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Diabetes screen during tuberculosis contact investigations highlights opportunity for new diabetes diagnosis and reveals metabolic differences between ethnic groups

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ABSTRACT

Type 2 diabetes (T2D) is a prevalent risk factor for tuberculosis (TB), but most studies on TB-T2D have focused on TB patients, been limited to one community, and shown a variable impact of T2D on TB risk or treatment outcomes. We conducted a cross-sectional assessment of sociodemographic and metabolic factors in adult TB contacts with T2D (versus no T2D), from the Texas-Mexico border to study Hispanics, and in Cape Town to study South African Coloured ethnicities. The prevalence of T2D was 30.2% in Texas-Mexico and 17.4% in South Africa, with new diagnosis in 34.4% and 43.9%, respectively. Contacts with T2D differed between ethnicities, with higher smoking, hormonal contraceptive use and cholesterol levels in South Africa, and higher obesity in Texas-Mexico ($p < 0.05$). PCA analysis revealed striking differences between ethnicities in the relationships between factors defining T2D and dyslipidemias. Our findings suggest that screening for new T2D in adult TB contacts is effective to identify new T2D patients at risk for TB. Furthermore, studies aimed at predicting individual TB risk in T2D patients, should take into account the heterogeneity in dyslipidemias that are likely to modify the estimates of TB risk or adverse treatment outcomes that are generally attributed to T2D alone.

List of abbreviations: T2D, Type 2 diabetes; TB, Tuberculosis; WHO, World Health Organization; BMI, body-mass index; LDL-c, Low-density lipoprotein cholesterol; HDL-c, High-density lipoprotein cholesterol; HIV, Human immunodeficiency virus; HOMA-IR, homeostasis model assessment for insulin resistance; LTBI, Latent TB infection; PCA, Principal Component Analysis; ANCOVA, Analysis of covariance

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1. Introduction

The growing pandemic of type 2 diabetes mellitus (T2D) is a challenge to tuberculosis (TB) control. Individuals with T2D have a 3-fold increased risk of TB, particularly if they have poor glucose control or additional T2D complications [1–3]. However, the increased TB risk in patients with T2D varies widely between studies, regions and populations, with risk estimates ranging from 0.99 to 7.83. Likewise, at the population level, the contribution of T2D to TB is generally between 10 and 20%, with substantial variation depending on the local epidemiology [1,4].

Once a patient with T2D develops TB, they appear to be more likely to have delays in the conversion of sputum smears from positive to negative during TB treatment, to fail treatment, or to relapse [5–7]. However, not all studies report these associations between adverse treatment outcomes and T2D, and if so, there are variations in their magnitude. This heterogeneity illustrates the complexity of studying T2D as a risk factor for TB and may be explained by variability in study populations with respect to T2D (e.g., glucose control, medications, comorbidities), sociodemographics and access to healthcare, or variations in study designs [8]. Few interactions between T2D and other host characteristics have been described, as suggested for T2D plus smoking or micro and macro-vascular diseases [9–12]. While more studies of this nature are needed among TB patients, there are even fewer studies in TB contacts with T2D. This is a particularly important population for TB control given that TB contacts have one of the highest risks for TB progression (5% in the first year of exposure to a pulmonary TB patient), and those with T2D will magnify this risk by 3-fold [3,13].

The goal of the present study was to compare sociodemographic and metabolic risk factors for TB among TB contacts with T2D from two distant communities with differing ethnicities and cultures. We enrolled South African Coloureds in the Western Cape of South Africa (TB 625/100,000/year; HIV < 6%; T2D range 8–28%), and Hispanics in south Texas (T2D 19%; HIV 0.14/100,000; TB 10/100,000/year) and northern Mexico (T2D 15%; TB 32/100,000/year) [1,14–16]. Our study revealed two major findings: A high frequency of new T2D among the TB contacts from both regions, and striking differences between ethnicities in metabolic and sociodemographic characteristics that are likely to modify the risk of TB conferred by T2D.

2. Methods

Participants were enrolled at clinics in south Texas (Hidalgo and Cameron County Health Departments), northern Mexico (Centro Regional de Tuberculosis in Reynosa; 'Texas-Mexico' in this study) and South Africa (public healthcare clinics around the Tygerberg Academic Hospital in Cape Town; 'South Africa' in this study). Close contacts were defined as sharing at least 5 h per week in a house or closed space with a confirmed pulmonary TB source. Active TB was ruled out based on lack of signs and symptoms compatible with TB, and by normal chest x-ray (routine in Texas and South Africa, and upon physician request in Mexico). At both study sites, we enriched for T2D by initially enrolling contacts 30–65 years old and eventually elevating the lower age to 35 years. In South Africa, all eligible participants were screened for T2D by HbA1c and FBG to determine accurate prevalence data. From those, all participants with an HbA1c ≥ 6.5% were fully enrolled into the study and blood samples were collected for the downstream analysis, whereas only randomly selected participants with HbA1c ≤ 6.5% were enrolled on the basis of one normoglycemic participant per participant with hyperglycemia. Exclusion criteria included a body-mass index (BMI) < 18.5, HIV infection, type 1 diabetes, cancer and recent infections. The study was approved by the institutional review boards of the participating institutions and participants signed a free informed consent.

