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Trends in HbA1c levels and implications for diabetes screening in tuberculosis cases undergoing treatment in India

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SUMMARY

SETTING: The optimal timing of screening for diabetes mellitus (DM) among tuberculosis (TB) cases is unclear due to the possibility of stress hyperglycemia.

DESIGN: We evaluated adult (≥ 18 years) pulmonary TB cases at treatment initiation as well as at 3 months, 6 months and 12 months. DM was identified by self-report (known DM) or glycated hemoglobin (HbA1c) $\geq 6.5\%$ (new DM). Trends in HbA1c levels during treatment were assessed using non-parametric tests.

RESULTS: Of the 392 participants enrolled, 75 (19%) had DM, 30 (40%) of whom had new DM. Of the 45 participants with known DM, respectively 37 (82%) and 40 (89%) received medication to lower glucose levels at treatment initiation and completion; one participant with new DM initiated glucose-lowering medication during follow-up. The median HbA1c level in participants with known, new and no DM was respectively 10.1% (interquartile range [IQR] 8.3–11.6), 8.5% (IQR 6.7–11.5) and 5.6% (IQR 5.3–5.9) at treatment initiation, and 8.7% (IQR 6.8–11.3), 7.1% (IQR 5.89.5) and 5.3% (IQR 5.1–5.6) at treatment completion ($P < 0.001$). Overall, 5 (12%) with known and 13 (43%) with new DM at treatment initiation had reverted to HbA1c $< 6.5\%$ by treatment completion ($P = 0.003$); the majority of reversions occurred during the first 3 months, with no significant reversions beyond 6 months.

CONCLUSION: HbA1c levels declined with anti-tuberculosis treatment. Repeat HbA1c testing at treatment completion could reduce the risk of misdiagnosis of DM.

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Conflicts of interest: none declared.

Abstract

Le moment optimal du dépistage du diabète (DM) parmi les cas de tuberculose (TB) n'est pas clair en raison de la possibilité d'hyperglycémie de stress.

Nous avons évalué des cas de TB pulmonaire adulte (≥ 18 ans) lors de la mise en route du traitement, à 3 mois, à 6 mois et à 12 mois. Le DM a été identifié par autodéclaration (DM connu) ou par une HbA1c $\geq 6,5\%$ (DM nouveau). Les tendances de l'HbA1c pendant le traitement ont été évaluées grâce à des tests non paramétriques.

Sur les 392 participants enrôlés, 75 (19%) avaient un DM; 30 (40%) d'entre eux avaient un DM nouveau. Sur les 45 participants ayant un DM connu, 37 (82%) et 40 (89%) ont reçu un médicament hypoglycémiant, respectivement, lors de l'initiation du traitement et de son achèvement; un participant atteint d'un DM nouveau a débuté; un traitement hypoglycémiant pendant le suivi. L'HbA1c médiane des participants ayant un DM connu, nouveau et pas de DM a été respectivement de 10,1% (intervalle interquartile [IQR] 8,3–11,6), 8,5% (IQR 6,7–11,5) et 5,6% (IQR 5,3–5,9) à la mise en route du traitement et de 8,7% (IQR 6,8–11,3), 7,1% (IQR 5,8–9,5) et de 5,3% (IQR 5,1–5,6) à l'achèvement du traitement ($P < 0,001$). Au total, 5 (12%) patients ayant un DM connu et 13 (43%) ayant un DM nouveau lors de la mise en route du traitement ont ramené leur HbA1c à moins de 6,5% lors de l'achèvement du traitement ($P = 0,003$); la majorité de ces réversions est survenue pendant les 3 premiers mois, sans reversion significative au-delà de 6 mois.

Les niveaux d'HbA1c ont baissé avec le traitement de la TB. Le dosage répété de l'HbA1c lors de l'achèvement du traitement pourrait réduire les diagnostics abusifs de DM.

Abstract

No es claro cuál es el calendario óptimo para la detección de la diabetes (DM) en los casos de tuberculosis (TB), debido a una posible hiperglucemia de estrés.

Se evaluaron casos de TB pulmonar en adultos (≥ 18 años) al comienzo del tratamiento y a los 3 meses, 6 meses y 12 meses. La DM se definió por autorreferencia (DM conocida) o por una glucohemoglobina (HbA1c) $\geq 6,5\%$ (caso nuevo de DM). Se examinó la evolución de la concentración de HbA1c durante el tratamiento mediante pruebas no paramétricas.

