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Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus

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SUMMARY

SETTING—Although diabetes mellitus (DM) is an established risk factor for active tuberculosis (TB) disease, little is known about the association between pre-DM, DM, and latent tuberculous infection (LTBI).

OBJECTIVE—To estimate the association between DM and LTBI.

DESIGN—We conducted a cross-sectional study among recently arrived refugees seen at a health clinic in Atlanta, GA, USA, between 2013 and 2014. Patients were screened for DM using glycosylated-hemoglobin (HbA1c), and for LTBI using the QuantiFERON®-TB (QFT) test. HbA1c and QFT results, demographic information, and medical history were abstracted from patient charts.

RESULTS—Among 702 included patients, 681 (97.0%) had HbA1c and QFT results. Overall, 54 (7.8%) patients had DM and 235 (33.8%) had pre-DM. LTBI was prevalent in 31.3% of the refugees. LTBI prevalence was significantly higher ($P < 0.01$) among patients with DM (43.4%) and pre-DM (39.1%) than in those without DM (25.9%). Refugees with DM (adjusted OR [aOR] 2.3, 95%CI 1.2–4.5) and pre-DM (aOR 1.7, 95%CI 1.1–2.4) were more likely to have LTBI than those without DM.

CONCLUSION—Refugees with DM or pre-DM from high TB burden countries were more likely to have LTBI than those without DM. Dysglycemia may impair the immune defenses involved in preventing *Mycobacterium tuberculosis* infection.

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Keywords

hemoglobin A1c; QuantiFERON test; refugee; vitamin D

The increasing emergence of diabetes mellitus (DM) has considerably affected developing countries where tuberculosis (TB) is endemic. Six of the 10 countries projected to have the greatest DM burdens by the year 2035—China, India, Brazil, Indonesia, Pakistan and Russia—are classified as high TB burden countries by the World Health Organization (WHO).[1] The intersection of DM and TB has substantial public health implications: patients with DM are approximately three times more likely to develop active TB than those without DM,[2] and globally an estimated 15–25% of annual incident TB cases are attributable to DM.[3,4] The growing evidence of the harmful confluence between DM and TB demonstrates an urgent need to better understand this syndemic.

While the association between DM and risk of active TB has been well documented,[2,5,6] data describing the relationship between pre-DM, DM, and latent tuberculous infection (LTBI) are scarce. LTBI is defined as asymptomatic infection with *Mycobacterium tuberculosis* in which the bacteria are contained by the host's immune system. Approximately one third of the world's population has LTBI, and this large reservoir of *M. tuberculosis* is a significant impediment to TB eradication.[7] The lifetime risk of LTBI progressing to active TB is estimated at 10%, with an increased risk among those with immunosuppressive conditions.[7] Although DM increases the risk of active TB disease, it is unclear if the excess disease is due to primary progression to active TB disease, risk of LTBI, reactivation of LTBI to active TB disease, or a combination of these mechanisms. In vivo and in vitro studies have suggested that DM may affect vulnerability to *M. tuberculosis* infection due to its effects on innate and adaptive immunity.[8,9] However, whether the initial immune response to TB exposure and subsequent development of LTBI differs in patients with DM compared to those without DM is unclear. Clarification about the relationship between DM and risk of LTBI is critical for effective disease control and prevention.

The purpose of the present study was to examine whether patients with DM and pre-DM were at increased risk of having LTBI; our study was carried out at a clinic for recently arrived refugees in the United States who come from regions with high incidence of active TB.

STUDY POPULATION AND METHODS

We conducted a cross-sectional study among recently arrived refugees at the DeKalb County Board of Health Refugee Clinic (metro Atlanta, GA, USA) between October 2013 and August 2014. All adult (age ≥21 years) US Department of State refugees who had undergone new patient health screening during the study period were eligible. As standard of care, all new patients at DeKalb County Refugee Clinic underwent a venous blood draw and were screened for DM using glycosylated hemoglobin (HbA1c), LTBI using the QuantiFERON®-TB Gold In-Tube test (QFT; Cellestis, Carnegie, VIC, Australia), and vitamin D deficiency using total volume of 25-hydroxyvitamin D (25OHD). For this study,

results of the HbA1c, QFT, and 25OHD tests were abstracted from patient charts. Demographic information and pertinent medical history were also obtained via chart review.

