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Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru

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ABSTRACT

Background: Dysglycemia (i.e., prediabetes or diabetes) in patients with tuberculosis (PWTB) is associated with increased odds of mortality and treatment failure. Whether such association holds true when dysglycemia is transient or persistent is unknown. In this study, we tested the association between persistent dysglycemia (PD) during anti-tuberculosis (TB) treatment and unfavorable treatment outcomes in PWTB from Lima, Peru.

Methods: PWTB enrolled between February and November 2017 were followed for 24-months. Dysglycemia was measured through fasting glucose and HbA1c at baseline during the 2nd- and 6th-month of TB treatment. PD was defined as dysglycemia detected in 2 different visits. The association between PD and unfavorable TB treatment outcome was evaluated using logistic regression.

Results: Among 125 PWTB, PD prevalence was 29.6%. PD was associated with more lung lesion types, higher bacillary loads, low hemoglobin (Hb), and high body mass index (BMI). Unfavorable TB treatment outcome was associated with older age, higher BMI, more lung lesion types, and PD. After adjusting for age, Hb levels, smoking, and smear grade, PD was independently associated with unfavorable treatment outcomes (adjusted odds ratio (aOR): 6.1; 95% CI: 1.9–19.6).

Conclusion: PD is significantly associated with higher odds of unfavorable TB treatment outcomes. Dysglycemia control during anti-TB treatment gives the opportunity to introduce appropriate interventions to TB management.

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Introduction

In 2020, 1.5 million people died due to tuberculosis (TB), especially in low and middle income countries, and because of recent efforts to improve these numbers using National Tuberculosis Control Programs (NTPs), its incidence is decreasing but at a slow pace (World Health Organization, 2021). It is widely documented that high-risk conditions, such as malnutrition, smoking, AIDS, and dysglycemia (Almeida-Junior et al., 2016, Calderon et al., 2019, Huang et al., 2014, Odone et al., 2014, World Health Organization, 2015) compromise the NTPs performance in its task of reducing TB burden, despite specific interventions (World Health Organization, 2015), such as comprehensive health care as a complementary strategy for active cases and contact tracing, as well as the universalization of first-line drug susceptibility testing and screening for comorbidities such as HIV and diabetes mellitus (DM) (Cole et al., 2020).

Dysglycemia, which in this study includes DM and prediabetes mellitus (PDM), influences TB risk, clinical and radiographic presentations, and TB treatment outcomes and has been extensively studied in recent years. Indeed, DM is described to be associated with increased risk of progression from latent to active TB (Jeon and Murray, 2008), with the persistence of acid-fast bacilli (AFB) in sputum (Gil-Santana et al., 2016) and with unfavorable TB treatment outcomes and death (Arriaga et al., 2021, Baker et al., 2011). Importantly, DM in people with pulmonary TB (PWTB) has also been shown to increase the risk of *Mycobacterium tuberculosis* (MTB) transmission to close contacts (Arriaga et al., 2021). Moreover, PDM has been frequently reported in PWTB (Almeida-Junior et al., 2016) and is thought to increase the chance of TB among household contacts (Shivakumar et al., 2018). However, it is still unanswered if the presence of PDM has any effect on anti-TB therapy. The World Health Organization (WHO) and the NTPs recommend detection and management of DM in PWTB (Lin et al., 2019, Ministerio de Salud Peru, 2013), but despite these recommendations, most PWTB are still unaware of their glycemic status, and the effect of dysglycemia on anti-TB treatment outcomes remains uncertain. A previous study conducted in Lima, Peru, reported a high prevalence of dysglycemia in PWTB (14%) and highlighted the programmatic limitations for the identification and treatment of non-diabetic dysglycemia (Calderon et al., 2019). Because TB increases insulin resistance and stress-induced hyperglycemia, an overdiagnosis can be observed during the acute phase of TB (Dungan et al., 2009), but dysglycemic states may persist throughout treatment (Calderon et al., 2019) for epigenetic changes that cause persistent increase in proatherogenic gene expression (El-Osta et al., 2008). Therefore, patients with higher glycemic levels show clinical, radiological, and biochemical manifestations (Barreda et al., 2020) that in turn could be associated with unfavorable anti-TB outcomes.

The objective of this study was to assess whether persistent dysglycemia (PD) is associated with unfavorable TB treatment outcomes in a cohort of PWTB from 14 health centers and 1 public reference hospital in Lima, Peru.

Patients and methods

Settings and study design

We analyzed a prospective cohort of PWTB (Calderon et al., 2019) recruited between February and November 2017 and followed up for 24 months after TB treatment initiation. The study was performed in 2 districts of North Lima, Peru, with a high TB burden, recruiting patients from 14 health centers and from Public Hospital Sergio Bernales.

Study patients with TB

Adult patients (aged ≥ 18 years) with pulmonary TB diagnosed by the study units were screened for inclusion. TB diagnosis and follow-up monitoring were based on AFB smear microscopy, MTB culture in Lowenstein Jensen medium, chest radiograph aspects (assessed by an experienced radiologist), and clinical findings as described elsewhere (Calderon et al., 2019, Ministerio de Salud Peru, 2013). In addition, drug susceptibility testing was performed using BD BACTEC™ MGIT™ 960 at the study laboratories to support a proper treatment following national and international recommendations (Ministerio de Salud Peru, 2013).