Diabetes classification was based on hyperglycemia (fasting plasma glucose ≥126 mg/dL), HbA1c ≥ 6.5% or self-report, and pre-T2D as HbA1c 5.7–6.49% [17]. Macro- and micro-vascular pathologies were self-reported. The frequency of alcohol consumption and the average number of alcoholic drinks consumed in a typical day were established using validated questions described previously [18]. Alcohol excess was defined as drinking ≥7 drinks/episode at least weekly or binge drinking (≥10 drinks/episode at least twice a month), and alcohol abuse was defined as consumption of more than 7 drinks per day on a daily basis. Drug use was based on self-reported use of injectable or non-injectable illicit drugs at least twice per week. Latent TB infection (LTBI) was based on QuantiFERON-Gold In-Tube (Qiagen). Plasma LDL cholesterol (LDL-c) was measured in South Africa, and calculated for Texas [Total cholesterol - HDL-c - (Triglycerides *0.20)] [19]. Insulin resistance was based on the homeostasis model assessment (HOMA-IR) [fasting plasma glucose (mM)*fasting serum insulin (mU/L)/22.5] on participants who did not use insulin [20].

Data were entered into RedCap (Vanderbilt University) and exported into SAS (v9.4 Cary, NC) or SPSS (v23.0 Armonk, NY) for analysis. Chi-square or Fisher's exact tests were used to compare categorical variables and two-sample test proportions to identify differences between study sites. Mixed-model designs for analysis of covariance (ANCOVA) were performed and the F statistic transformed to Cohen-d. A Latent Factor analysis using Principal Components approach (PCA) was done and Varimax axes rotation was used for eigen vector interpretation. P values were considered significant if ≤ 0.05, and marginally significant if < 0.1.

3. Results

3.1. Characteristics of all TB contacts

We enrolled 95 contacts (after screening 247 for T2D) in South Africa, and 106 in Texas-Mexico (46 in Mexico and 60 in Texas; all those screened were enrolled). The contacts from both sites were predominantly females, but differed in several aspects: In Texas-Mexico nearly all (98%) were Hispanic whites and in South Africa all were South African Coloureds, a mixed ancestry population with Khoisan, Bantu, European and Asian roots. The Texas-Mexico contacts were younger, more educated and obese (Fig. 1A; p < 0.001), while those in South Africa were more likely to smoke and there was a higher proportion of females reporting contraceptive use (Table 1; p < 0.003). Their medical history differed between study sites in various ways (Table S1). Those in Texas-Mexico were more likely to have a family history of T2D (p = 0.005), take anti-inflammatory medications (p = 0.002) or vitamin supplements (p = 0.001) and were less likely to have previous TB or current LTBI (p < 0.001).

3.2. Prevalence of pre-T2D and T2D

In Texas-Mexico we identified 32 contacts with T2D (30.2%) and 26 with pre-T2D (24.5%; 54.7% with both). In South Africa, we screened for elevated HbA1c in 247 TB contacts and identified 43 with T2D (17.4%) and 56 with pre-T2D (22.7%; 40.1% with both). Thus, the prevalence of T2D and pre-T2D was high in both communities, and significantly higher in Texas-Mexico (p = 0.007). Among those with T2D, 34.4% were newly diagnosed in Texas-Mexico and 43.9% in South Africa. In South Africa, we invited all of the pre-screened contacts with T2D and a similar number of no T2D controls (without taking into account pre-T2D status) for full enrollment [total n = 95; 41 (43.2%) with T2D and 21 (22.1%) with pre-T2D].

3.3. Sociodemographics and medical history by T2D status and study site

Analysis was done by T2D status (2 categories) and also including pre-T2D (3 categories), but the latter results are only described when there were detectable differences in the pre-T2D group. The contacts with T2D (versus no T2D) were older at both study sites, and in South