Measures and definitions

The primary exposure was DM status, measured by HbA1c and classified according to 2015 American Diabetes Association guidelines: no DM (≤5.6%), pre-DM (≥5.7–6.4%), and DM (≥6.5%).[10] HbA1c was measured in 1 ml of whole blood collected in ethylenediaminetetra-acetic acid tubes and processed using immunoturbidimetry (Quest, Tucker, GA, USA). Patients with HbA1c <6.5% with a previous diagnosis of DM indicated in their medical chart were also defined as DM. Presence of LTBI was determined by a positive QFT test result, as previously described.[11] The QFT was performed by County Wide Services (CWS) Laboratory following the manufacturer's instructions and Centers for Disease Control and Prevention guidelines.[12] Patients were considered to have LTBI if the QFT results were positive and chest radiographs were negative. Total volume of circulating plasma 25OHD was measured in venous blood by liquid chromatography tandem mass spectrometry (Quest) and categorized per the Clinical Practice Guidelines of the Endocrine Society; 25OHD concentration <20 ng/ml was considered vitamin D deficient.[13]

The following covariates were obtained by chart review: age, body mass index (BMI), sex, current smoking status (self-reported current user of cigarettes), and country of origin. In addition, TB incidence in country of origin was defined as moderate (<100), medium (100–299), or high (≥300) incidence (annual new cases per 100 000 population) according to 2014 WHO classifications.[14,15] Additional laboratory results obtained included hemoglobin, human immunodeficiency virus (HIV) serologic status, hepatitis B (HBsAb and HBsAg), hepatitis C virus serology, and syphilis (rapid plasma reagin [RPR]) test results.

Data analyses

All analyses were performed using SAS 9.3 (Statistical Analysis System, Cary, NC, USA). Bivariate analyses (χ^2 test for categorical variables and the Wilcoxon or Kruskal-Wallis for non-normally distributed continuous variables) were used to determine the association of participant characteristics, including DM status, with LTBI. A multivariable logistic model was used to estimate the association between participants' DM status (categorized into a three-level variable: no DM, pre-DM, and DM) and LTBI status, which was adjusted for age, sex, BMI, and TB burden in country of origin, smoking status, and plasma 25OHD. Covariates included in the model were chosen based on observed bivariate associations with DM and LTBI, directed acyclic graph theory,[16] and previous literature. We assessed the heterogeneity of the effect of pre-DM and DM on LTBI across dichotomous categories of vitamin D using the Breslow-Day test. Additional multivariable logistic models were used to assess the interaction between DM status and 25OHD levels using their product term; the likelihood ratio test was used to determine the significance of the interaction term. A two-sided P value < 0.05 was considered statistically significant for all analyses.

Ethical approval

The study was approved by the Institutional Review Boards (IRB) of Emory University, Atlanta, GA, and the Georgia Department of Public Health, Atlanta, GA, USA.

RESULTS

A total of 715 adult patients (aged ≥21 years) were seen at the DeKalb County Refugee Clinic (metro Atlanta, GA, USA) between October 2013 and August 2014 and met the inclusion criteria. Chart abstraction was available for 98.2% (702/715) of the eligible patients and included in the analyses. The 702 included patients came from 54 countries; 695 (99.0%) had HbA1c results, 694 (98.9%) had QFT results, and 681 (97.0%) had both HbA1c and QFT results. Of those with HbA1c results, 54 (7.8%) had DM and 235 (33.8%) had pre-DM (Table 1). LTBI prevalence was 31.8% (221/694). The majority of the refugees were male (55.0%); the most common countries of origin were Burma (30.9%), Bhutan (22.9%), Iraq (12.0%), and Somalia (10.0%).