De los 392 participantes inscritos, 75 sufrían DM (19%) y de ellos 30 fueron casos nuevos (40%). De los 45 participantes con DM conocida, 37 recibían fármacos hipoglucemiantes al comienzo del tratamiento antituberculoso (82%) y 40 pacientes al completarlo (89%); un participante con diagnóstico nuevo de DM inició el tratamiento hipoglucemiante durante el seguimiento. La mediana de la HbA1c al comienzo del tratamiento antituberculoso en los pacientes con DM conocida fue 10,1% (amplitud intercuartílica [IQR] 8,3–11,6), en los casos nuevos de DM fue 8,5% (IQR 6,7–11,5) y en los pacientes sin DM fue 5,6% (IQR 5,3–5,9) y al final del tratamiento este valor fue 8,7% (IQR 6,8–11,3), 7,1% (IQR 5,8–9,5) y 5,3% (IQR 5,1–5,6), respectivamente ($P < 0,001$). En general, cinco pacientes con DM conocida (12%) y 13 casos nuevos de DM (43%) al comienzo del tratamiento antituberculoso revirtieron la HbA1c a $< 6,5\%$ al final del tratamiento ($P=0,003$); la mayoría de las reversiones ocurrió durante los primeros 3 meses y después de los 6 meses no se observaron reversiones significativas.

Los valores de la HbA1c disminuyen con el tratamiento antituberculoso. El hecho de repetir la determinación de la HbA1c al finalizar el tratamiento podría disminuir los diagnósticos incorrectos de DM.

Keywords

TB; DM; transient hyperglycemia; glycated hemoglobin; India

THE TUBERCULOSIS (TB) and diabetes mellitus (DM) co-epidemic has received considerable attention in recent years. DM is likely to increase the risk of TB nearly three-fold and result in unfavorable treatment outcomes.^{1,2} TB cases are also more likely to have DM than the general population, and the prevalence of DM in adults with newly diagnosed pulmonary TB (PTB) in endemic settings is 5% to 35%.^{3–7} Approximately 415 million adults worldwide have DM, nearly 80% of whom live in low- and middle-income countries.⁸ Furthermore, nearly half of all DM cases worldwide remains undiagnosed.⁸ India is home to nearly one third of the global TB burden, with 2.7 million incident cases and over 400 000 deaths in 2016.⁹ India also hosts the world's largest burden of DM, with over 69 million adults living with the disease in 2015.⁸ A recent study from southern India reported a strikingly high prevalence of DM, nearing 55% among adults with PTB,¹⁰ and DM may account for approximately 15% of the disease burden in high TB burden countries.¹¹

Given the high prevalence of DM in TB cases, a disproportionately high burden of undiagnosed DM in many low- and middle-income countries with ongoing TB epidemics, and the deleterious association between the two diseases, the World Health Organization (WHO) recently recommended bidirectional screening in people with TB and DM in endemic settings.^{12,13} However, the optimal implementation of this strategy is hampered by numerous challenges, a critical one being stress hyperglycemia.^{14,15} Chronic infections, including TB, can induce transient hyperglycemia, and early studies have shown a decrease in the proportion of TB cases with hyperglycemia diagnosed by oral glucose tolerance testing (OGTT) or fasting blood glucose (FBG) assessments after initiation of anti-tuberculosis treatment.^{3,16} Since then, glycated hemoglobin (HbA1c) testing has been widely used for DM screening worldwide. While OGTT and FBG assessments measure the glycemic status of an individual during the few hours before testing, HbA1c levels correlate with average ambient blood glucose levels during the preceding 2–3 months,¹⁷ potentially serving as a stable test for DM screening during the acute phase of TB.

The primary objective of the present analysis was to characterize trends in HbA1c levels during anti-tuberculosis treatment and its potential impact on DM screening from an ongoing cohort study of new adult PTB cases with and without DM in Western India.