Clinical data and definition of dysglycemia and persistent dysglycemia

Data on clinical characteristics, chest radiographic findings, comorbidities, and TB treatment outcomes were obtained by reviewing medical records as authorized by local Institutional Review Board (IRB) and recorded in Socios En Salud Informatic System (SEIS) software [5, 16].

DM or PDM conditions were categorized as dysglycemia and were assessed by an endocrinologist as described previously (Barreda et al., 2020, Calderon et al., 2019). DM and PDM were defined in agreement with the American Diabetes Association (ADA) guidelines (International Diabetes Federation, 2017) as HbA1c ≥ 6.5% or fasting glucose ≥ 126 mg/dL, and HbA1c 5.7 – 6.4% or fasting glucose 100 – 125 mg/dL, respectively. PD was defined when the patient had dysglycemia (i) in each (all) study visit, (ii) at baseline and 2nd-month visit, (iii) at baseline and 6th-month visit, or (iv) at 2nd-month visit and 6th-month. Patients with dysglycemia at only 1 study visit were classified as normoglycemic.

Data on white blood cell count (WBC) as well as hemoglobin (Hb), serum cholesterol (Chol), serum triglycerides (TG), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum albumin levels were retrieved from the electronic medical records and analyzed.

TB Treatment outcome

Information about TB treatment outcome was obtained through follow-up visits, which took place in the 2nd, 6th, and 24th month after treatment initiation. TB treatment outcome was defined as favorable or unfavorable according to WHO guidelines (World Health Organization, 2010), and these categories are shown in **Supplementary Table 1**. A favorable outcome was defined as cure or TB treatment completion. Death, relapse, or failure of the scheme received were considered as unfavorable outcomes. Patients who were “lost to follow-up” or “not evaluated” as TB treatment outcome were excluded as done by other authors (Arriaga et al., 2021, Carvalho et al., 2021).

Data analysis

Kolmogorov Smirnov test was used to test the normality of study population distribution. Characteristics of PWTB are presented as median and interquartile ranges (IQRs) as measures of central tendency and dispersion for continuous variables and frequency or percentages for categorical variables. Continuous variables were compared using the Mann-Whitney *U* test (between 2 groups) or the Kruskal-Wallis test with Dunn’s multiple comparisons (between >2 groups). Categorical variables were compared using a two-sided Pearson’s chi-square test with Yates’s correction or the Fisher’s two-tailed test in 2×3 or 2×2 tables.

Hierarchical cluster analysis (Ward’s method, with bootstrap 100×) was performed to describe associations with PD and un-

favorable outcomes. Values of each biochemical and hematologic parameter were $\log_{10}$ transformed. Mean values for each indicated clinical group were z-score normalized.

We performed 2 multivariate logistic regression analyses: the first regression analysis to assess the association between unfavorable TB treatment outcome and PD and the second regression analysis to assess the association between unfavorable TB treatment outcome and persistent non-diabetic dysglycemia. For both regression analyses we used variables with a univariate p-value<0.2 and adjusted for the following potential confounding variables: age, body mass index (BMI), Hb, and lung lesion types. In addition, we included smoking and AFB smear grade because these variables may have an effect on the degree of lung inflammation or indirectly indicate the extension of pulmonary TB disease (Almeida-Junior et al., 2016, Gil-Santana et al., 2016), as shown in **Supplementary Table 2**.

All analyses were prespecified. Two-sided p-value≤0.05 after adjusting for multiple comparisons (Bonferroni method) was considered statistically significant. Analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA) and GraphPad Prisma version 8 (Software Inc., San Diego, CA, USA).

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Ethical issues

Written informed consent was obtained from all participants and investigations were conducted in accordance with the Declaration of Helsinki and Peruvian regulations. The study was approved by the Institutional Committee of Ethics for Humans (CIEI, approval number: 458–22–16 of November 30, 2016), an autonomous committee established at the Universidad Peruana Cayetano Heredia, authorized by National Institute of Health in Peru.

Results

From February to November 2017, 143 microbiologically confirmed PWTB attending the primary health care centers were screened in this cohort and 125 patients with active TB were included in the study, in which 4 PWTB requested voluntary withdrawal for several reasons. In contrast, and in accordance with our analysis plan, we excluded 3 patients with a diagnosis of HIV infection and 11 patients were lost to follow-up or were not evaluated (**Supplementary Figure 1A**).

All diagnostic tests for dysglycemia were performed by the study staff at each scheduled visit up to 6th month. Eventually, TB treatment outcomes were evaluated on scheduled visits up to the 24th months. More detailed information of study procedures is shown in **Supplementary Figure 1B**.

PD and normoglycemia were detected respectively in 29.6 % (95% CI: 22.3 – 38.1) and in 52% of PWTB (95% CI: 43.24% – 60.76%). Non-PD was found in 18.4% (95% CI: 11.6% – 25.2%) of PWTB.