Patients with DM were more likely to be older (median age 48.1 vs. 32.9 years) and have a higher BMI (median 29.1 vs. 23.6 kg/m^2) compared to those without DM ($P < 0.01$). Among patients with DM, median random blood glucose was 137 mg/dl (interquartile range [IQR] 108–214) and median HbA1c was 7.2% (IQR 6.6–9.8). Patients with DM had significantly lower plasma 25OHD levels (median 19 vs. 21 ng/ml, $P=0.03$) than those without (pre-DM and no DM combined).

LTBI was significantly more common among patients with DM (43.4%) and pre-DM (39.1%) compared to those without DM (25.9%, $P < 0.01$) (Table 2). Similarly, median HbA1c was higher in patients with LTBI (5.7% vs. 5.5%) than those without LTBI ($P < 0.01$). Patients with LTBI were more likely to be older (median age 34.7 vs. 32.0), male (58.5% vs. 54.0%), hepatitis B HbsAB positive (66.1% vs. 55.9%), and to come from medium or high TB incidence countries (97.3% vs. 92.8%) ($P < 0.05$ for all comparisons).

Among the 54 patients with DM, 24 (44.4%) gave a history of prior DM diagnosis and 30 (55.6%) were newly diagnosed with DM (Table 3). LTBI prevalence was similar in patients with (43.5%) and without (43.3%) a previous DM diagnosis. Among those with a previous DM diagnosis, 45.8% (11/24) were receiving any DM medication and 25.0% (6/24) had HbA1c <6.5%. Those with a new diagnosis of DM were significantly more likely to be male (63.3% vs. 30.4%, $P < 0.01$) and had higher plasma vitamin D levels (median 22 vs. 15 ng/ml, $P < 0.01$) than those with a previous diagnosis.

In multivariable analysis, there was a significant association between DM (adjusted odds ratio [aOR] 2.3, 95% confidence interval [CI] 1.2–4.5), pre-DM (aOR 1.7, 95%CI 1.1–2.4) and prevalent LTBI (Table 4). Both previously diagnosed DM (aOR 2.7, 95%CI 1.0–7.1) and newly diagnosed DM (aOR 2.0, 95%CI 0.9–4.6) were associated with prevalent LTBI. We detected a statistical interaction between DM status and 25OHD deficiency ($P < 0.01$); among those with 25OHD deficiency (<20 ng/ml), the adjusted odds of LTBI in those with DM (aOR 4.4, 95%CI 1.8–11.2) and pre-DM (aOR 2.6, 95%CI 1.5–4.7) was significantly greater than those without DM (Table 5). The effect of DM or pre-DM on LTBI prevalence was not significant among patients with a 25OHD concentration ≥20 ng/ml.

DISCUSSION

Although DM is a well-established risk factor for active TB disease, to our knowledge this is the first study to describe an association of both DM and pre-DM with LTBI. Among newly arrived refugees in the United States, LTBI was significantly more common among those with DM and pre-DM than in those without DM. In multivariable analyses adjusted for confounders, the only risk factors for LTBI were DM or pre-DM and TB incidence in the country of origin. Importantly, we reported that 25OHD modifies the effect of DM on LTBI. Among patients with low 25OHD deficiency, 51.9% of those with DM had LTBI compared to 18.3% in those without DM. Our findings indicate a potential role of screening for LTBI in patients with DM from high TB incidence settings, and provide novel information to better understand the convergence of the DM and TB epidemics.

Screening for DM in patients with active TB is widely recommended, especially where DM prevalence is high.[17] LTBI screening in DM patients, particularly those who lived in high TB settings, may help identify a high-risk population for preventive TB treatment.[3] Among newly arrived refugees seen at the DeKalb County Refugee Clinic, 55.6% (30/54) of the DM patients were newly diagnosed. Given the high proportion of newly diagnosed DM and our observed association between DM and LTBI, our preliminary findings suggest that screening for DM in similar refugee clinic settings may be an efficient approach for identifying patients at high risk of active TB.

Although the increased risk of active TB disease among those with DM is recognized,[2,5,18] to date few data are available on the association between LTBI and DM. We are unaware of previous studies that have determined LTBI prevalence among DM patients compared to those without DM. At least two previous studies have reported high LTBI prevalence among patients with DM, but neither of these included a control group and they therefore could not estimate the association between DM and LTBI.[19,20] Unlike previous studies, we had a comparison group of patients without DM. Our study is thus the first to report an adjusted prevalence OR for the association between DM and pre-DM with LTBI.

