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Latent Tuberculosis Infection and Subclinical Coronary Atherosclerosis in Peru and Uganda

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Background. Tuberculosis (TB) has been linked to an increased risk of atherosclerotic cardiovascular disease (ASCVD). We assessed whether latent TB infection (LTBI) is associated with subclinical coronary atherosclerosis in 2 TB-prevalent areas.

Methods. We analyzed cross-sectional data from studies conducted in Lima, Peru, and Kampala, Uganda. Individuals ≥40 years old were included. We excluded persons with known history of ASCVD events or active TB. Participants underwent QuantiFERON-TB (QFT) testing to define LTBI and computed tomography angiography to examine coronary atherosclerosis. A Coronary Artery Disease–Reporting Data System (CAD-RADS) score ≥3 defined obstructive CAD (plaque causing ≥50% stenosis).

Results. 113 and 91 persons with and without LTBI, respectively, were included. There were no significant differences between LTBI and non-LTBI participants in terms of age (median [interquartile range]; 56 [51–62] vs 55 [49–64] years; $P = .829$), male sex (38% vs 42%; $P = .519$), or 10-year ASCVD risk scores (7.1 [3.2–11.7] vs 6.1 [2.8–1.8]; $P = .533$). CAD prevalence (any plaque) was similar between groups (29% vs 24%; $P = .421$). Obstructive CAD was present in 9% of LTBI and 3% of non-LTBI individuals ($P = .095$). LTBI was associated with obstructive CAD after adjusting for ASCVD risk score, HIV status, and study site (adjusted OR, 4.96; 95% CI, 1.05–23.44; $P = .043$). Quantitative QFT TB antigen minus Nil interferon-γ responses were associated with obstructive CAD (adjusted OR, 1.2; 95% CI, 1.03–1.41; $P = .022$).

Conclusions. LTBI was independently associated with an increased likelihood of subclinical obstructive CAD. Our data indicate that LTBI is a nontraditional correlate of ASCVD risk.

Keywords. latent tuberculosis infection; atherosclerosis; coronary artery disease; coronary computed tomography angiography.

Approximately one-quarter of the world's population has latent tuberculosis (TB) infection (LTBI) and 10 million people develop TB disease each year [1, 2]. Tuberculosis and cardiovascular diseases (CVDs) are leading infectious and noninfectious causes of death globally [3]. The impact of these 2 conditions is not independent, with recent studies showing that individuals with a history of TB disease have increased risk of myocardial infarction [4], coronary syndrome [5], ischemic stroke [6], and peripheral arterial disease [7]. Furthermore, patients with TB have an increased risk of long-term CVD mortality [8, 9].

Latent TB infection is now recognized as a heterogeneous condition with a wide spectrum of host–pathogen interactions, including the potential for intermittent mycobacterial replication and dynamic immune responses [10–13]. Studies have shown that persons with LTBI may have elevated markers of immune activation compared with their LTBI-negative counterparts [14, 15]. Immune activation can promote atherosclerosis development [16], and thus the augmented immune activation in persons with LTBI may contribute to atherosclerotic CVD (ASCVD) risk. We previously reported that LTBI was associated with acute myocardial infarction after adjusting for traditional ASCVD risk factors [17]. In the present study, we aimed to characterize subclinical coronary atherosclerosis burden in middle- and older-age asymptomatic individuals with and without LTBI living in 2 TB-endemic areas.

METHODS

We analyzed cross-sectional data from studies conducted at the Hospital Nacional Dos de Mayo Clinical Research Unit in Lima, Peru (Peru site), and the Joint Clinical Research Centre in Kampala, Uganda (Uganda site). At the Peru site, persons between 40 and 70 years of age were recruited from markets and outpatient medicine clinics in the Lima downtown area between March 2018 and October 2019 and were included in this analysis.

