioMedicine **2015**; 2:334–40.
9. Huaman MA, Deepe GS Jr, Fichtenbaum CJ. Elevated circulating concentrations of interferon-gamma in latent tuberculosis infection. Pathog Immun **2016**; 1:291–303.
10. Nou E, Lo J, Grinspoon SK. Inflammation, immune activation, and cardiovascular disease in HIV. AIDS **2016**; 30:1495–509.
11. Drozd DR, Kitahata MM, Althoff KN, et al. Increased risk of myocardial infarction in HIV-infected individuals in North America compared with the general population. J Acquir Immune Defic Syndr **2017**; 75:568–76.
12. Chung WS, Lin CL, Hung CT, et al. Tuberculosis increases the subsequent risk of acute coronary syndrome: a nationwide population-based cohort study. Int J Tuberc Lung Dis **2014**; 18:79–83.
13. Sheu JJ, Chiou HY, Kang JH, Chen YH, Lin HC. Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke **2010**; 41:244–9.
14. Huaman MA, Kryscio RJ, Fichtenbaum CJ, et al. Tuberculosis and risk of acute myocardial infarction: a propensity score-matched analysis. Epidemiol Infect **2017**; 145:1363–7.
15. Wang SH, Chien WC, Chung CH, et al. Tuberculosis increases the risk of peripheral arterial disease: a nationwide population-based study. Respirology **2017**; 22:1670–6.
16. Thygesen K, Alpert JS, Jaffe AS, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation **2012**; 126:2020–35.

17. QuantiFERON-TB Gold (QFT) ELISA [package insert]. Germantown, Maryland: Qiagen; **2016**.

18. Epstein SE, Zhu J, Najafi AH, Burnett MS. Insights into the role of infection in atherogenesis and in plaque rupture. Circulation **2009**; 119:3133–41.

19. Huaman MA, Henson D, Ticona E, Sterling TR, Garvy BA. Tuberculosis and cardiovascular disease: linking the epidemics. Trop Dis Travel Med Vaccines **2015**; 1:10.

20. Dutta NK, Karakousis PC. Latent tuberculosis infection: myths, models, and molecular mechanisms. Microbiol Mol Biol Rev **2014**; 78:343–71.

21. King CA, John S, Kenneth J, Mehta S. *Mycobacterium tuberculosis* infection induces persistent non-resolving inflammation. Am J Trop Med Hyg **2014**; 91(5_Suppl_1):390.

22. Zak DE, Penn-Nicholson A, Scriba TJ, et al; ACS and GC6-74 cohort study groups. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet **2016**; 387:2312–22.

23. Wergeland I, Assmus J, Dyrhol-Riise AM. T regulatory cells and immune activation in *Mycobacterium tuberculosis* infection and the effect of preventive therapy. Scand J Immunol **2011**; 73:234–42.

24. Biraro IA, Egesa M, Kimuda S, et al. Effect of isoniazid preventive therapy on immune responses to *Mycobacterium tuberculosis*: an open label randomised, controlled, exploratory study. BMC Infect Dis **2015**; 15:438.

25. Wilkinson KA, Kon OM, Newton SM, et al. Effect of treatment of latent tuberculosis infection on the T cell response to *Mycobacterium tuberculosis* antigens. J Infect Dis **2006**; 193:354–9.

26. Xu Q, Willeit J, Marosi M, et al. Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis. Lancet **1993**; 341:255–9.

27. Zhu J, Katz RJ, Quyyumi AA, et al. Association of serum antibodies to heat-shock protein 65 with coronary calcification levels: suggestion of pathogen-triggered autoimmunity in early atherosclerosis. Circulation **2004**; 109:36–41.

28. Zhang Y, Xiong Q, Hu X, et al. A novel atherogenic epitope from *Mycobacterium tuberculosis* heat shock protein 65 enhances atherosclerosis in rabbit and LDL receptor-deficient mice. Heart Vessels **2012**; 27:411–8.

29. Mahajan S, Dkhar HK, Chandra V, et al. *Mycobacterium tuberculosis* modulates macrophage lipid-sensing nuclear receptors PPARγ and TR4 for survival. J Immunol **2012**; 188:5593–603.

30. Lovewell RR, Sassetti CM, VanderVen BC. Chewing the fat: lipid metabolism and homeostasis during *M. tuberculosis* infection. Curr Opin Microbiol **2016**; 29:30–6.

31. Palanisamy GS, Kirk NM, Ackart DF, et al. Uptake and accumulation of oxidized low-density lipoprotein during *Mycobacterium tuberculosis* infection in guinea pigs. PLoS One **2012**; 7:e34148.

32. Podrez EA, Febbraio M, Sheibani N, et al. Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species. J Clin Invest **2000**; 105:1095–108.

33. Mehta JL, Chen J, Hermonat PL, Romeo F, Novelli G. Lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1): a critical player in the development of atherosclerosis and related disorders. Cardiovasc Res **2006**; 69:36–45.

34. Agarwal S, Sud K, Thakkar B, Menon V, Jaber WA, Kapadia SR. Changing trends of atherosclerotic risk factors among patients with acute myocardial infarction and acute ischemic stroke. Am J Cardiol **2017**; 119:1532–41.

35. Lee MR, Huang YP, Kuo YT, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and metaanalysis. Clin Infect Dis **2017**; 64:719–27.

36. Belknap R, Daley CL. Interferon-gamma release assays. Clin Lab Med **2014**; 34:337–49.

37. Wingfield T, Schumacher SG, Sandhu G, et al. The seasonality of tuberculosis, sunlight, vitamin D, and household crowding. J Infect Dis **2014**; 210:774–83.

38. Ugarte-Gil C, Kerry S, van Crevel R, Critchley J, Moore D. Screening individuals with diabetes for latent tuberculosis infection: preliminary data from the TANDEM program in Peru. Int J Tuberc Lung Dis **2016**; 20:S176.

39. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The prevalence of latent tuberculosis infection in the United States. Am J Respir Crit Care Med **2016**; 194:501–9.