MATERIALS AND METHODS

Study population

We consecutively enrolled newly diagnosed adult (≥ 18 years) PTB cases at the Byramjee-Jeejeebhoy Government Medical College-Sassoon General Hospitals (BJGMC-SGH) and Dr D Y Patil Medical College (DYPMC) in Pune, India, from December 2013. Individuals with

rifampicin-resistant TB, human immunodeficiency virus coinfection, anti-tuberculosis treatment exceeding 7 days or previous history of TB were excluded. PTB cases were diagnosed by the presence of acid-fast bacilli (AFB) on smear microscopy, *Mycobacterium tuberculosis* DNA on Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay or *M. tuberculosis* growth on liquid culture. Sputum specimens were decontaminated using the sodium hydroxide-sodium chloride method after direct AFB staining. Centrifuged sputum specimens were inoculated on a BACTEC™ MGIT™ (Mycobacteria Growth Indicator Tube) (BD, Sparks, MD, USA) before incubation.

All study participants provided written informed consent in their native language. The study protocol was approved by the Institutional Review Boards of Johns Hopkins Medicine, Baltimore, MD, USA; BJGMC-SGH, Pune; and DYPMC, Pune, India.

Definitions of diabetes

HbA1c testing was performed using high-performance liquid chromatography (BioRad Laboratories, Hercules, CA, USA)¹⁸ at enrollment (TB treatment initiation) as well as at 3 months, 6 months (treatment completion) and 12 months. Participants reporting current use of medication to lower glucose levels or a self-reported physician diagnosis at enrollment were classified as having known diabetes (KDM), irrespective of their HbA1c level. Newly diagnosed diabetes (NDM) was classified as HbA1c $\geq 6.5\%$ in participants without KDM at enrollment. Pre-DM was classified as having a HbA1c level between 5.7% and 6.5% in participants without KDM at enrollment.

Participants received either an FBG or random blood glucose (RBG) test (Cobas c111; Roche Diagnostics, Rotkreuz, Switzerland) on venous blood at enrollment. As the primary objective of our study was to measure trends in HbA1c during anti-tuberculosis treatment, we did not use blood glucose results for classifying DM in our cohort.

Statistical analysis

Participant characteristics were compared by glycemic status (euglycemia, pre-DM or DM) at enrollment using the Kruskal-Wallis test for non-normally distributed continuous data and Fisher's exact test for categorical data. The median and interquartile range (IQR) of HbA1c levels and the proportion of participants who changed their glycemic status were compared between follow-up visits using the Wilcoxon sign-rank and McNemar's χ^2 tests, respectively. Change in glycemic status was defined as reversion (change in diagnostic classification towards the euglycemic end of the glycemic spectrum) or progression (change in diagnostic classification towards the diabetic end of the glycemic spectrum) (Appendix Figure A.1).^{*} Logistic regression was used to measure the odds ratio (OR) for reversion in participants with NDM compared with those with KDM. Receiver-operator characteristic curve (ROC) analysis was performed to identify a baseline HbA1c threshold to classify participants with NDM who retained an HbA1c level of $\geq 6.5\%$ following anti-tuberculosis

^{*}The appendix is available in the online version of this article, at <http://www.ingentaconnect.com/content/iuatld/ijtld/2018/00000022/00000007/art00016>

treatment. Statistical significance was determined at $P < 0.05$. Analyses were performed using Stata v13.0 (StataCorp, College Station, TX, USA).

RESULTS

We enrolled 690 adult PTB cases; 438 (63%) had completed at least 6 months of follow-up at the time of this report and were included in the analysis. We excluded 46 (10%) participants in whom HbA1c data were unavailable at any visit during the first 6 months of follow-up (Appendix Figure A.2). Participants with unavailable HbA1c results were similar to those with HbA1c results in terms of their enrollment characteristics. The median (IQR) age and body mass index (BMI) of our cohort at enrollment was respectively 31 years (IQR 23–44) and 17 kg/m² (IQR 15–20).

HbA1c levels at TB treatment initiation

Of the 392 participants included in our analysis, 201 (51%) had hyperglycemia (pre-DM or DM) and 75 (19%) had DM at enrollment; 40% (30 of 75) had NDM (Figure 1). The median HbA1c level in participants with KDM and NDM was respectively 10.1% (IQR 8.3–11.6) and 8.5% (IQR 6.7–11.5) ($P = 0.10$). Median self-reported duration of DM among those with KDM was 2 years (IQR 1–5). Of 45 participants with KDM, 37 (82%) were on glucose-lowering medications. Three participants with KDM and one with NDM initiated glucose-lowering medications by 6 months of anti-tuberculosis treatment. Participants with NDM were younger ($P = 0.05$), had lower BMI ($P = 0.02$), shorter time to *M. tuberculosis* growth on liquid culture ($P = 0.04$), tended to have higher smear grade ($P = 0.08$) and were less likely to have a first-degree relative with DM ($P = 0.06$) than those with KDM (Table 1).