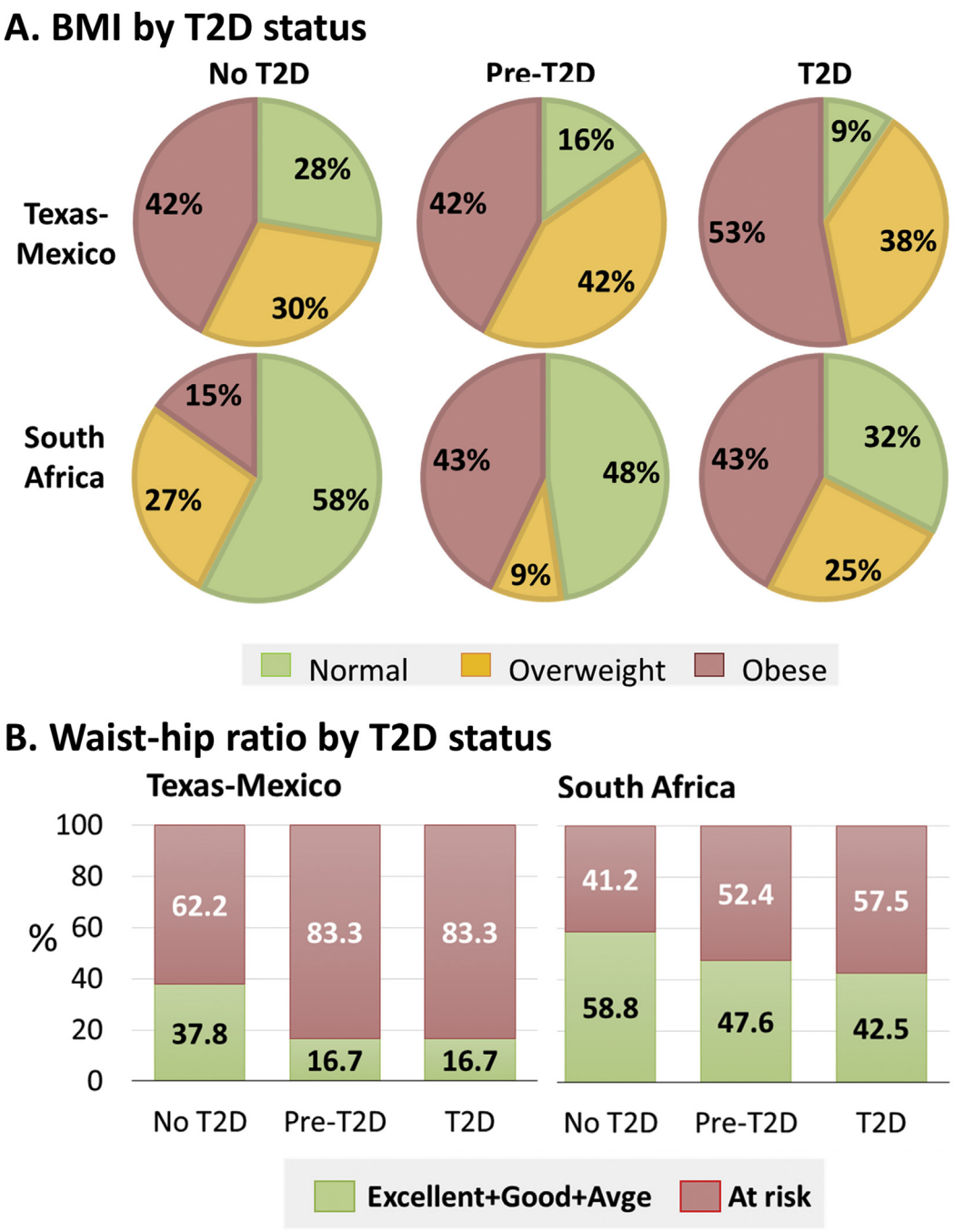

Fig. 1. Body-mass index and waist-hip ratio in contacts by T2D status and enrollment site. A. Body-mass index was classified as normal, overweight or obese (see methods). B. Waist-hip ratio estimates were categorized into two groups: excellent plus good or average, or at risk, with cut-offs differing by sex (see methods). The proportion of the contacts in each category is shown by T2D status.

Africa they were also more likely to be obese and female (Table 1). Contacts with T2D (versus no T2D) from both study sites were more likely to have a family history of T2D, and a higher frequency of macro or micro-vascular complications. Between study sites, the T2D contacts from Texas-Mexico (versus South Africa) had a higher level of education, were more obese and had higher waist-hip ratios, but reported less smoking ($p < 0.001$) or hormonal contraceptive use (Table 1; $p = 0.003$). The T2D patients from Texas-Mexico (versus South Africa) were more likely to take anti-inflammatory medications ($p = 0.006$) and vitamin supplements ($p = 0.017$), but they were less likely to have a previous history of TB ($p = 0.013$) or current LTBI ($p = 0.008$; Table S1).

3.4. Glucose metabolism-related characteristics by T2D status and study site

There were three differences between the T2D contacts from both study sites with respect to glucose metabolism. First, there was a trend for a higher proportion of elevated HbA1c in the presence of otherwise normal fasting plasma glucose in South Africa (34.1%) versus Texas-Mexico (18.2%); Fig. 2; ($p = 0.128$). The second difference was related to insulin resistance. As expected, insulin levels and insulin resistance (HOMA-IR) were higher among the T2D contacts (Table 2), but insulin resistance was also higher in the no T2D contacts from Texas-Mexico versus South Africa ($p = 0.017$). We hypothesize this difference was related to the higher BMI and triglycerides in Texas-Mexico (Tables 1 and 2; Figs. 1 and 4), given that insulin resistance is associated with

Table 1
Sociodemographic characteristics of TB contacts, by study site and T2D status.[a]