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At the Uganda site, persons aged 45 years and older who were participating in the mUTIMA (Ugandan study of HIV effects on the myocardium and atherosclerosis) cohort study between June 2017 and October 2019 were included. The Uganda site population included persons living with human immunodeficiency virus (PLWH) and participants without human immunodeficiency virus (HIV) with at least 1 additional risk factor for ASCVD other than age. Persons living with HIV were on stable antiretroviral therapy and were required to have an HIV viral load of 1000 copies/mL or less within the 6 months prior to study entry. Exclusion criteria at both sites were pregnancy, use of chemotherapy or immunomodulating agents, laboratory evidence of renal disease (glomerular filtration rate <60 mL/minute), or known history of coronary artery disease (CAD), ischemic stroke, or peripheral artery disease. Because this analysis focused on LTBI, persons with a prior history of active TB verified by review of medical records were excluded from the analysis. Individuals with a history of allergy or contraindication to receive B-blockers and/or nitroglycerine were also excluded, as these drugs were used in coronary computed tomography (CT) angiography (CCTA) examinations. All participants provided demographic and clinical information, underwent interferon-γ release assay (IGRA) to define LTBI status, and completed a CCTA to examine coronary atherosclerosis.

Demographic and Clinical Data

Trained study personnel administered study questionnaires at the Peru and Uganda sites. All participants provided information on age, sex at birth, race, and presence of comorbidities including hypertension, diabetes mellitus, dyslipidemia, and current tobacco use. Available medical records were reviewed to verify accuracy of self-reported history of hypertension, diabetes mellitus, and dyslipidemia. During the pre-CCTA study visit, blood pressure, height, and weight were recorded. Blood was obtained for creatinine and fasting cholesterol levels including total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol.

Interferon-γ Release Assay

QuantiFERON-TB (QFT) testing was performed to define LTBI based on the manufacturer's specifications [18, 19]. A trained laboratory technician performed the QFT assays at each site. The QuantiFERON-TB Gold Plus (QFT-Plus) was used at the Peru site. The QuantiFERON-TB Gold In-Tube (QFT-GIT) was used at the Uganda site. Participants with a positive QFT test as per the assay's definition were considered to have LTBI. Participants with an indeterminate QFT test result were excluded from this analysis.

Coronary Computed Tomography Angiography

Participants underwent a CCTA using a 160-slice Toshiba Aquilion Prime CT scanner at the Peru site or a 128-slice Siemen's Somatom CT scanner at the Uganda site following guidelines from the Society of Cardiac Computed Tomography [20, 21]. Prospective electrocardiogram (ECG) gating was used for participants with regular heart rate, whereas retrospective ECG gating was used if heart rate was irregular. Participants received a B-blocker 30 to 60 minutes prior to the CCTA examination to lower their heart rate under 65 beats per minute. Oral atenolol 50 to 100 mg was used at the Peru site, while oral metoprolol 100 mg was used at the Uganda site. Sublingual nitroglycerin 0.5 mg was given at the time of the study for coronary vasodilation to optimize CCTA image quality, unless the participant was found to have a systolic blood pressure less than 90 mm Hg. Iodinated contrast was administered intravenously based on local protocols and patient characteristics. Participants also completed a noncontrast ECG-gated coronary calcium score examination to calculate the Agatston score [22].

Stored CCTA DICOM images were interpreted by an expert CCTA reader blinded to the subjects' demographic and clinical characteristics including LTBI status. Coronary artery disease (any plaque) was defined as the presence of plaque in any of the coronary segment, using a 18-segment classification modified from the American Heart Association [23]. The Coronary Artery Disease–Reporting Data System (CAD-RADS) was used to assess coronary stenosis severity per patient and per coronary segment [24]. Briefly, the CAD-RADS included a 0- to 5-point scale on stenosis severity (0 = no plaque or stenosis; 1 = 1–24% stenosis [minimal]; 2 = 25–49% stenosis [mild]; 3 = 50–69% stenosis [moderate]; 4 = 70–99% stenosis [severe]; 5 = 100% stenosis [total occlusion]). Obstructive CAD was defined by a CAD-RADS of 3 or greater, as previously described [25]. The segment involvement score (SIS) was calculated as the total number of coronary segments with atherosclerotic plaque [26]. The segment stenosis score (SSS) was calculated as the total number of coronary segments with plaque weighted by the degree of stenosis as previously described [27].