HbA1c levels during TB treatment

The median HbA1c level in participants with KDM decreased from 10.1% (IQR 8.3–11.6) at enrollment to 9.0% (IQR 7.3–11.1) by 3 months ($P = 0.04$), with no significant change by 6 months (8.7%, IQR 6.8–11.3, $P = 0.85$) of anti-tuberculosis treatment. Six-month percentage change in the HbA1c level among participants with KDM was –7% (95% confidence interval [CI] –13 to 0, $P = 0.05$). Similarly, the median HbA1c level in participants with NDM decreased from 8.5% (IQR 6.7–11.5) at enrollment to 7.3% (IQR 5.8–9.5) by 3 months ($P < 0.001$), with no significant change by 6 months (7.1%, IQR 5.9–8.7, $P = 0.80$) of anti-tuberculosis treatment. The 6-month percentage change in the HbA1c level among participants with NDM was –14% (95%CI –19 to –8, $P < 0.001$). Similar trends in the median HbA1c level were observed in participants with pre-DM and euglycemia at enrollment, falling from 6.0% (IQR 6.1) at enrollment to 5.6% (IQR 5.4–5.8) by 6 months of anti-tuberculosis treatment among those with pre-DM ($P < 0.001$; 6-month percentage change of –7% [95%CI –8 to –6]), and from 5.4% (IQR 5.2–5.6) at enrollment to 5.2% (IQR 5.0–5.4) by 6 months of anti-tuberculosis treatment among those with euglycemia ($P < 0.001$; 6-month percentage change of –2% [95%CI –3 to –1]) (Figures 2A and 2B, Table 2).

A subset of 194 (49%) participants completed 12 months of follow-up at the time of this report: 83 (43%) with euglycemia, 65 (34%) with pre-DM and 46 (24%) with DM at

enrollment. The median HbA1c level dropped further to respectively 5.4% (IQR 5.2–5.7, $P < 0.001$) and 5.1% (IQR 4.9–5.3, $P = 0.05$) by 12 months among participants with pre-DM and euglycemia at enrollment. We did not find a significant change in HbA1c levels beyond 6 months of anti-tuberculosis treatment among participants with KDM or NDM.

HbA1c reversion during anti-tuberculosis treatment

The proportion of participants with DM declined from 19% at enrollment to 15% by 6 months of anti-tuberculosis treatment ($P < 0.001$). Two participants with KDM had HbA1c $< 6.5\%$ at enrollment and were excluded from the reversion analysis. An HbA1c level below 6.5% by 6 months of anti-tuberculosis treatment was seen in 18 (25%) participants with DM at enrollment: 13 (72%) had NDM and 5 (28%) had KDM ($P = 0.003$). Logistic regression analysis adjusted for age, sex, bacterial load, smoking, alcohol consumption and BMI at enrollment found that participants with NDM were nearly five times more likely to revert their HbA1c level to a non-diabetic range by 6 months of anti-tuberculosis treatment (adjusted OR [aOR] 4.51, 95%CI 1.06–19.12, $P = 0.04$) compared with KDM. The proportion of participants with pre-DM decreased from 32% to 15% by 6 months of anti-tuberculosis treatment ($P < 0.001$); 87 (69%) participants with pre-DM at enrollment had an HbA1c level in the euglycemic range at 6 months (Figure 3). Of the 18 and 87 participants with DM and pre-DM who reverted by 6 months of TB treatment, respectively 12 (67%) and 75 (88%) did so within the first 3 months ($P < 0.01$) (Table 2). We did not find significant diabetic reversions beyond 6 months of anti-tuberculosis treatment in the subset of participants completing 12 months of follow-up.