The sociodemographic, clinical, radiographic, and laboratory characteristics of PWTB who presented with PD compared with patients with non-PD and normoglycemia are described in **Table 1**. Patients with PD presented with more lung lesion types (p<0.001), a higher bacillary load (p=0.013), a higher BMI (p=0.039), and low Hb levels (p<0.001) and were older than patients with normoglycemia or patients with non-PD (**Table 1**). The characteristics of PWTB stratified by TB treatment outcomes are described in **Table 2**. Twenty-nine PWTB (23%; 95% CI: 16.7% – 31.3%) presented with an unfavorable TB treatment outcome, and they were more frequently older (median age: 51.3 vs. 27.9 years p<0.001), had a higher BMI (p=0.01), and had more lung lesion types (p=0.01) and PD (p<0.001) than PWTB with favorable outcomes. Both study groups were similar with regard to a number of other characteristics, including sex, history of prior TB, asthma, renal disease, alcohol use, smoking, illicit drugs use, and TB- and DM-related symptoms. Hb levels and AFB or culture positivity at baseline were also not significantly associated with unfavorable TB treatment outcomes. The characteristics of PWTB stratified according to TB treatment outcomes are displayed in Supplementary Table 2.

The dynamicity of the dysglycemia status in PWTB included in the study, until reaching the category of PD, is shown in a Sankey diagram in **Figure 1A**. The prevalence of PD (62.1%; 95% CI: 44.4% – 79.7%) was significantly higher in PWTB with unfavorable TB treatment outcomes than in those with favorable outcomes (p<0.001; **Figure 1B**). In addition, the median distribution of fasting glucose and HbA1c levels in PD in PWTB showed significant differences between patients with favorable (p=0.001; **Figure 1C** left panel) and unfavorable TB outcomes (p=0.037; **Figure 1C** right panel). The glycemic status (DM, PDM) through the study visits (**Supplementary Figure 2A and 2B)** and the comparison of the TB treatment outcomes between PD subgroups is shown in **Supplementary Figure 2C.**

We performed a hierarchical cluster analysis using different laboratory baseline parameters measured in peripheral blood to assess whether it was possible to identify specific signatures that could characterize PWTB presenting with PD and unfavorable outcomes (**Figure 2A**). This approach revealed that patients who mostly had both PD and unfavorable outcomes presented with a different profile marked by significantly lower values of high-density lipoprotein (HDL) (p=0.09), albumin (p=0.048), and Hb (p=0.036) levels. This same subpopulation of patients also exhibited a distinctive profile marked by significantly higher levels of WBC counts (p=0.036), cholesterol (p<0.01), ALT (p=0.01), and AST (p=0.024) (**Figure 2B**) with the exception of total serum proteins and low-density lipoprotein (LDL) levels, which were not statistically different.

To further investigate whether the characteristics of PWTB were directly associated with PD and TB treatment outcomes, we performed a multivariate logistic regression analysis, and it is shown in **Figure 3**. We found that smoking, Hb levels, and AFB smear were not independently associated with unfavorable treatment outcomes in PWTB (p>0.05). Older PWTB (aOR=1.04, 95% CI: 1.01 - 1.08), and those with PD were more likely of having an unfavorable TB treatment outcome (aOR: 6.1, 95% CI: 1.9 – 19.6).

In addition, the same variables were assessed in a multivariate logistic regression model to evaluate the association of them with TB treatment outcomes in non-diabetic PWTB with PD (**Supplementary Table 3**). Smoking, Hb levels, and the AFB grade were not independently associated with unfavorable treatment outcomes in PWTB. However, non-diabetic PWTB with PD were at least 7-fold more likely of having an unfavorable TB treatment outcome (aOR: 6.9; 95% CI: 1.7 – 26.9) when adjusted by age in years (aOR=1.05, 95% CI: 1.01 - 1.09).

Discussion

In this cohort of newly diagnosed PWTB in North Lima, PD, which includes both DM and PDM throughout the course of anti-TB treatment, was independently associated with unfavorable TB treatment outcomes. This finding supports the results of our previous studies in which patients affected with DM or PDM were associated with poor clinical profiles, such as low Hb levels, high

Table 1
Characteristics of patients with pulmonary TB stratified by persistent dysglycemia.