Several hypotheses have been proposed to explain the mechanism of hyperglycemia in the pathogenesis of LTBI.[9] Poor glycemic control is associated with macrophage glycation and the defective sentinel hypothesis, in which monocytes fail to absorb *M. tuberculosis* due to reduced activation in alveolar macrophages.[9,21,22] A sequence analysis of CD271 glycation in mesenchymal stem cells by Bhattacharyya et al. found that glycation of the CD271 functional domain of mesenchymal stem cells may occur in long-standing, uncontrolled DM.[23] This phenomenon has the potential to modulate the life span of $CD271^+$ cells, which may provide a niche for *M. tuberculosis* in LTBI.[23] Furthermore, antimicrobial peptide (AMP) gene expression has been associated with LTBI, active TB and DM.[24–26] Differential expression of AMP, such as human β-defensin-2, in patients with DM may contribute to the increased risk of LTBI and active TB.[24] Vitamin D deficiency is associated with TB, and the immune-modulatory role of vitamin D on immunity to TB has been studied extensively.[27]

Vitamin D deficiency is associated with both an increased risk of active TB and an increased risk of progression from LTBI to active TB.[28] In addition, vitamin D deficiency is associated

with DM and insulin resistance, including abnormal pro-inflammatory response in macrophages.[29,30] While we did not find that vitamin D deficiency was associated with LTBI, we did report that the median 25OHD plasma level among patients with DM (19 ng/ml IQR 13–26) was significantly lower than in those without DM (21 ng/ml IQR 16–27). We also reported an interaction between vitamin D deficiency and LTBI prevalence: the effect of DM on LTBI was very strong (aOR 4.4) among patients with low vitamin D levels. This finding suggests that low 25OHD and DM may interact synergistically to increase the risk of LTBI.

There are limitations in our study. First, as the study population included only refugees in the United States, the results cannot be generalized to persons living in the refugees' countries of origin. Additional studies are needed to examine the association between DM and LTBI in other populations, for example among samples of persons from a low TB burden region with and without DM. Second, as our study was cross-sectional, we were unable to quantify DM duration. We could not therefore estimate the association between DM chronicity and LTBI. Nonetheless, we measured DM and pre-DM using HbA1c, the American Diabetes Association's recommended screening tool for DM. HbA1c screening provides an estimate of glucose control over the previous 3-month period, an advantage over random blood glucose. Third, as our study was not able to determine whether the primary outcome (LTBI) followed the exposure (DM) in time, we cannot rule out the possibility that LTBI increased the prevalence of DM. Although we used a cross-sectional design and cannot demonstrate temporality, we report a robust association between DM and LTBI using validated standard screening tests to measure DM and LTBI. Importantly, QFT was used to measure LTBI prevalence, an advantage over tuberculin skin testing, given the increased specificity in our patient population with high bacille Calmette-Guérin vaccination rates.[11]

CONCLUSION

With over 95% of the nine million annual TB cases occurring in low- and middle-income countries, and the burden of DM shifting toward these regions, it is critical to better understand the relationship between DM, pre-DM and LTBI to target those populations at highest risk for developing active TB. The results of this study not only show a positive association between DM and LTBI, they also suggest that the rate of LTBI increases with higher HbA1c levels. This supports the theory that dysglycemia impairs host immune defenses involved in preventing LTBI. The potential synergistic mechanisms between vitamin D and DM and the resulting risk of tuberculous infection merit further investigation.