Data Management and Statistical Analysis

Study data were entered and stored in REDCap [28]. Stata (version 12.0; StataCorp, College Station, TX) and SAS (version 9.4; SAS Institute, Inc, Cary, NC) were used for statistical analyses. Categorical variables were summarized as frequencies and percentages, whereas continuous variables were summarized as medians accompanied by interquartile ranges (IQRs). We used chi-square or Fisher's exact test for bivariate comparisons of categorical variables. We used Mann-Whitney-Wilcoxon tests for bivariate comparisons of continuous variables. Univariate and multivariate logistic regression models were used to assess the relationship between LTBI and coronary atherosclerosis parameters, adjusted for 10-year ASCVD risk scores, HIV status, and site location (Peru or Uganda). These variables were selected a priori based on knowledge of potential confounders. The American

College of Cardiology/American Heart Association 10-year ASCVD risk score was used to estimate participants' ASCVD risk as a function of age, sex, race, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, history of diabetes mellitus, hypertension, and tobacco use [29]. Logistic regression models were also used to examine the relationship between coronary atherosclerosis and the quantitative interferon-γ values obtained in the QFT assay. The QFT TB antigen data source was the interferon-γ values in the QFT-Plus TB1 antigen tube in Peru and the QFT-GIT TB antigen tube in Uganda. Of note, interferon-γ values in the QFT-GIT TB antigen and QFT-Plus TB1 antigen tubes are comparable and strongly correlate with each other [30]. Results of logistic regression models were presented as odds ratios (ORs) accompanied by 95% confidence intervals (CIs). A *P* value less than .05 was considered statistically significant.

Ethical Considerations

The Peru and Uganda study protocols were reviewed by the University of Cincinnati Institutional Review Board (IRB). The Peru site study was approved by the Ethical Committee of the Hospital Nacional Dos de Mayo and the Office of Public Health Strategic Interventions at the Ministry of Health in Lima, Peru. The Uganda site study was approved by the University Hospitals IRB in Cleveland, Ohio, and the Joint Clinical Research Center IRB in Kampala, Uganda. The IRB reviews at the University of Cincinnati and Case Western Reserve University included routine review by radiation safety committees.

RESULTS

Of the 204 study participants included in this analysis, 113 (55%) had a positive QFT test and were classified as having LTBI, whereas 91 (45%) had a negative QFT test and were classified as not having LTBI. All 69 participants in Peru were HIV negative. Of the 135 participants in Uganda, 84 (62%) were HIV negative and 51 (38%) were PLWH on stable antiretroviral therapy. Persons living with HIV had a median CD4 count of 572 cells/μL (IQR, 433–746 cells/μL) and a median most recent HIV viral load of 20 copies/mL or less (IQR, ≤20 to ≤20). All participants denied prior history of LTBI treatment.

Table 1 shows the characteristics of the study population by LTBI status and site location. Compared with participants in Peru, participants in Uganda were older (median [IQR] age, 57 [52–62] vs 53 [47–61] years; $P = .004$), had higher rates of hypertension (87% vs 16%; $P < .001$), and greater 10-year ASCVD risk scores (median [IQR], 7.2 [3.5–12.6] vs 5 [1.5–9.2]; $P = .002$). These differences were expected given the variations in inclusion criteria between the 2 sites. There were no significant differences in terms of age, sex, comorbidities, cholesterol levels, or 10-year ASCVD risk scores between individuals with and without LTBI.

Table 2 shows coronary atherosclerosis findings from CCTA examinations. Overall, the prevalence of CAD (any plaque) was 27%. No differences in CAD prevalence were found between LTBI and no-LTBI groups (29% vs 24%; $P = .421$). The overall prevalence of obstructive CAD (CAD-RADS ≥3) was 7%. Compared with persons without LTBI, persons with LTBI exhibited a trend towards a higher prevalence of obstructive

Table 1. Characteristics of the Study Population by Latent Tuberculosis Infection