	Texas-Mexico				South Africa				Texas-Mexico vs South Africa[b]		
	All	Type 2 diabetes			All	Type 2 diabetes			All	No T2D	T2D
		No T2D	T2D	P		No T2D	T2D	P	P	P	P
	n = 106	74 (69.8%)	32 (30.2%)		n = 95	54 (56.8%)	41 (43.2%)				
Age in yrs (median, IQR)	44(13)	42.5(13)	49(16)	**0.011**	49(14)	45.5(13)	53(13)	**< 0.001**			
Age groups				**0.082**				0.107			
30 to 35	17(16%)	15(20.3%)	2(6.3%)		10(10.5%)	8(14.8%)	2(4.9%)		0.253	0.248	0.795
36 to 59	77(72.6%)	53(71.6%)	24(75.0%)		78(82.1%)	44(81.5%)	34(82.9%)		0.110	0.197	0.407
60 to 65	12(11.3%)	6(8.1%)	6(18.8%)		7(7.4%)	2(3.7%)	5(12.2%)		**< 0.001**	0.310	0.434
Sex				0.248				**0.021**	0.563	0.791	0.407
Male	35(33%)	27(36.5%)	8(25.0%)		28(29.5%)	21(38.8%)	7(17.1%)				
Female	71(67%)	47(63.5%)	24(75.0%)		67(70.5%)	33(61.2%)	34(82.9%)				
Highest Education				0.830				0.859			
Elementary	12(11.8%)	8(10.8%)	4(14.3%)		10(10.5%)	6(11.1%)	4(9.8%)		0.770	0.957	0.554
Middle	26(25.5%)	18(24.3%)	8(28.6%)		28(29.5%)	14(25.9%)	14(34.1%)		0.526	0.836	0.616
High school	24(23.5%)	19(25.7%)	5(17.9%)		52(54.7%)	31(57.4%)	21(51.1%)		**< 0.001**	**< 0.001**	**0.004**
College	40(39.2%)	29(39.2%)	11(39.3%)		5(5.3%)	3(5.6%)	2(4.9%)		**< 0.001**	**< 0.001**	**< 0.001**
Smoking				0.606				0.114			
Never smoked	68(64.2%)	46(62.2%)	22(68.8%)		17(20.2%)	11(23.4%)	6(16.2%)		**< 0.001**	**< 0.001**	**< 0.001**
Past smoker	15(14.2%)	10(13.5%)	5(15.6%)		6(7.1%)	1(2.1%)	5(13.5%)		**< 0.001**	**0.024**	0.800
Current smoker	23(21.7%)	18(24.3%)	5(15.6%)		61(72.6%)	35(74.5%)	26(70.3%)		**< 0.001**	**< 0.001**	**< 0.001**
Alcohol excess	7(6.6%)	5(6.8%)	2(6.3%)	0.645	4(4.2%)	2(3.7%)	2(4.9%)	0.778	0.476	0.447	0.795
Drugs	5(4.7%)	4(5.4%)	1(3.1%)	0.522	10(10.6%)	8(14.8%)	2(4.9%)	0.134	0.118	**0.071**	0.701
Contraceptive hormones[c]	4(5.6%)	4(8.5%)	0(0%)	0.184	13(19.4%)	9(27.3%)	4(11.8%)	0.109	**0.003**	**0.005**	**0.044**
Waist-Hip ratio[d]				0.153				0.174	**0.001**	**0.006**	**0.018**
Normal	26(26.3%)	21(30.4%)	5(16.7%)		47 (49.5%)	30 (54.5%)	17(42.5%)				
At risk	73(73.7%)	48(69.6%)	25(83.3%)		48 (50.5%)	24 (44.4%)	24 (58.5%)				
BMI (median, IQR)	29.4(7.9)	29.1(8.2%)	30.1(7.2%)	0.500	26.2(10.5)	24.8(8.6%)	28.5(10.8%)	**0.008**	**0.002**	**< 0.001**	0.421
BMI categories				0.237				**0.064**			
Normal (18.5–24.9)	20(19.0%)	17(23.3%)	3(9.4%)		42(44.7%)	29(54.7%)	13(31.7%)		**< 0.001**	**< 0.001**	**0.022**
Overweight (25–29.9)	37(35.2%)	25(34.2%)	12(37.5%)		21(22.3%)	11(20.7%)	10(24.4%)		**0.044**	**0.095**	0.226
Obese (30+)	48(45.7%)	31(42.5%)	17(53.1%)		31(33.0%)	13(24.5%)	18(43.9%)		**0.066**	**0.035**	0.435

[a] Data expressed as n(column %) unless specified.
[b] p-value using two sample proportion using column percentage.
[c] Females only.
[d] Waist:hip ratio classified as normal (< 0.90 in males; < 0.86 in females) or at risk if higher; Bold p values are significant or borderline significant.

obesity and can be driven by free fatty acids, which are triglyceride metabolites [21]. Thus, we evaluated the relationships between BMI or triglycerides on HOMA-IR. As expected, in each country we found that HOMA-IR values were positively correlated with triglycerides (rho = 0.34 in Texas-Mexico; rho = 0.37 in South Africa; $p < 0.001$) and BMI (rho = 0.38 in Texas-Mexico; rho = 0.53 in South Africa; $p < 0.001$; Fig. S1). Because these bivariate analyses showed dispersion (an indication of error due to the contribution of other variables to HOMA-IR), we tested several models. Smoking, drugs, alcohol and contraceptives were not associated with HOMA-IR. The model with the best fit for the HOMA-IR variable required adjustment for study site, age and sex, and the interaction between BMI*-triglycerides (Cohen d = 0.95, $p < 0.001$, Fig. 3A). We further visualized these adjusted relationships with 3D surface plots (Fig. 3B–C).

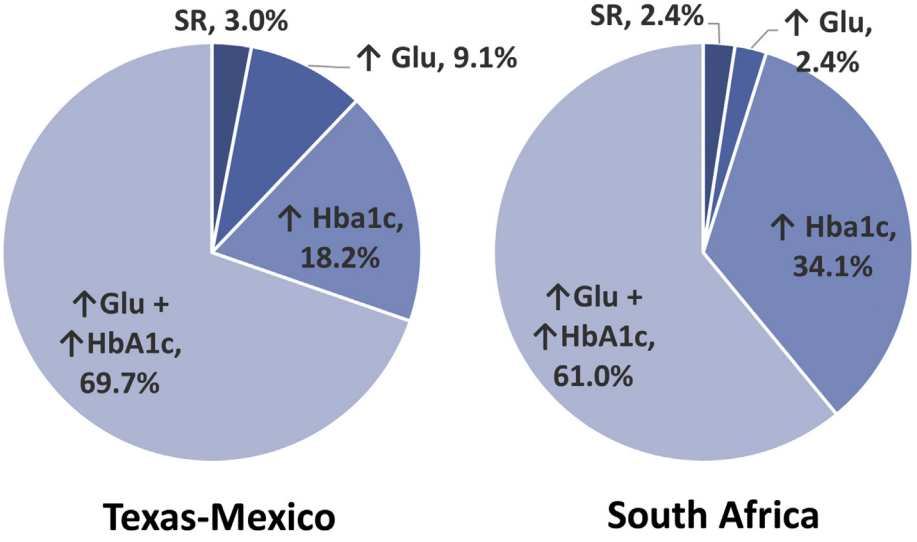

Fig. 2. Criteria for diagnosis of T2D by study site. T2D diagnosis was based on the current WHO guidelines (see methods). The proportion of contacts fulfilling each criterium for T2D classification is indicated by study site. SR = self-reported only; ↑ Glu = hyperglycemia only; ↑ HbA1c = HbA1c ≥ 6.5% only; ↑ Glu + HbA1c = Both high glucose and HbA1c.