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Table 1

Characteristics of adult refugee patients stratified by DM status

	No DM (*n* = 406, 58.4%) *n* (%)	**Pre-DM (*n* = 235, 33.8%) *n* (%)**	**DM (*n* = 54, 7.8%) *n* (%)**	**Total (*n* = 695, 100%) *n* (%)**	***P* value**
Demographics					
Age, years					
Median [IQR]	32.9 [26.6–42.3]	37.5 [26.8–44.2]	48.1 [39.9–57.6]	36.1 [26.6–42.3]	<0.01*
<25	80 (19.8)	40 (17.1)	2 (3.8)	122 (17.7)	<0.01*
25–44	272 (67.3)	138 (59.0)	20 (37.7)	430 (62.2)	
45–64	43 (10.6)	48 (20.5)	20 (37.7)	111 (16.1)	
≥65	9 (2.2)	8 (3.4)	11 (21.8)	28 (4.1)	
Sex					
Female	171 (42.3)	111 (48.3)	27 (50.9)	309 (45.0)	0.23
Male	233 (57.7)	119 (51.7)	26 (49.1)	378 (55.0)	
TB incidence in country of origin†					
<100	24 (5.9)	13 (5.5)	3 (5.6)	40 (5.8)	<0.01*
100–299	222 (54.7)	164 (69.8)	37 (68.5)	354 (60.9)	
≥300	160 (39.4)	58 (24.7)	14 (25.9)	232 (33.4)	
Current smoker					
Unknown	5 (1.2)	6 (2.6)	0	11 (1.6)	0.54
No	303 (75.0)	179 (76.5)	40 (76.9)	522 (75.7)	
Yes	96 (23.8)	49 (20.9)	12 (23.1)	157 (22.8)	
Clinical information					
Body mass index, kg/m^2					
Median [IQR)	23.6 [20–26]	25.2 [22–28]	29.1 [24–34]	24.0 [21–27]	<0.01*
<18.5	35 (8.6)	16 (6.8)	3 (5.6)	54 (7.8)	
18.5–24.9	242 (59.6)	96 (40.9)	15 (27.8)	353 (50.8)	
25–29.9	98 (24.1)	93 (39.6)	14 (25.9)	205 (29.5)	
≥30.0	31 (7.6)	30 (12.8)	22 (40.7)	83 (11.9)	<0.01*
Random blood glucose, mg/dl					

	No DM (n = 406, 58.4%) n (%)	Pre-DM (n = 235, 33.8%) n (%)	DM (n = 54, 7.8%) n (%)	Total (n = 695, 100%) n (%)	P value
Median [IQR]	90 [84–96]	94 [87–103]	137 [108–214]	92 [86–101]	<0.01*
<70	7 (1.7)	2 (0.9)	0	9 (1.3)	<0.01*
70–99	318 (78.5)	156 (66.4)	10 (18.9)	484 (69.9)	
100–125	75 (18.5)	66 (28.1)	13 (24.5)	154 (22.2)	
≥126	5 (1.2)	11 (4.7)	30 (56.6)	46 (6.6)	
Glycated hemoglobin, %					
Median [IQR]	5.4 [5.2–5.5]	5.8 [5.7–6.0]	7.2 [6.6–9.8]	5.6 [5.4–5.8]	<0.01*
Hemoglobin, mg/dl					
<12.1	33 (8.3)	25 (11.0)	2 (3.9)	60 (8.8)	0.91
12.1–17.3	351 (87.8)	198 (86.8)	47 (92.2)	596 (87.8)	
>17.3	16 (4.0)	5 (2.2)	2 (3.9)	23 (3.4)	
Vitamin D, ng/ml					
Median [IQR]	21 [16–27]	21 [16–27]	19 [13–26]	21 [15–27]	0.17
<20	171 (42.3)	94 (40.7)	27 (50.9)	292 (42.4)	0.03‡
20–30	159 (39.4)	96 (41.6)	19 (35.9)	274 (39.8)	0.71
>30	74 (18.3)	41 (17.8)	7 (13.2)	122 (17.7)	
Syphilis, rapid plasma reagin test					
Negative	400 (98.5)	228 (97.0)	51 (98.1)	679 (98.0)	0.53
Positive	5 (1.2)	7 (3.0)	1 (1.9)	13 (1.9)	
Unknown	1 (0.3)	0	0	1 (0.1)	
Hepatitis B, HBsAb					
Negative	173 (42.9)	91 (38.9)	20 (37.7)	284 (41.2)	0.53
Positive	230 (57.1)	143 (61.1)	33 (62.3)	406 (58.8)	
Hepatitis B, HBsAg					
Negative	389 (96.3)	232 (98.7)	53 (100.0)	674 (97.4)	0.08
Positive	15 (3.7)	3 (1.3)	0	18 (2.6)	
Hepatitis C, antibody					
Negative	399 (98.5)	230 (97.9)	51 (98.1)	681 (98.4)	0.67
Positive	5 (1.2)	5 (2.1)	1 (1.9)	11 (1.6)	