	Peru			Uganda			Total		
Characteristics	No LTBI (n = 27)	LTBI[a] (n = 42)	*P*[b]	No LTBI (n = 64)	LTBI (n = 71)	*P*[b]	No LTBI (n = 91)	LTBI (n = 113)	*P*[b]
Age, years	51 (43–66)	54 (47–60)	.777	57 (53–62)	57 (52–62)	.949	55 (49–64)	56 (51–62)	.829
Male sex at birth, n (%)	15 (56)	19 (45)	.403	23 (36)	24 (34)	.795	38 (42)	43 (38)	.519
Hypertension,[c] n (%)	4 (15)	7 (17)	.838	54 (84)	64 (90)	.313	58 (64)	71 (63)	.894
Diabetes mellitus,[c] n (%)	4 (15)	11 (26)	.264	20 (31)	20 (28)	.695	24 (26)	31 (27)	.865
Hyperlipidemia,[c] n (%)	9 (33)	11 (26)	.523	7 (11)	15 (21)	.109	16 (18)	26 (23)	.341
Current smoking, n (%)	1 (4)	4 (10)	.641	1 (2)	5 (7)	.212	2 (2)	9 (8)	.116
Systolic BP, mm Hg	116 (105–130)	120 (110–130)	.877	140 (122–160)	137 (121–162)	.984	130 (116–150)	128 (115–145)	.519
Diastolic BP, mm Hg	70 (70–80)	78 (70–80)	.488	81 (72–88)	79 (70–93)	.899	79 (70–87)	79 (70–88)	.989
BMI, kg/m^2	26.4 (24.3–27.9)	27.2 (25.9–29.1)	.041	28.1 (25.2–32.7)	29.9 (24.9–33.5)	.600	27.3 (24.5–30.9)	28 (25.6–32)	.248
Total cholesterol, mg/dL	188 (164–211)	201 (179–222)	.127	205 (180–237)	191 (167–226)	.067	198 (175–233)	193 (173–224)	.415
LDL cholesterol, mg/dL	105 (92–131)	114 (102–134)	.379	130 (111–166)	128 (106–149)	.179	128 (102–160)	123 (103–143)	.279
HDL cholesterol, mg/dL	46 (38–53)	43 (37–47)	.203	54 (45–68)	53 (43–66)	.671	49 (43–60)	47 (39–61)	.211
ASCVD score	4.2 (0.7–8.2)	5.4 (1.7–9.8)	.522	6.4 (3.2–11.8)	7.9 (4.1–12.7)	.428	6.1 (2.8–10.8)	7.1 (3.2–11.7)	.533
Creatinine, mg/dL	0.73 (0.58–0.94)	0.64 (0.57–0.74)	.094	0.79 (0.63–0.92)	0.77 (0.65–0.93)	.636	0.78 (0.62–0.92)	0.73 (0.6–0.88)	.365

Numeric variables are presented as median with interquartile ranges in parentheses. Categorical variables are presented as number of subjects with percentages in parentheses. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTBI, latent tuberculosis infection.

[a]LTBI defined by a positive QuantiFERON-TB test.

[b]*P* values derived by Mann-Whitney-Wilcoxon test for numeric variables. *P* values derived by chi-square or Fisher's exact test for categorical variables. Fisher's exact test was used when a cell had 5 events or less.

[c]History of diabetes mellitus, hypertension, and hyperlipidemia were defined by self-report and verified in available medical records.

Table 2. Coronary Atherosclerosis Parameters Characterized in Computed Tomography Angiography