Characteristics	Persistent Dysglycemia (n= 37)	No Persistent Dysglycemia* (n= 88)	p-value
Age (years)-median (IQR)	47.3 (34.9 - 58.3)	27.5 (22.3 - 36.2)	**<0.001**
Male sex-n (%)	21 (56.8)	58 (65.9)	0.417
BCG vaccination-n (%)	33 (89.2)	82 (94.3)	0.449
Prior TB -n (%)	9 (24.3)	13 (14.8)	0.209
BMI-median (IQR)	23.7 (22.1-26.4)	22.3 (20.3-24.9)	**0.039**
BMI categories -n (%)			0.399
Obesity	1 (2.8)	2 (2.4)	0.567
Overweight	13 (36.1)	19 (22.4)	0.103
Underweight	4 (11.1)	6 (7.1)	0.270
Normal	18 (50.0)	58 (68.2)	Ref.
Lung lesion types-n (%)			**<0.001**
1 type	3 (8.3)	6 (27.3)	
2 types	13 (36.1)	2 (9.1)	
3 types	20 (55.6)	14 (63.6)	
AFB smear -n (%)			0.060
1+	6 (16.2)	20 (23.0)	
2+	6 (16.2)	8 (9.2)	
3+	11 (29.7)	12 (13.8)	
Scanty	1 (2.7)	4 (4.6)	
Negative	13 (35.1)	43 (49.4)	
L-J Culture -n (%)			0.747
1+	16 (44.4)	12 (57.1)	
2+	5 (13.9)	4 (4.7)	
3+	2 (5.6)	4 (4.7)	
<1+	3 (8.3)	10 (11.6)	
Negative	10 (27.8)	26 (30.2)	
MDR-n (%)	7 (35.0)	11 (22.0)	0.364
Smoking-n (%)	7 (18.9)	21 (24.1)	0.641
Cannabis use-n (%)	4 (10.8)	13 (14.9)	0.776
Other illicit drugs use-n (%)	5 (13.5)	9 (10.3)	0.757
Alcohol use-n (%)	16 (43.2)	47 (54.0)	0.328
Hemoglobin (g/dL) -median (IQR)	11.1 (10.0-12.2)	12.4 (11.2-13.4)	**0.001**
Fasting glucose-median (IQR)	110.1 (100.4 -218.9)	91.9 (86.1-97.7)	**<0.001**
HbA1c-median (IQR)	6.0 (5.3 -10.8)	5.0 (4.8-5.3)	**<0.001**
Glycemic status at baseline – n (%)			**<0.001**
Diabetes	18 (48.6)	0 (0.0)	
Prediabetes	17 (45.9)	23 (26.1)	
Normoglycemia*	2 (5.4)	65 (73.9)	
Use of metformin – n (%)**	14 (37.8)	2 (2.3)	**<0.001**
Hypertension – n (%)	6 (16.2)	0 (0.0)	NA
Asthma – n (%)	1 (2.7)	7 (8.0)	0.268
Renal disease – n (%)	1 (2.7)	2 (2.3)	0.893
TB and DM symptoms – n (%)			
Cough	34 (91.9)	81 (92.0)	0.977
Fever	14 (37.8)	42 (47.7)	0.310
Dyspnea	23 (62.2)	60 (68.2)	0.515
Night sweats	23 (62.2)	48 (54.5)	0.433
Non appetite	21 (56.8)	52 (59.1)	0.809
Weight loss	27 (73.0)	63 (71.6)	0.875
Polyuria	17 (45.9)	33 (37.5)	0.379
Polydipsia	16 (43.2)	43 (48.9)	0.566
Malaise	29 (78.4)	68 (77.3)	0.892
Slow scarring	7 (18.9)	11 (12.6)	0.364

Data represent no. (%). *Sixty-five patients, categorized as non-persistent dysglycemia group were normoglycemic at each visit. ** Use of metformin was indicated in patients with diabetes diagnosis. Hypertension, asthma, renal disease as defined by the World Health Organization and described in Methods. Prior TB: diagnosis of active tuberculosis before this study. Abbreviatures: IQR: Interquartile range. BCG: Bacillus Calmette–Guérin, BMI: Body Mass Index, Hb: Hemoglobin, HbA1c: Glycated Hemoglobin, AFB: Acid-Fast Bacilli, L-J: Löwenstein-Jensen, MDR: Multi Drug Resistant. Ref.: Reference value, NA: not applicable.

liver enzymes levels, and abnormal lipid values, among others (Barreda et al., 2020).

Our data is part of a larger cohort in which prevalence of TB-DM (14.4%) was not different from that previously reported (14%) (Calderon et al., 2019). In a recently published manuscript, with data from the Tuberculosis Management Information System of the Peruvian NTP, the prevalence of DM in PWTB was 9.7%, similar to the prevalence reported in our study (Ugarte-Gil et al., 2021). However, the authors of the above-mentioned article did not provide further evidence of the association between DM and unfavorable TB treatment outcomes due to limitations of the Peruvian reporting system. Our study shows discrepancies in the prevalence of unfavorable TB treatment results from the Peruvian NTP report; therefore, we consider that our observations may be more reliable, in particular, in cases of unfavorable outcomes (treatment failure, loss of follow-up, patients not evaluated, and transfers) because of the extended 24-month follow-up. In the NTP reporting system (Ugarte-Gil et al., 2021), TB treatment outcome is generally recorded only once, at the end of treatment.

As per our knowledge, this is the first description about the frequency of PD among patients being treated for TB and its potential effect on TB treatment outcome. Our work is also novel in show-

Table 2
Characteristics of patients with pulmonary TB stratified by TB treatment outcome.