Table 2
Lipids, insulin and insulin resistance by T2D status and study site.

	Texas-Mexico				South Africa				Texas-Mexico vs South Africa[b]		
	ALL	Type 2 diabetes			ALL	Type 2 diabetes			All	No T2D	T2D
		No T2D	T2D	P		No T2D	T2D	P	P	P	P
Lipid profiles (n, column %)[a]											
Triglycerides				**0.003**				**0.008**	**0.065**	**0.077**	**0.083**
Normal	66(62.3%)	53(71.6%)	13(40.6%)		70(74.5%)	45(84.9%)	25(61.0%)				
High	40(37.7%)	21(28.4%)	19(59.4%)		24(25.5%)	8(15.1%)	16(39.0%)				
Total cholesterol				**0.063**				**0.076**	**< 0.001**	**0.003**	**0.019**
Normal	95(89.6%)	69(93.2%)	26(81.3%)		62(66.0%)	39(73.6%)	23(56.1%)				
High	11(10.4%)	5(6.8%)	6(18.8%)		32(34.0%)	14(25.9%)	18(45%)				
LDL				0.404				**0.023**	**0.004**	0.430	**< 0.001**
Normal	70(66%)	47(63.5%)	23(71,9%)		41(45.6%)	29(55.8%)	12(31.6%)				
High	36(34%)	27(36.5%)	9(28.1%)		49(54.4%)	23(43.4%)	26(70.3%)				
Male HDL (cut-off = 40)				0.685				**0.010**	**< 0.001**	**< 0.001**	0.641
Normal	11(31.4%)	8(29.6%)	3(37.5%)		21(77.8%)	18(90%)	3(42.9%)				
Low	24(68.6%)	19(70.4%)	5(62.5%)		6(22.2%)	2(10%)	4(57.1%)				
Female HDL (cut-off = 50)				**0.075**				0.389	0.131	0.180	**0.071**
Normal	28(39.4%)	22(46.8%)	6(25%)		35(52.2%)	19(57.6%)	16(47.1%)				
Low	43(60.6%)	25(53.2%)	18(75%)		32(47.8%)	14(41.2%)	18(54.5%)				
Glucose, HbA1c, insulin and HOMA-IR as estimate of insulin resistance (median, IQR)											
Glucose (mg/dL)	104.5(35)	96.5(20)	167.5(114.5)	**< 0.001**	97.3(59.5)	86.5(19.8)	163.1(132.4)	**< 0.001**	**0.072**	**< 0.001**	0.306
HbA1c (%)	5.7(1.5)	5.5(0.4)	8.0(2.9)	**< 0.001**	6.0(2)	5.5(0.7)	7.9(3.5)	**< 0.001**	**0.090**	0.683	0.605
Insulin (mU/L)[c]	11.6 (9.2)	11.1 (8.4)	13.6 (9.4)	0.133	11.7(11.9)	9.8(8.9)	15.6(20.5)	**< 0.001**	0.960	**0.077**	0.194
HOMA-IR[c]	3.3 (3.2)	2.7 (2.0)	6.7 (4.4)	**< 0.001**	2.8 (4.7)	1.9(2.4)	5.9(5.6)	**< 0.001**	0.832	**0.017**	0.376

[a] Values in mg/dL.
[b] p-value using two sample proportion using column percentage.
[c] Data from non-insulin users only; Bold values are significant or borderline significant.

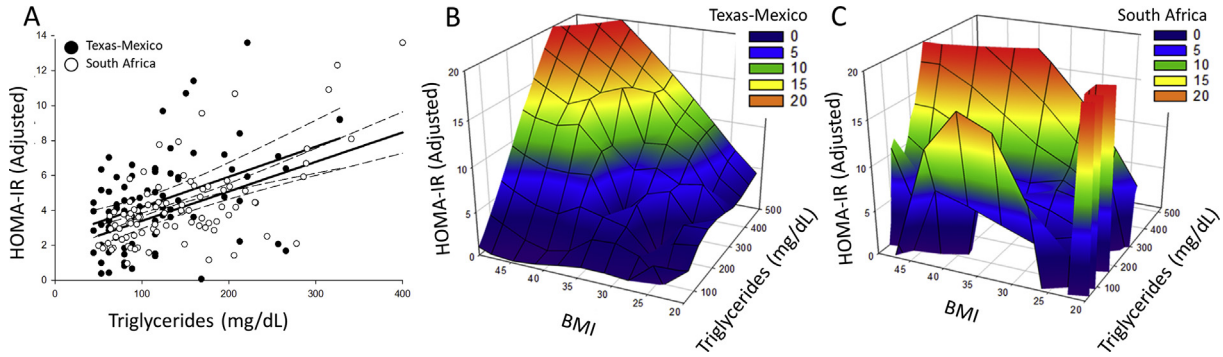

Fig. 3. Relationship between adjusted HOMA-IR, BMI and triglycerides. (A) Scatter plot of correlation between adjusted HOMA-IR and triglycerides (mg/dL) by study site. The effect size was d = 0.95 for triglycerides*BMI (p < 0.001). Analysis was made with ANCOVA with adjustment for site, age, BMI, sex, triglycerides and sex*site, sex*age and BMI*triglycerides. (B and C) Surface plots of the relationships between adjusted HOMA-IR, BMI and triglycerides in Texas-Mexico and South Africa. In South Africa there were few individuals with triglycerides below 200 mg/dl, computing unstable coefficients and increasing noise in these points.