	Peru			Uganda			Total		
Characteristics	No LTBI (n = 27)	LTBI[a] (n = 42)	*P*[b]	No LTBI (n = 64)	LTBI (n = 71)	*P*[b]	No LTBI (n = 91)	LTBI (n = 113)	*P*[b]
CAD (any plaque), n (%)	9 (33)	16 (38)	.799	13 (20)	17 (24)	.612	22 (24)	33 (29)	.421
CAD-RADS score	0 (0–1)	0 (0–1)	.463	0 (0–0)	0 (0–0)	.626	0 (0–0)	0 (0–1)	.366
CAD-RADS, n (%)			.705			.099			.104
0 = no plaque	18 (67)	26 (62)		51 (79)	54 (76)		69 (76)	80 (71)	
1 = 1–24% stenosis	7 (26)	9 (21)		2 (3)	5 (7)		9 (10)	13 (12)	
2 = 25–49% stenosis	2 (7)	4 (10)		8 (12)	5 (7)		10 (11)	9 (8)	
3 = 50–69% stenosis	0	3 (7)		1 (2)	7 (10)		1 (1)	10 (9)	
4 = 70–99% stenosis	0	1 (2)		1 (2)	0		1 (1)	1 (1)	
5 = total occlusion	0	0		1 (2)	0		1 (1)	0	
Obstructive CAD, n (%)	0	4 (10)	.150	3 (5)	7 (10)	.332	3 (3)	11 (9)	.095
SIS (all; n = 204)	0 (0–2)	0 (0–2)	.612	0 (0–0)	0 (0–0)	.739	0 (0–0)	0 (0–1)	.495
SIS (if SIS >0; n = 55)	3 (2–3)	3 (2–6)	.623	2 (1–5)	2 (1–2)	.227	2 (2–3)	2 (1–3)	.536
SSS (all; n = 204)	0 (0–2)	0 (0–2)	.567	0 (0–0)	0 (0–0)	.744	0 (0–0)	0 (0–1)	.482
SSS (if SSS >0; n = 55)	3 (2–3)	4 (2–8)	.452	3 (2–8)	2 (2–4)	.224	3 (2–5)	3 (2–6)	.617
CAC (all; n = 204)	0 (0–22)	0 (0–15)	.970	0 (0–0)	0 (0–0)	.658	0 (0–0)	0 (0–1)	.619
CAC (if CAC >0; n = 54)	26 (22–163)	55 (15–135)	.899	76 (14–593)	33 (3–87)	.194	59 (16–191)	42 (12–105)	.301

Numeric variables are presented as median with interquartile ranges in parentheses. Categorical variables are presented as number of subjects with percentages in parentheses. Abbreviations: CAC, coronary artery calcium score; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease–Reporting Data System; LTBI, latent tuberculosis infection; SIS, segment involvement score; SSS, segment stenosis score.

[a]LTBI defined by a positive QuantiFERON-TB test.

[b]*P* values derived by Mann-Whitney-Wilcoxon test for numeric variables. *P* values derived by chi-square or Fisher's exact test for categorical variables. Fisher's exact test was used when a cell had 5 events or less.

CAD (9% vs 3%; *P* = .095) in bivariate analyses. There were no significant differences in SIS, SSS, or coronary calcium scores by LTBI status.

Table 3 shows the characteristics of the study population by obstructive CAD. In multivariate analysis, LTBI was associated with increased odds of obstructive CAD (adjusted OR, 4.96; 95% CI, 1.05–23.44; *P* = .043) (Table 4) after adjusting for 10-year ASCVD score, HIV status, and site location. In a sensitivity analysis, we conducted a multivariate logistic regression including potential confounders that had a *P* value of .1 or less

Table 3. Characteristics of the Study Population by Obstructive Coronary Artery Disease

	Peru			Uganda			Total		
Characteristics	No OCAD (n = 65)	OCAD (n = 4)	*P*[a]	No OCAD (n = 125)	OCAD (n = 10)	*P*[a]	No OCAD (n = 190)	OCAD (n = 14)	*P*[a]
Age, years	52 (47–60)	61 (58–65)	.076	56 (52–62)	65 (60–72)	.002	55 (50–62)	63 (60–70)	<.001
Male sex at birth, n (%)	32 (49)	2 (50)	1.000	42 (34)	5 (50)	.317	74 (39)	7 (50)	.414
Hypertension,[b] n (%)	9 (14)	2 (50)	.117	108 (86)	10 (100)	.361	117 (62)	12 (86)	.088
Diabetes mellitus,[b] n (%)	13 (20)	2 (50)	.204	36 (29)	4 (40)	.482	49 (26)	6 (43)	.210
Hyperlipidemia,[b] n (%)	17 (26)	3 (75)	.070	20 (16)	2 (20)	.666	37 (20)	5 (36)	.170
Current smoking, n (%)	4 (6)	1 (25)	.265	6 (5)	0	1.000	10 (5)	1 (7)	.552
Systolic BP	118 (108–130)	125 (110–135)	.416	137 (120–159)	147 (124–168)	.332	129 (115–145)	140 (123–162)	.184
Diastolic BP	74 (70–80)	74 (65–84)	.774	80 (71–91)	78 (73–82)	.456	79 (70–88)	78 (71–82)	.612
BMI, kg/m^2	26.9 (25.6–28.1)	28.5 (26.9–33.3)	.098	29.2 (25.3–32.9)	28.9 (24.4–32.2)	.753	27.5 (25.4–31.6)	28.9 (24.9–32.2)	.586
Total cholesterol, mg/dL	196 (174–218)	199 (183–234)	.411	195 (174–231)	218 (185–288)	.219	195 (174–226)	207 (184–253)	.162
LDL cholesterol, mg/dL	113 (96–131)	125 (112–142)	.397	128 (108–159)	152 (130–224)	.061	124 (102–149)	136 (124–184)	.052
HDL cholesterol, mg/dL	43 (37–49)	49 (42–53)	.433	54 (44–66)	52 (36–60)	.502	49 (42–61)	50 (37–56)	.787
ASCVD risk score	4.2 (1.4–9.1)	9.7 (7.1–18)	.057	6.5 (3.4–11.6)	19.4 (7.9–43.5)	<.001	6.1 (2.8–10.8)	17.4 (7.9–25)	<.001
Latent TB infection,[c] n (%)	38 (59)	4 (100)	.150	64 (51)	7 (70)	.332	102 (54)	11 (79)	.095
HIV status	0	0	NA	49 (39%)	2 (20%)	.318	49 (26%)	2 (14%)	.525