Characteristics	Unfavorable treatment outcome (n=29)	Favorable treatment outcome (n=96)	p–value
Age (years) – median (IQR)	51.3 (33.6–58.8)	27.9 (22.6–39.8)	**<0.001**
Sex – n (%)			1.000
Male	18 (62.1)	61 (63.5)	
Female	11 (37.9)	35 (36.5)	
BCG vaccination– n (%)	28 (96.6)	87 (91.6)	0.700
Prior TB – n (%)	5 (17.2)	17 (17.7)	1.000
BMI (kg/m^2) –median (IQR)	23.9 (21.8–26.5)	22.3 (20.4–24.7)	**0.010**
BMI categories – n (%)			0.100
Obesity	2 (7.1)	1 (1.1)	0.100
Overweight	11 (39.3)	21 (22.6)	0.010
Underweight	4 (14.3)	6 (6.5)	0.100
Normal	11 (39.3)	65 (69.9)	Ref.
Lung lesion types– n (%) *			**0.010**
1 type	4 (14.3)	32 (34.0)	
2 types	9 (32.1)	27 (28.7)	
3 types	15 (53.6)	35 (37.2)	
AFB smear – n (%)			0.115
1+	4 (13.8)	22 (23.2)	
2+	4 (13.8)	10 (10.5)	
3+	9 (31.0)	14 (14.7)	
Scanty	1 (3.4)	4 (4.2)	
Negative	11 (37.9)	45 (47.4)	
L-J Culture – n (%)			0.309
1+	14 (50.0)	42 (45.7)	
2+	1 (3.6)	8 (8.7)	
3+	1 (3.6)	5 (5.4)	
<1+	2 (7.1)	11 (12.0)	
Negative	10 (35.7)	26 (28.3)	
MDR– n (%)	2 (16.7)	7 (12.1)	0.646
Smoking– n (%)	10 (34.5)	18 (18.9)	0.126
Cannabis consumption – n (%)	3 (10.3)	14 (14.7)	0.759
Other illicit drug consumption– n (%)	3 (10.3)	11 (11.6)	1.000
Alcohol use– n (%)	16 (55.2)	47 (49.5)	0.673
Hemoglobin (g/dL) – median (IQR)	11.4 (10.3–12.8)	12.25 (10.9–13.3)	0.091
Fasting Glucose (g/dL) –median (IQR)	103.4 (95.3–135.6)	92.9 (87.3–99.8)	**<0.001**
HbA1c (%) – median (IQR)	5.3 (5.1–6.5)	5.1 (4.8–5.3)	**0.001**
Dysglycemia at baseline – n (%)	28 (96.6)	30 (31.3)	**<0.001**
Glycemic status at baseline – n (%)			**<0.001**
Diabetes	9 (31.0)	9 (9.4)	**<0.001**
Prediabetes	19 (65.5)	21 (21.9)	**<0.001**
Normoglycemia	1 (3.4)	66 (68.8)	Ref.
Use of metformin – n (%)**	6 (20.7)	10 (10.4)	0.147
Persistent Dysglycemia (%)	**20 (69.0)**	**17 (17.7)**	**<0.001**
Hypertension – n (%)	2 (6.9)	4 (4.2)	0.624
Asthma – n (%)	1 (3.4)	7 (7.4)	0.679
Renal disease – n (%)	1 (3.4)	2 (2.1)	0.554
TB and DM symptoms – n (%)			
Cough	26 (89.7)	89 (92.7)	0.696
Fever	10 (34.5)	46 (47.9)	0.144
Dyspnea	19 (65.5)	64 (66.7)	1.000
Night sweats	15 (51.7)	56 (58.3)	0.531
No appetite	18 (62.1)	55 (57.3)	0.674
weight loss	22 (75.9)	68 (70.8)	0.646
Polyuria	12 (41.4)	38 (39.6)	1.000
Polydipsia	11 (37.9)	48 (50.0)	0.293
Malaise	23 (79.3)	74 (77.1)	1.000
Slow scarring	4 (13.8)	14 (14.7)	1.000

Data represent no. (%). Hypertension, asthma, renal disease as defined by the World Health Organization and described in Methods. The variable "Lung lesion types" refers to the presence of the 3 different types of lung lesions as cavities, infiltrates and fibrous tracts in the radiographic lung profile. ** Use of metformin was indicated in patients with diabetes diagnosis. Prior TB: diagnosis of active tuberculosis before this study. Abbreviatures: IQR: Interquartile range. BCG: Bacillus Calmette–Guérin, BMI: Body Mass Index, Hb: Hemoglobin, HbA1c: Glycated Hemoglobin, AFB: Acid-Fast Bacilli, L-J: Löwenstein-Jensen, MDR: Multi Drug Resistant. Ref.: Reference value.

ing the increased risk of unfavorable TB treatment outcomes in patients with DM or PDM during anti-TB treatment, reflected in our definition of PD. Non-diabetic dysglycemia often does not present any alarm among general physicians and even among endocrinologists, and therefore, no specific care or recommendation has ever been proposed in TB treatment guidelines worldwide. Assuming that TB can induce acute stress-related hyperglycemia, which may lead to epigenetic changes that increases the risk of TB progression and complications even after blood glucose levels have returned to normal (Magee et al., 2018a), further research should be carried out to establish the need for specific treatment for dysglycemia in these cases.