	No DM (*n* = 406, 58.4%) *n* (%)	Pre-DM (*n* = 235, 33.8%) *n* (%)	DM (*n* = 54, 7.8%) *n* (%)	Total (*n* = 695, 100%) *n* (%)	*P* value
Alcohol use					
No	301 (74.3)	179 (76.5)	44 (84.6)	524 (75.8)	0.47
Yes	91 (22.5)	49 (20.9)	8 (15.4)	148 (21.4)	
Unknown	13 (3.2)	6 (2.6)	0	19 (2.8)	
HIV status					
Negative	401 (98.8)	229 (97.9)	50 (96.2)	680 (98.3)	0.53
Positive	4 (1.0)	4 (1.7)	2 (3.9)	10 (1.5)	
Not done	1 (0.3)	1 (0.4)	0	2 (0.3)	

*Statistically significant, χ^2 (categorical) or Kruskal-Wallis (medians) two-sided *P* value < 0.05.

†Annual active cases per 100 000 population: low (<100), medium (100–300), and high burden (>300) TB countries defined according to the WHO 2014 TB report.[14]

‡One-sided Wilcoxon rank sum test comparing median vitamin D levels in those with DM and those without DM (combined pre-DM and no DM).

DM = diabetes mellitus; IQR = interquartile range; TB = tuberculosis; HbsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; WHO = World Health Organization; IU = international unit.

Table 2

Characteristics of adult refugee patients with LTBI, Dekalb County Refugee Clinic, 2013–2014

	Negative QFT (*n* = 473, 68.2%) *n* (%)	Positive QFT (*n* = 221, 31.8%) *n* (%)	Total* (*n* = 694, 100%) *n* (%)	*P* value
Demographics				
Age				
Median [IQR]	32.0 [26.4–41.0]	34.7 [27.3–46.3]	32.9 [26.6–42.3]	0.01†
<25	90 (19.2)	35 (16.0)	125 (18.1)	0.01
25–44	301 (63.8)	127 (58.3)	428 (62.0)	
45–64	64 (13.6)	45 (20.6)	109 (15.8)	
≥65	17 (3.6)	11 (5.1)	28 (4.1)	†
Sex				
Female	216 (46.0)	90 (41.5)	306 (44.5)	<0.01†
Male	254 (54.0)	127 (58.5)	381 (55.5)	
TB incidence in country of origin‡				
<100	34 (7.2)	6 (2.7)	40 (5.8)	0.04†
100–299	279 (59.0)	145 (65.6)	424 (61.1)	
≥300	160 (33.8)	70 (31.7)	230 (33.1)	
Current smoker				
No	366 (77.4)	171 (77.4)	537 (77.4)	0.99
Yes	107 (22.6)	50 (22.6)	157 (22.6)	
Clinical information				
DM status				
No DM	297 (63.3)	104 (47.7)	401 (58.4)	<0.01†
Pre-DM	142 (30.3)	91 (41.7)	233 (33.9)	
DM	30 (6.4)	23 (10.6)	53 (7.7)	
Glycated hemoglobin, %				
Median [IQR]	5.5 [5.3–5.8]	5.7 [5.4–6.0]	5.6 [5.4–5.8]	<0.01†
Random blood glucose, mg/dl				
Median [IQR]	92 [85–99]	92 [86–105]	92 [86–100]	0.17
On LTBI treatment				
No	387 (82.0)	15 (6.9)	402 (58.2)	0.58
Yes	85 (18.0)	204 (93.1)	289 (41.8)	
Body mass index, kg/m^2				
Median [IQR]	23.9 [21–27]	24.1 [21–27]	24.0 [21–27]	0.76
<18.5	35 (7.4)	19 (8.6)	54 (7.8)	0.13
18.5–24.9	246 (35.5)	107 (48.4)	353 (50.9)	
25–29.9	128 (27.1)	75 (29.3)	203 (29.3)	
≥30.0	64 (13.5)	20 (9.1)	84 (12.1)	
Vitamin D, ng/ml				
Median [IQR]	20 [15–27]	21 [16–27]	21 [15–27]	0.42