Numeric variables are presented as median with interquartile ranges in parentheses. Categorical variables are presented as number of subjects with percentages in parentheses. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OCAD, obstructive coronary artery disease; TB, tuberculosis.

[a]*P* values derived by Mann-Whitney-Wilcoxon test for numeric variables. *P* values derived by chi-square or Fisher's exact test for categorical variables. Fisher's exact test was used when a cell had 5 events or less.

[b]History of diabetes mellitus, hypertension, and hyperlipidemia were defined by self-report and verified in available medical records.

[c]Latent TB infection defined by a positive QuantiFERON-TB test.

Table 4. Results of Multivariate Logistic Regression of Obstructive Coronary Artery Disease (Dependent Variable) and Latent Tuberculosis Infection

Variable	Adjusted Odds Ratio (95% CI)	*P*
ASCVD risk score (per 1% increase in risk)	1.1 (1.05–1.16)	<.001
Latent tuberculosis infection[a]	4.96 (1.05–23.44)	.043
HIV infection	1.24 (.21–7.37)	.814
Site (Peru vs Uganda)	.83 (.4–1.72)	.625

The data fit the model well (goodness-of-fit test, $P = .416$). No collinearity or interactions were observed in the model; N = 204.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HIV, human immunodeficiency virus.
[a]Latent tuberculosis infection defined by a positive QuantiFERON-TB test.

in bivariate analyses. The association between LTBI and obstructive CAD remained significant (adjusted OR, 4.8; 95% CI, 1.06–21.79; $P = .042$) after adjusting for 10-year ASCVD score, age, hypertension, and LDL cholesterol.

We then examined the relationship between obstructive CAD and the quantitative interferon-γ responses in the QFT assay among all participants. The distribution of interferon-γ values in response to *Mycobacterium tuberculosis* antigens (QFT TB Ag), in background (QFT Nil), and in background-corrected *M. tuberculosis* antigen responses (QFT TB Ag minus Nil) are shown in Table 5. Persons with obstructive CAD had a higher magnitude of QFT TB Ag interferon-γ responses compared with persons without obstructive CAD (interferon-γ [IQR], 6.63 [0.6–10] vs 0.67 [0.17–3.19] IU/L; $P = .009$). In multivariate analysis, QFT TB Ag interferon-γ values were independently associated with obstructive CAD (adjusted OR, 1.2; 95% CI, 1.07–1.45; $P = .005$) after adjusting for 10-year ASCVD risk score, HIV status, and site location. Individuals with obstructive CAD had similar QFT Nil interferon-γ responses in bivariate analysis (0.19 [0.11–1.36] vs 0.15 [0.09–0.33]; $P = .148$). In multivariate analysis, however, QFT Nil interferon-γ values were independently associated with obstructive CAD (adjusted OR, 1.7; 95% CI, 1.16–2.54, $P = .007$) after adjusting for 10-year ASCVD risk score, HIV status, and site location. Finally, persons with obstructive CAD displayed higher QFT TB Ag minus Nil quantitative interferon-γ responses (4.65 [0.49–8.33] vs 0.43 [0.01 vs 2.71]; $P = .011$). QFT TB Ag minus Nil interferon-γ values were independently associated with obstructive CAD (adjusted OR, 1.2; 95% CI, 1.03–1.41; $P = .022$) after adjusting for 10-year ASCVD risk score, HIV status, and site location.