At both study sites, the simultaneous increase in BMI and triglycerides was correlated with increased adjusted HOMA-IR, but in South Africa some individuals also had high adjusted HOMA-IR despite normal triglycerides. This ANCOVA model revealed a third difference in glucose metabolism between study sites: a differential contribution of sex to adjusted HOMA-IR by study site, with higher insulin resistance in women from South Africa (mean 5.5, 95% CI 4.7, 6.2) versus Texas-Mexico (mean 3.9, 95% CI 3.2, 4.7; Fig. S2).

3.5. Lipid metabolism-related characteristics by study site and T2D status

The contacts from both study sites differed in their lipid profiles (Table 2). The most prevalent dyslipidemias were high triglycerides and low HDL (among females) in Texas-Mexico and high LDL-c cholesterols in South Africa (p < 0.05). The contacts with T2D (versus no T2D) from both study sites were more likely to have high triglycerides and total cholesterol (Table 2). Sex also had an effect on altered HDL-c, with differences between countries. Smoking, drugs, alcohol and contraceptives were not associated with lipids in either country.

We expanded on the observed differences by analyzing the influence of study sites, T2D status, sex and age, on the various lipid levels. We found that triglycerides were higher in Texas-Mexico and in T2D patients (Cohen-d = 0.43–0.44; Fig. 4A). Total cholesterol was higher in South Africans (Cohen-d = 0.67), but was not affected by T2D status (Fig. 4B). HDL-c was lower in pre-T2D and T2D in Texas-Mexico (Cohen-d = 0.43 and 0.5; Fig. 4C). Finally, LDLs had an interaction effect between study site and T2D status (Cohen-d = 0.38) (Fig. 4D). In summary, lipid levels were mainly influenced by study site and T2D status.

3.6. Relationship between metabolic factors underlying T2D at both study sites

Our analysis of two study populations indicated variable relationships between metabolic factors that define T2D (hyperglycemia, HbA1c, HOMA-IR), obesity (BMI, waist-hip ratio) and dyslipidemias (triglycerides, total cholesterol, LDL-c and HDL-c). To further understand these relationships, we conducted a Latent Factor analysis of