Therefore, non-diabetic dysglycemia in PWTB must not be overlooked because it has been shown to be a risk factor for progression to DM (Tabák et al., 2012), leading to a higher risk of unfavorable TB treatment outcome, as has been previously described

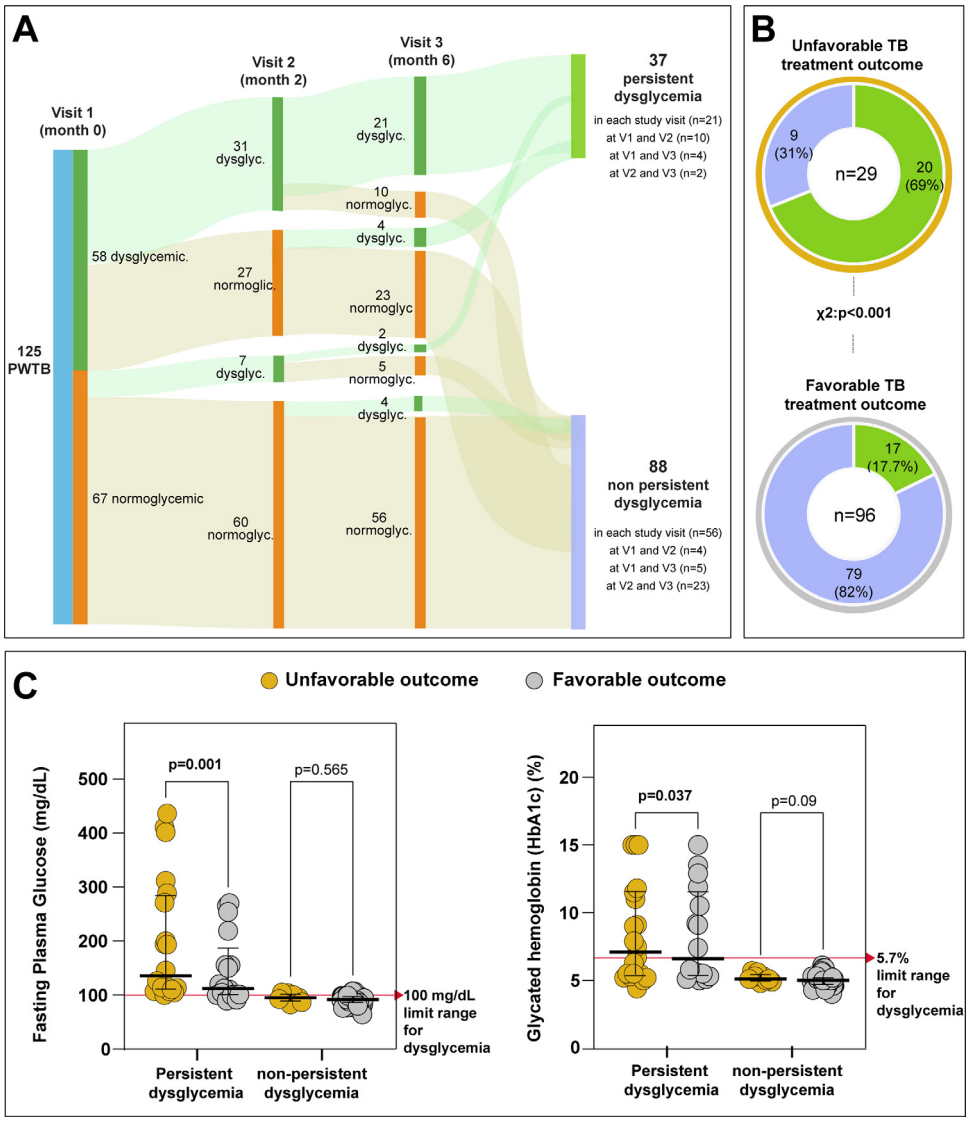

Figure 1. Glycemic status of the patients with TB stratified by treatment outcome. (A) Sankey diagram of dysglycemic status identification and categorization of persistent dysglycemia. **(B)** Frequency of persistent dysglycemia by TB treatment outcome. Data were compared using the chi-square (χ^2) test. **(C)** Scatter plots depicting the persistent dysglycemia and no persistent dysglycemia stratified by treatment outcome in the baseline were plotted. Lines represent median values and IQR. The differences in median values (and IQR) between groups were compared using the Mann-Whitney *U* test. Abbreviatures: TB: tuberculosis; IQR: Interquartile range

by other authors as well (Arriaga et al., 2021, Baker et al., 2011, Jeon and Murray, 2008).

We have tried to capture that phenomenon of persistent transient high levels of glycemia (El-Osta et al., 2008, Magee et al., 2013) might affect TB treatment outcome, evaluating changes in the fasting glucose or HbA1c levels periodically, similar to other studies (Kornfeld et al., 2016, Magee et al., 2018a). In our study, the glycated Hb levels changed slightly during TB treatment, whereas fasting glucose was more sensitive in revealing some effect on TB treatment outcomes. This could be explained as high blood glucose levels would cause persistent effects, despite subsequent normoglycemia, by inducing long-lasting activating epigenetic changes, which lead to some of the variations in the risk of complications that could not be explained by the HbA1c (El-Osta et al., 2008).

Our findings indicate that dysglycemia should not be screened only at TB diagnosi, but rather should be screened throughout the course of anti-TB therapy and should be properly treated to achieve an effective control of glycemic status (Boillat-Blanco et al., 2016) and thus avoid unfavorable treatment outcomes. Testing and monitoring for dysglycemia at the time of diagnosis and during TB treatment can be clinically useful in improving the outcome of TB treatment.