To explore the relationship between LTBI and obstructive CAD in PLWH, we conducted a subanalysis of obstructive CAD restricted to PLWH at the Uganda site (n = 51). Of 17 PLWH with LTBI, 1 (6%) had obstructive CAD. Of 34 PLWH without LTBI, 1 (3%) had obstructive CAD. Latent TB infection was not significantly associated with obstructive CAD in PLWH (adjusted OR, 2.11; 95% CI, .11–37) after adjusting by 10-year ASCVD risk score. Quantitative QFT TB Ag minus Nil interferon-γ responses were associated with obstructive CAD in PLWH (adjusted OR, 1.5; 95% CI, 1–2.32; $P = .050$) after adjusting by 10-year ASCVD risk score.

DISCUSSION

We found that LTBI was independently associated with increased odds of subclinical obstructive CAD, after adjusting for 10-year ASCVD risk score, HIV status, and recruitment site. To our knowledge, this is the first study to characterize coronary atherosclerosis burden by LTBI status. Our data indicate that LTBI is a nontraditional correlate of ASCVD risk.

Studies have shown that persons with TB disease carry an increased risk of ASCVD events, including acute myocardial infarction [4], acute coronary syndrome [5], ischemic stroke [6], and peripheral arterial disease [7]. A recent meta-analysis estimated a pooled relative risk of 1.5 for major adverse cardiac events in people with TB compared with people without TB [8]. This meta-analysis included studies with an average follow-up time of 5 years after TB diagnosis. Furthermore, long-term all-cause mortality is approximately 3-fold higher in people treated for TB compared with the general population or matched controls, with most deaths attributable

Table 5. Quantitative Interferon-γ Responses in the QuantiFERON-TB Assay by Obstructive Coronary Artery Disease

	Peru			Uganda			Total		
QFT Quantitative IFNg Responses	No OCAD (n = 65)	OCAD (n = 4)	*P*[a]	No OCAD (n = 125)	OCAD (n = 10)	*P*[a]	No OCAD (n = 190)	OCAD (n = 14)	*P*[a]
QFT TB Ag,[b] IFNg	0.97 (0.26–3.7)	6.6 (5.8–8.7)	.009	0.51 (0.12–2.9)	5 (0.3–10)	.075	0.67 (0.17–3.2)	6.63 (0.6–10)	.009
QFT Nil, IFNg	0.25 (0.15–0.67)	1.4 (0.7–2.5)	.019	0.12 (0.1–0.19)	0.12 (0.1–0.26)	.267	0.15 (0.1–0.33)	0.19 (0.11–1.4)	.148
QFT TB Ag minus Nil, IFNg	0.44 (0.03–2.6)	5.1 (4.7–6.6)	.016	0.42 (0.01–2.7)	2.2 (0.14–9.1)	.101	0.43 (0.01–2.7)	4.7 (0.49–8.3)	.011

Data presented as median with interquartile ranges in parenthesis.
Abbreviations: IFNg, interferon-γ (in IU/mL); OCAD, obstructive coronary artery disease; QFT, QuantiFERON-TB; QFT TB Ag, QuantiFERON TB Antigen responses; QFT Ag minus Nil, QuantiFERON TB Antigen minus Nil responses; QFT Nil, QuantiFERON Nil responses.
[a]*P* values derived by Mann-Whitney-Wilcoxon test.
[b]QFT TB Ag data source was TB1 Antigen in Peru from QFT-Plus assay and TB Antigen in Uganda from QFT-GIT assay.

to CVD [9]. We previously showed that persons with a first-time acute myocardial infarction had 2-fold increased odds of having LTBI [17], whereas others recently reported that LTBI was associated with coronary artery stenosis in persons presenting with chest pain who underwent percutaneous coronary angiography for clinical assessment of CAD [31]. In the present study, we found that asymptomatic individuals with LTBI and no known history of ASCVD events exhibited a higher likelihood of subclinical obstructive CAD. Notably, obstructive CAD defined by a CAD-RADS of 3 or greater in CCTA predicts the occurrence of subsequent cardiac events [25]. Prospective studies are needed to determine if our cross-sectional findings translate into an increased risk of future ASCVD events among those with LTBI, and whether LTBI treatment modifies such risk.