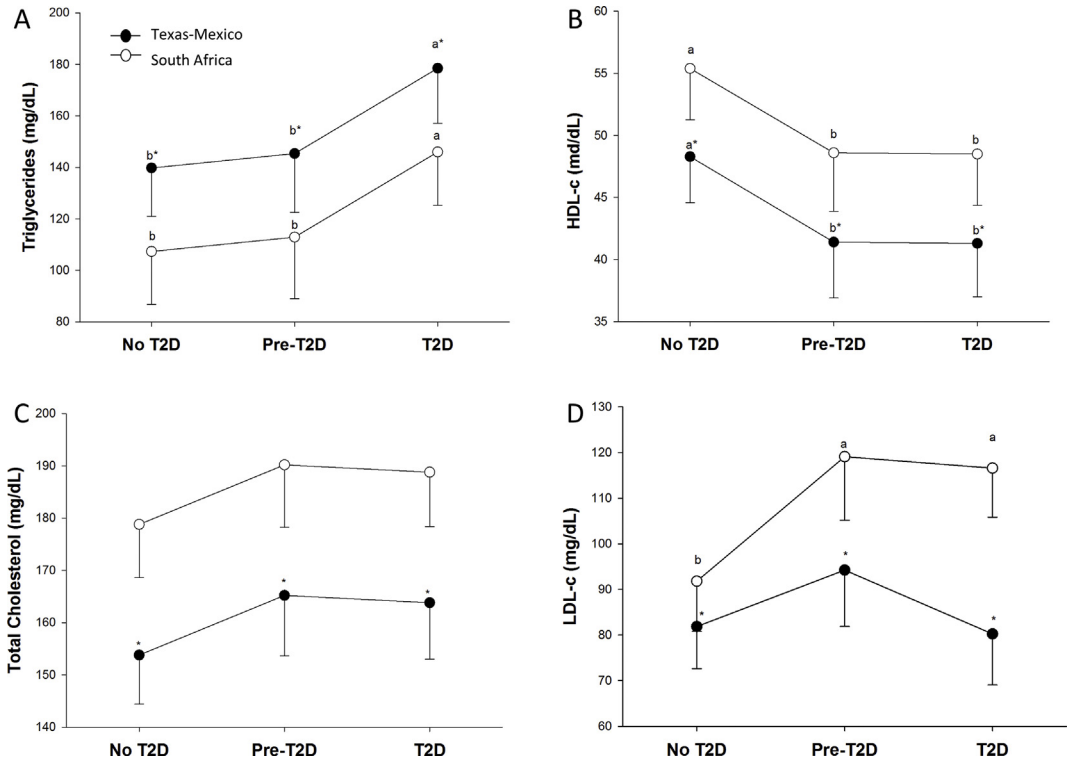

Fig. 4. Dyslipidemia by study site and T2D status. Analysis of covariance contrasts lipid serum concentration (outcomes A-D) by T2D status (no T2D, pre-T2D and T2D) and between sites, after controlling for age and sex. Fisher contrast was used for T2D status as indicator variable (fixed factor), study site (random factor) and the model was adjusted for sex and age. A) Triglycerides were higher in Texas-Mexico (Cohen-d = 0.43, p = 0.002), and in T2D patients (Cohen-d = 0.44, p = 0.003), but not pre-T2D. B) Total cholesterol was higher in South Africa (Cohen-d = 0.67, p = 0.0001), but was not affected by T2D status. C) HDL-c was lower in pre-T2D (0.011) and T2D (Cohen-d = 0.43, p = 0.006), in Texas-Mexico (Cohen-d = 0.5, p = 0.001). D) LDLs had an interaction effect between study site and T2D status (Cohen-d = 0.38, p = 0.045). Vertical lines indicate 95% confidence intervals; Common letters indicate homogenous groups within T2D groups and * indicates differences by study site.

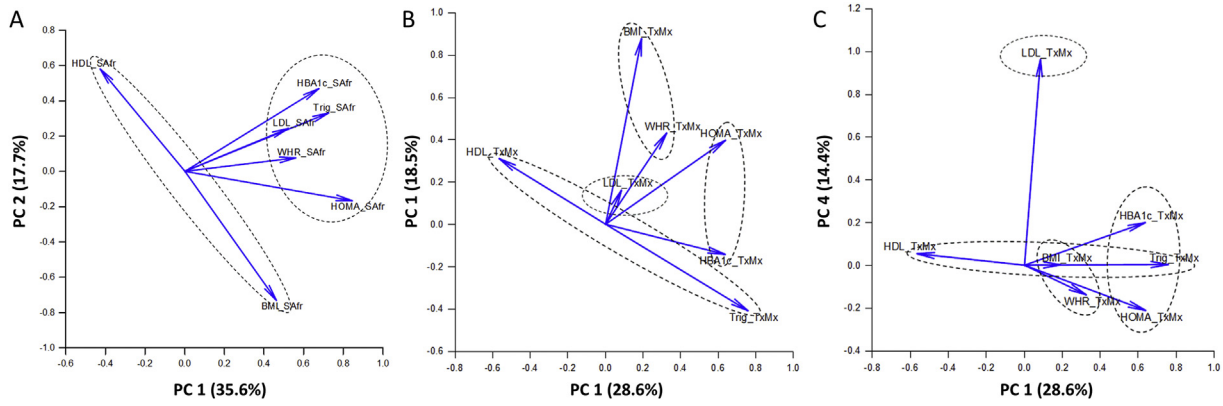

Fig. 5. Relationship between variables related to BMI and glucose and lipid metabolism in South Africa and Texas-Mexico. Analysis and visualization of the correlations between variables defining T2D (HbA1c, HOMA-IR), obesity (waist-hip ratio, BMI) and lipid metabolism (LDL-c, HDL-c, triglycerides) by PCA analysis. The Kaiser-Meier-Olkin sampling adequacy was 0.627 for South Africa and 0.5 for Texas-Mexico, and Barttlet's test of sphericity was < 0.001 for both sites. A) In South Africa the first two components (PC 1 with correlated variables HbA1c, HOMA-IR, triglycerides, LDL, and waist-hip ratio, and PC2 with inversely correlated variables BMI and HDL) explained 53% of the variability. B and C) The data from Texas-Mexico required four components (PC1 with triglycerides and HDL-c; PC2 with HOMA-IR and HbA1c; PC3 with waist-hip ratio and BMI; PC4 with LDL-c) to explain 79% of the total variability. Figure C shows the rotated component matrix of B to illustrate the separation of LDL from the other variables. SAfr, South Africa; TxMx, Texas-Mexico.

these variables using PCA for each study site. We found that South Africa had two components that explained 53% of variability on the seven variables, while Texas-Mexico required four components to describe the relationships between these same variables, and explained 79% of total variability (Fig. 5; Table S2).

4. Discussion

To our knowledge, this is the first study to provide an in-depth description of the sociodemographic and metabolic characteristics of adult contacts of TB patients from two distant communities with different ethnicities: The Texas-Mexico border region in North America and the Western Cape of South Africa. We report two major findings. First, both communities revealed high prevalence rates (at least 40%) of

combined pre-T2D and T2D, and at least 30% of undiagnosed T2D. These statistics provide support for evaluating the expansion of current TB contact screening protocols to include T2D screening. Second, our analysis revealed differences in epidemiologic factors (smoking, education and contraceptive use) and metabolic status (glycated hemoglobin, insulin resistance, dyslipidemia and obesity) between the T2D patients from both ethnicities. Sex had a differential influence by study site on the metabolic status. Definition of these complex relationships is a critical step forward in understanding how these factors affect the magnitude of the contribution of T2D to the risk and adverse outcomes for TB in different ethnic groups.

Previous studies have shown that the screening of TB patients for T2D is effective to detect new T2D, particularly in developing countries where T2D awareness is lower [1,4,22]. We now find that screening for T2D among adult TB contacts, a population at high risk for TB, can be very effective in identifying individuals with T2D. In Texas-Mexico a lack of T2D awareness was observed on both sides of the border [6/15 (40%) in Texas; 5/17 (29.4%) in Mexico]. Thus, T2D screening among contacts is not only beneficial in developing countries as suggested in a recent report from India, but also in populations with severe health disparities from developed countries [23]. The participating counties in south Texas are among the poorest counties in the US, and the enrolled TB contacts were in the lowest 20% percentile of this community (data not shown) [24]. In South Africa, the proportion of new T2D among all T2D patients was even higher at 43.9%, a figure consistent with the estimated lack of T2D awareness in nearly two thirds of the adults with T2D in sub-Saharan Africa [25]. Possible explanations for the high proportion of new T2D among TB contacts is the low access to healthcare in populations at risk for TB, who generally belong to the lower socioeconomic strata [1]. This provides further support for the contribution of TB clinics as hubs for new T2D diagnosis.