	Negative QFT (*n* = 473, 68.2%) *n* (%)	Positive QFT (*n* = 221, 31.8%) *n* (%)	Total* (*n* = 694, 100%) *n* (%)	*P* value
<20 ng/ml	209 (44.7)	83 (38.1)	292 (42.6)	0.45
20–30 ng/ml	172 (36.8)	100 (45.9)	272 (39.7)	
>30 ng/ml	87 (18.6)	35 (16.1)	122 (17.8)	
Syphilis, rapid plasma reagin test				
Negative	463 (97.9)	216 (98.6)	679 (98.1)	0.50
Positive	10 (2.1)	3 (1.4)	13 (1.9)	
Hepatitis B, HBsAb				
Negative	208 (44.1)	74 (33.9)	282 (40.9)	0.01†
Positive	264 (55.9)	144 (66.1)	408 (59.1)	
Hepatitis B, HBsAg				
Negative	459 (97.3)	214 (97.7)	673 (97.4)	0.72
Positive	13 (2.8)	5 (2.3)	18 (2.6)	
Hepatitis C, antibody				
Negative	466 (98.9)	213 (97.3)	679 (98.4)	0.10
Positive	5 (1.1)	6 (2.7)	11 (1.6)	
Alcohol use				
No	353 (75.0)	171 (78.1)	524 (76.0)	0.49
Yes	103 (21.9)	44 (20.1)	147 (21.3)	
Unknown	15 (3.2)	4 (1.8)	19 (2.8)	
HIV status				
Negative	465 (98.6)	215 (98.2)	680 (98.4)	0.68
Positive	6 (1.3)	4 (1.8)	10 (1.5)	
Not done	1 (0.2)	0	1 (0.1)	

*Some columns may not total 100% due to missing data (variables with >3% missing are reported as unknown).

†Statistically significant, χ^2 (categorical) or Wilcoxon rank (medians) two-sided *P* value < 0.05.

‡Incident active TB cases per 100 000 population, per WHO 2014 TB report.[14]

LTBI = latent tuberculous infection; QFT = QuantiFERON®-TB Gold In-Tube test; IQR = interquartile range; TB = tuberculosis; DM = diabetes mellitus; HbsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; WHO = World.

Table 3

Characteristics of adult refugee patients with DM

	New DM diagnosis (*n* = 30, 55.6%) *n* (%)	Previous DM diagnosis (*n* = 24, 44.4%) *n* (%)	Total DM* (*n* = 54) *n* (%)	*P* value
Demographic information				
Age				
Median [IQR]	45.5 [37.8–55.3]	51.0 [44.5–66.9]	47.9 [40.8–60.5]	0.08
<25	2 (6.7)	0	2 (3.8)	0.12
25–44	13 (43.3)	7 (30.4)	20 (37.7)	
45–64	10 (33.3)	10 (43.5)	20 (37.7)	
≥65	5 (16.7)	6 (26.1)	11 (20.8)	
Sex				
Female	11 (36.7)	16 (69.6)	27 (50.9)	0.02†
Male	19 (63.3)	7 (30.4)	26 (49.1)	
TB incidence in country of origin‡				
<100	1 (3.3)	2 (8.3)	3 (11.1)	0.32
100–299	19 (63.3)	18 (75.0)	34 (63.0)	
≥300	10 (33.3)	4 (16.7)	14 (25.9)	
Clinical information				
Body mass index, kg/m^2				
Median [IQR]	28.3 [23.5–32.4)	30.2 [25.5–34.5]	29.1 [24.0–34.2]	0.36
Any diabetes medications				
No	30 (100)	13 (54.2)	42 (77.8)	<0.01†
Yes	0	11 (45.8)	12 (22.2)	
Random plasma blood glucose, mg/dl				
Median [IQR]	117 [104–163)	157 [109–269]	137 [108–214]	0.05
Glycated hemoglobin, %				
Median [IQR]	6.9 [6.6–7.8)	7.6 [6.6–10.7]	7.2 [6.6–9.8]	0.52
Vitamin D, ng/ml				
Median [IQR]	22 [15–29]	15 [10–20]	19 [13–26]	<0.01†
Latent TB infection				
QFT-negative	17 (56.7)	13 (56.5)	30 (56.6)	0.99
QFT-positive	13 (43.3)	10 (43.5)	23 (43.4)	