Mycobacterium tuberculosis infection may contribute to atherosclerosis development through different mechanisms, including enhanced monocyte activation, T-cell activation, and molecular mimicry between mycobacterial and human heat shock protein (HSP) system epitopes [32]. Here we demonstrate that *M. tuberculosis*–specific cell-mediated responses captured in the QFT TB antigen tube were independently associated with obstructive CAD after adjusting for possible confounders. Whether augmented *M. tuberculosis*–specific immunity in response to existing or resolved mycobacterial antigen loads directly contributes to coronary atherosclerosis burden or rather is a marker of a more generalized, non–TB-specific proinflammatory state could be explored in future studies. Interferon-γ (type II interferon) is a proinflammatory cytokine that activates monocyte/macrophages and has a key role in *M. tuberculosis* infection control [33, 34]. When individuals with LTBI progress to TB, the expression of type II interferon genes may become less abundant, while a type I interferon overabundant signature develops in peripheral blood [35, 36]. There is increasing recognition of the pro-atherogenic potential of both type I and II interferon signals [37, 38]. Therefore, understanding the dynamic balance between type I and II interferon responses within the spectrum of *M. tuberculosis* infection may shed light into mechanisms of ASCVD in the context of TB and other infections with similar disease pathways.

This study had limitations. We used an IGRA (ie, QFT) to define LTBI according to current guidelines. IGRAs may produce false-negative or -positive results and thus future studies may consider including both tuberculin skin test (TST) and IGRA testing. However, it is important to note that IGRAs are preferred over TST in populations with high rates of bacille Calmette Guérin (BCG) vaccination because of increased specificity [39]. Furthermore, our overall LTBI rate (55%) is comparable to results of prior studies conducted in Peru and Uganda [17, 40]. Variations in inclusion criteria between enrollment sites led to overall differences in some ASCVD risk factors by country. However, cardiovascular risk factors were distributed similarly in the LTBI and non-LTBI populations across countries. Moreover, we adjusted for site location in all multivariate analyses. Our sample size may not have been large enough to detect more subtle differences in coronary atherosclerosis burden across groups, as the overall prevalence of obstructive CAD was low. Additionally, studies with larger representation of PLWH would be needed to better characterize the interplay between HIV, *M. tuberculosis* infection, and ASCVD. Despite sample size limitations, we were able to detect associations between obstructive CAD, LTBI, and well-established traditional ASCVD risk factors [29]. Of note, ASCVD risk score was a strong predictor of obstructive CAD in our population, which provides internal validity to our findings. Our cross-sectional assessment did not allow us to explore the relationship between LTBI and the development of obstructive CAD over time. Prospective studies would be needed to assess changes in atherosclerosis burden among individuals with LTBI. Although we used different CT scanners in Peru and Uganda, the images obtained from these scanners are comparable and not expected to impact our analysis nor have channeled plaque burden findings differently in individuals with LTBI versus without LTBI. High-end scanners as those used in this study usually have high image quality and reproducibility of plaque findings [41]. Furthermore, the median number of evaluable coronary segments was only 1 point different between CT scanners in our study (15 and 14 evaluable coronary segments in Peru and Uganda, respectively), indicating overall good quality of the CCTA examinations at both locations.

In conclusion, LTBI and *M. tuberculosis*–specific cell-mediated responses were independently associated with obstructive CAD. Studies are needed to define the mechanisms of increased coronary atherosclerosis burden in persons with LTBI and the possible effects of LTBI treatment on ASCVD risk. Recognizing LTBI as a potential nontraditional correlate of ASCVD risk may inform ongoing and future studies of CVD prediction and prevention globally.

Notes

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