High blood glucose levels were transient in a PWTB group, coincidentally as occurs in patients with other diseases (Dungan et al., 2009). Several metabolic indicators that are altered by inflammation have been observed; but we observed in our study that despite effective TB chemotherapy, the hyperinflammatory profile could persist during the intensive phase of treatment, as previously reported (Kumar et al., 2019). Similar to our study, other authors shown that not only dysglycemia is associated with a different inflammatory pattern, but also with anemia (Gil-Santana et al., 2019) and neutrophilia (Carvalho et al., 2021), which have been reported to be associated persistent hyperinflammatory response despite having started TB treatment.

Dysglycemia in PWTB has been associated with undesirable biochemical profiles and more extensive lesions on chest radiograph, as we described previously (Barreda et al., 2020). Our hierarchical cluster analysis further showed that the cellular and biochemical profile associated with PD was also linked to lung damage, elevation of WBC count, increased levels of liver transam-

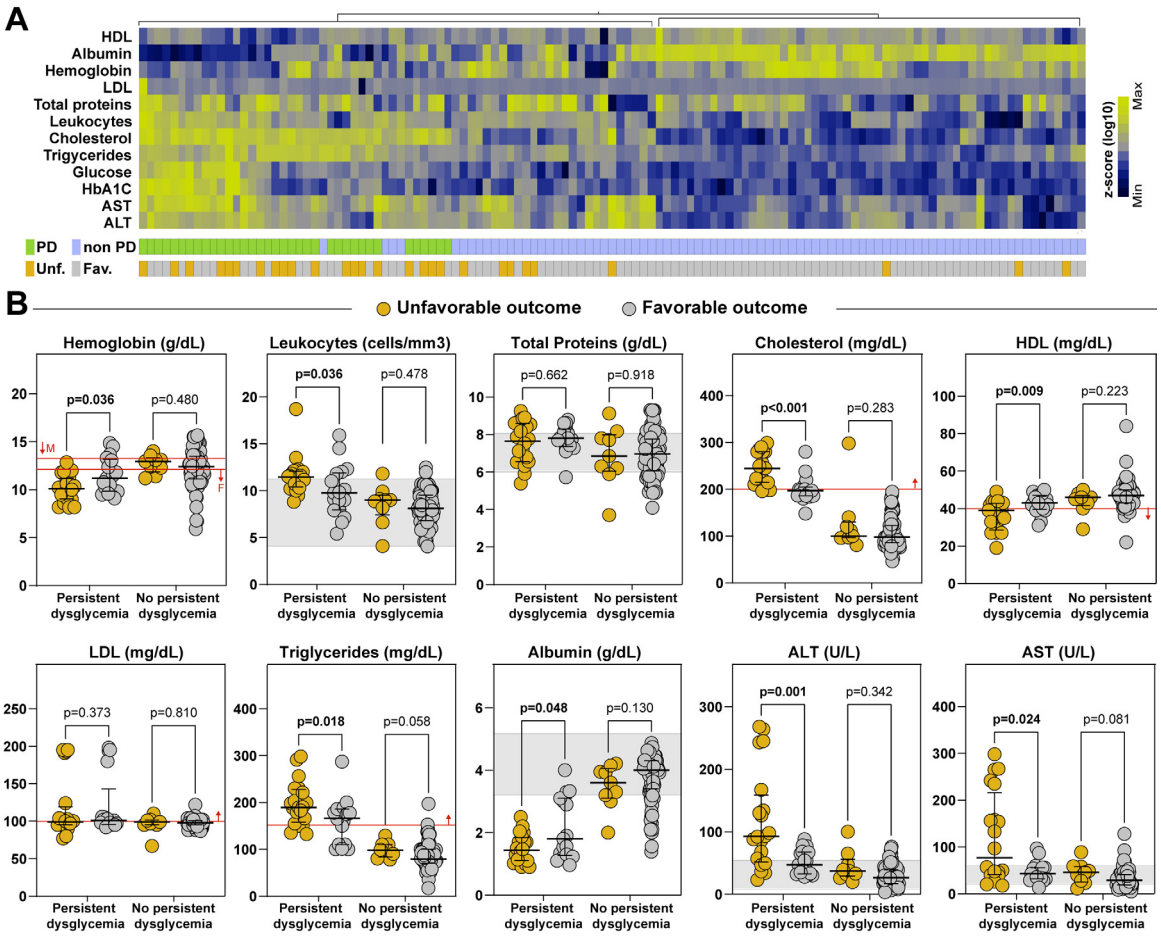

Figure 2. Laboratorial profiles of patients with TB by persistent dysglycemia condition. (A) Value of each parameter was $\log_{10}$ transformed. Mean values for each indicated clinical group were z-score normalized and a hierarchical cluster analysis (Ward's method with 100X bootstrap) was performed to present the overall laboratorial profiles. **(B)** Data represent median and interquartile ranges. The Mann-Whitney *U* test was employed to compare the values detected between the study subgroups. The red lines shown the range limit and gray lines indicate the normality values range. Abbreviatures: PD: Persistent dysglycemia; Unf.: Unfavorable; Fav.: Favorable; HbA1c: Glycated hemoglobin; HDL: High Density Lipoprotein; LDL: Low Density Lipoproteins; AST: Aspartate transaminase; ALT: alanine aminotransferase.