Our study across two continents also revealed metabolic differences in the TB contacts with T2D. South Africans had a higher proportion of high HbA1c in the presence of normal fasting blood glucose (Fig. 2). Our study is not the first to report disparities in HbA1c across ethnicities [15,26]. It has been hypothesized that higher HbA1c in Africans may result from slower erythrocyte turnover or metabolism [26,27]. Another possibility is that elevated HbA1c in the South African cohort is due to post-prandial glucose spikes despite normal fasting glucose. This is known to vary between ethnicities [28]. To evaluate an overestimation of T2D among the South African contacts, we estimated the proportion of T2D if we would have used an HbA1C cutoff point of 6.9% as suggested previously [29] (e.g self-report of T2D, glucose ≥ 126 and/or HbA1C ≥ 6.9%). However, we found that the T2D prevalence would be 42.1% with this variation, which is similar to the 43.2% calculated in our study.

Insulin resistance was associated with age and sex at both study sites. However, two findings lead us to hypothesize that insulin resistance is largely driven by the higher levels of obesity and triglycerides in Texas-Mexico, and possibly influenced by host genetics in the leaner population from South Africa. First, insulin resistance was associated with high BMI and triglycerides at both study sites, as would be expected for T2D being driven by obesity [30]. However, in South Africa, insulin resistance was also (unexpectedly) higher among individuals with normal triglycerides regardless of BMI, suggesting a genetic component. Second, another unique feature of the South African contacts was the higher insulin resistance among females, regardless of their BMI, triglycerides or age.

Lipid profiles also differed by ethnicity with elevated triglycerides more prevalent in Hispanics, and cholesterols in South African Coloureds (Table 2; Fig. 4). While higher triglycerides are generally related to obesity, higher cholesterol levels are likely attributed to host genetics [31]. We speculate that high cholesterol may increase TB risk beyond the baseline already conferred by T2D. Support for this is based on reports that host cholesterol favors *M. tuberculosis* survival and growth, increases TB susceptibility in a mouse model, and a lower risk of TB associated with statin therapy (which lowers cholesterol) [32,33]. The impact of triglycerides on TB risk is unclear, even though *Mtb* has been shown to modulate lipolysis and use fatty acids from the host cell [34].

The PCA analysis confirmed that our study sites differ in the relationships between metabolic elements associated with T2D, where some may increase TB risk (total or LDL cholesterol) and others may be protective (e.g. BMI). In South Africa, HOMA-IR and HbA1c were correlated with triglycerides, LDL-c and waist-hip ratio. These are known cardiovascular disease risk factors, particularly for T2D patients [35]. In contrast, in Hispanics, HOMA-IR and HbA1c failed to correlate with these cardiovascular risk factors (Fig. 5). These differences in the underlying metabolic status may contribute to the poorly understood variability in TB risk estimates among T2D patients worldwide [4,11]. For example, recent studies suggest that the higher death rate in TB-T2D patients is due to T2D complications, including a study in Tanzania [9,11,36,37]. Thus, one would predict that TB-T2D patients with cardiovascular diseases are more likely to die. Anecdotally, our studies in Texas-Mexico have failed to detect higher risk of death among TB-T2D patients versus TB alone, even after controlling for potential confounders [38].

Sociodemographic factors that increase TB risk were also distributed differently between both study site. Notably, the T2D patients from South Africa had higher smoking rates. Smoking is a risk factor for progression from latent to active TB [39], and the co-existence of T2D plus smoking has been associated with higher risk of TB or higher prevalence of MDR-TB or death during TB treatment [9,12,40]. A greater proportion of female participants at the South African site reported hormonal contraceptive use. We have shown that medroxyprogesterone acetate decreases *M. bovis* BCG-induced cytokine production in MPA users [41], and increases the *M. tuberculosis* burden in mice [42].

We recognize study limitations such as a relatively small sample size. Both study sites had a higher proportion of females, which reflect their higher willingness to participate in research studies. Thus, extrapolation of our findings to the entire community must be done with caution.

5. Conclusions

Our findings have two major implications. First, the high frequency of new T2D patients among adult TB contacts warrants further investigation into the expansion of routine TB contacts investigations to include T2D screening. These are likely to increase significantly the early diagnosis of T2D in economically disadvantaged populations at risk for serious T2D complications and TB development. Second, elucidation of the risk conferred by T2D towards TB development or TB treatment outcomes should be done in the context of other host sociodemographic and metabolic characteristics that may further boost or restrain *M. tuberculosis* survival. We posit that the combination of these variations confers differences in the “hierarchy” of TB risk and treatment outcomes, and future studies aimed at predicting TB risk among the millions of T2D patients worldwide should analyze these host variables.

Ethical approval

Participants signed an informed consent previously approved by the Institutional Review Boards of the University of Texas Health Houston, Secretaria de Salud de Tamaulipas or Stellenbosch University.

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Competing interests

The authors declare that they have no conflicts of interest.

Role of funding source

The funding sources did not play a role in the study design, collection analysis or interpretation of the data, or publication of the data.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tube.2018.08.007.

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