*Some columns may not total 100% due to missing data (variables with >3% missing are reported as unknown).

†Statistically significant, χ^2 (categorical) or Wilcoxon rank (medians) two-sided *P* value < 0.05.

‡Incident active TB cases per 100 000 population, per WHO 2014 TB report. [14]

DM = diabetes mellitus; IQR = interquartile range; TB Gold In-Tube test = tuberculosis; QFT = QuantiFERON®-TB Gold In-Tube test; WHO = World Health Organization.

Table 4

DM status and risk of latent tuberculous infection, DeKalb County Refugee Clinic, Atlanta, GA, USA

Characteristic	OR (95%CI)	aOR (95%CI)*
DM status		
No DM	1.00	1.00
Pre-DM	1.83 (1.30–2.58)	1.65 (1.13–2.39)
DM	2.19 (1.22–3.94)	2.27 (1.15–4.48)
Age, years		
<25	1.00	1.00
25–44	1.09 (0.70–1.69)	0.97 (0.60–1.55)
45–64	1.81 (1.05–3.12)	1.58 (0.88–2.84)
≥65	1.66 (0.71–3.91)	1.25 (0.49–2.84)
Sex		
Female	1.00	1.00
Male	1.17 (0.84–1.62)	1.25 (0.87–1.81)
BMI, kg/m^2		
<18.5	1.00	1.00
18.5–24.9	0.80 (0.44–1.46)	0.95 (0.49–1.83)
25–29.9	1.08 (0.58–2.02)	1.16 (0.59–2.32)
≥30.0	0.58 (0.27–1.22)	0.59 (0.25–1.37)
TB incidence in country of origin†		
<100	1.00	1.00
100–299	2.95 (1.21–7.18)	6.29 (1.86–21.21)
≥300	2.48 (1.00–6.17)	5.60 (1.63–19.28)
Current smoker		
No	1.00	1.00
Yes	1.00 (0.68–1.47)	0.89 (0.57–1.37)
Vitamin D level, ng/ml		
Normal (≥20)	1.00	1.00
Low (<20)	0.76 (0.55–1.06)	0.72 (0.50–1.02)

*Adjusted for age, sex, BMI, TB incidence in country of origin, smoking status, and vitamin D level.

†Incident active TB cases per 100 000 population, per WHO 2014 TB report. [14]

DM = diabetes mellitus; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; BMI = body mass index; WHO = World Health Organization.

Table 5

Interaction between DM status with vitamin D level and odds of latent tuberculous infection, DeKalb County Refugee Clinic, Atlanta, GA, USA

Vitamin D level	DM status	OR (95%CI)	aOR (95%CI)*
≥20 ng/ml			
	No DM	1.00	1.00
	Pre-DM	1.35 (0.86–2.10)	1.24 (0.77–2.00)
	DM	1.14 (0.49–2.68)†	1.22 (0.38–2.54)
<20 ng/ml			
	No DM	1.00	1.00
	Pre-DM	2.89 (1.64–5.10)	2.63 (1.45–4.74)
	DM	4.79 (2.05–11.21)†	4.44 (1.75–11.24)

*Multivariable model adjusted for age, sex, body mass index, TB incidence in country of origin, and smoking status.

†Breslow-day test for homogeneity statistically significant, $P < 0.05$.

DM = diabetes mellitus; OR = odds ratio; CI = confidence interval; aOR = adjusted OR.