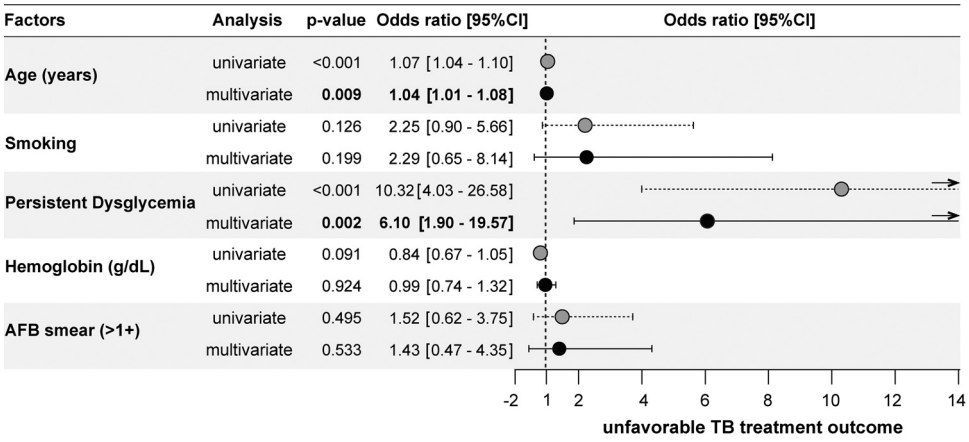

Figure 3. Logistic regression analysis of persistent dysglycemia on TB treatment outcomes. Logistic regression model was performed to evaluate the independent associations between the variables with p-value<0.2 results in the univariate analyses (Table 1) and unfavorable treatment outcome (treatment modification, failure, recurrence, and death). Adjustment was performed for each parameter: smoking (reference: no smoking), persistent dysglycemia (reference: no persistent dysglycemia), AFB smear >+1 (reference: AFB ≤+1). This model had an index of predictive power of 80%. Abbreviatures: AFB: Acid-fast bacilli. Unfavorable TB outcome was defined as treatment failure or modification, recurrence or death, whereas favorable outcome was cure or treatment completion. 95% CI: Confidence Interval.

inases, total cholesterol, and low Hb, as previously described (Chiang et al., 2014, Tabák et al., 2012). It is possible that the harmful effect of PD in the response to TB treatment is linked to the induction of chronic inflammation (Magee et al., 2018b).

Glycemic control has been recommended to decrease the risk of TB transmission (Almeida-Junior et al., 2016), has been shown to be associated with better outcomes (Dungan et al., 2009), and may influence the treatment outcome (Boillat-Blanco et al., 2016). PWTB-DM who were on metformin had better TB treatment results (Singhal et al., 2014). Unfortunately, in our study we did not have access to information about the treatment for dysglycemia in these patients, and therefore, we could not evaluate the positive effect of glycemic control in reducing the risk of unfavorable TB treatment outcomes.

Our study had several limitations. Information on oral glucose tolerance test, the gold standard of dysglycemia screening, was not available because we conducted this study under programmatic conditions of TB services. However, considering our PD detection model, the follow-up of 2 years was able to consolidate the effect on anti-TB treatment outcome. Another limitation of this study was missing information regarding the treatment of patients with dysglycemia included in the study, including the data such as severity or duration of organ damage from DM. As previously mentioned, endocrinologists in general are conservative in diagnosing patients with non-diabetic dysglycemia. For that reason, many patients did not have assured access to metformin or other hypoglycemic medication for the treatment of dysglycemia and that situation may not be different from what has routinely occurred in the management of PWTB. Therefore, this study highlights the necessity of reassessing PD control in PWTB to mitigate the risk of unfavorable TB treatment outcome. Finally, many of the variables identified to be associated with PD and unfavorable treatment outcome did not enter the final multivariate model, because they could be affected by sample size, requiring further future research. Likewise, it is important to note that although our data represent a sample of limited number of patients, it is representative of the population of PWTB in Lima, because our prevalence of diabetic dysglycemia and proportions of unfavorable outcomes were similar to those reported in previous studies and reports (Arriaga et al., 2021, Baker et al., 2011, Ugarte-Gil et al., 2021).

In conclusion, our study showed that persistent diabetic and non-diabetic dysglycemia were common in PWTB and both conditions were also significantly associated with an unfavorable TB treatment outcome. In addition to TB-DM management, our findings suggest that optimal control of whole dysglycemic condition (including PDM) should be part of TB management in Peru. Currently, few published studies have examined the clinical and care characteristics associated with dysglycemia, the outcome of TB treatment, or the time to MTB culture conversion. A strength of this study was the clinical evaluation of a prospective cohort of PWTB with dysglycemia. Our findings highlight the importance of linking services for the control of TB and dysglycemia and, although more research is needed, in our view this work presents useful data for a better management of dysglycemia in PWTB.

Potential conflicts of interest

The authors declared no conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Disclaimer

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Author's contributions

RIC and MBA conceived and designed the study, interpreted the data, and wrote the manuscript. RIC, MBA, NNB, OSS, and LL implemented the laboratory study and collected the data. RIC, BB-D, JPDF, and MBA performed the analysis. LL, BBA, ACC, and AK reviewed the manuscript. All authors should have made the final approval of the submitted version of this manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval to the version to be published.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.012.

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