HbA1c reversion and blood glucose

Nearly 70% of our cohort received RBG testing at enrollment. Overall, 27 (73%) participants with KDM had blood glucose in the diabetic range (≥ 126 mg/dl for FBG and ≥ 200 mg/dl for RBG) compared with 16 (59%) participants with NDM ($P = 0.01$); none had HbA1c $< 6.5\%$ or blood glucose in the diabetic range (Appendix Table A). Interestingly, 14 (67%) participants had HbA1c $\geq 6.5\%$ and blood glucose in the non-diabetic range, 71% of whom had NDM ($P = 0.03$) and reverted their HbA1c to the non-diabetic range by 6 months compared with only 4 (9%) participants with HbA1c $\geq 6.5\%$ and blood glucose in the diabetic range at enrollment ($P = 0.01$). Area under the curve analysis in a subset of 23 participants with NDM at TB treatment initiation and who completed 12 months of follow-up identified a HbA1c cut-off point of 7.5% at TB treatment initiation for correctly classifying all participants with an HbA1c level in the diabetic range at both 6 months and 12 months of follow-up; 91% of participants with NDM at TB initiation and with HbA1c $< 6.5\%$ at both 6 and 12 months had blood glucose in the non-diabetic range at enrollment.

DISCUSSION

Our study is among the first to describe longitudinal trends in HbA1c levels and their potential impact on DM screening in a well-characterized cohort of cases receiving anti-tuberculosis treatment in a high TB and DM burden setting.

HbA1c levels declined significantly during anti-tuberculosis treatment, irrespective of glycemic status at treatment initiation; the greatest decline was seen in participants with NDM. Transient hyperglycemia was common, with nearly 25% of participants with DM and 70% with pre-DM reverting their HbA1c levels to the non-diabetic and euglycemic range during TB treatment, respectively. Furthermore, changes in glycemic status were common during the first 3 months of anti-tuberculosis treatment, especially in PTB cases with NDM. Our data suggest the need for repeat HbA1c testing at least 3 months after TB treatment initiation, and ideally at treatment completion, to reduce the risk of misdiagnosis of DM and pre-DM in individuals with TB.

Despite a high proportion of TB cases with hyperglycemia at TB treatment initiation, 46% reverted their HbA1c levels to the euglycemic range by treatment completion. Transient hyperglycemia on OGTT and FBG has been reported during the acute phase of TB disease,^{3,5,16} and two recent studies from low DM and/or TB burden settings found similar reductions in HbA1c levels following TB treatment initiation.^{19,20} Our study extends these findings to a high TB and DM burden setting. HbA1c levels decreased during anti-tuberculosis treatment in all participants, irrespective of their glycemic status at treatment initiation. The greatest reduction in HbA1c levels was observed during the first 3 months of anti-tuberculosis treatment, with no significant change beyond 6 months. While the precise mechanisms of transient hyperglycemia in TB are unclear, insulin resistance due to inflammatory stress and a long duration of illness before HbA1c testing may have played a role.¹⁵

Among participants with DM at TB treatment initiation, nearly 25% reverted their HbA1c levels to the non-diabetic range by 6 months; no significant reversions occurred beyond this time. Participants with NDM were at greatest risk of reverting their HbA1c to the non-diabetic range by TB treatment completion. Our results are consistent with studies describing transient hyperglycemia in comparable populations.^{10,20,21} Compared with participants with KDM, those with NDM were less likely to have characteristics typical of conventional diabetic phenotypes (e.g., older age, higher BMI and family history of DM), more likely to have higher bacterial burden at TB treatment initiation, exhibit greater percentage declines in HbA1c levels during anti-tuberculosis treatment, and more likely to have blood glucose in the non-diabetic range and lower HbA1c levels at TB treatment initiation. These individuals might represent a distinct phenotype of 'transient DM' due to increased susceptibility to TB-induced hyperglycemia and may be misdiagnosed during screening. Importantly, our findings may also reflect unmasking of subclinical insulin resistance among individuals with an epigenetic predisposition to DM. Similar to gestational DM and stress hyperglycemia in hospitalized patients, whether transient DM in TB is associated with an increased risk of subsequent DM and microvascular disease needs further study.^{22,23}

Our study had two main limitations. First, we did not perform OGTT to confirm DM diagnosis; however, stress-induced transient hyperglycemia has been reported with OGTT.^{5,15,16} Second, declines in HbA1c levels during follow-up may be explained, in part, by regression to the mean (RTM). However, HbA1c is a stable test with minimal within-individual variability,²⁴ and we found consistent declines in absolute as well as percentage

HbA1c levels during anti-tuberculosis treatment irrespective of glycemic status at treatment initiation. Given the biological plausibility and previous evidence of transient hyperglycemia in TB, and the pragmatic nature of our study, RTM is unlikely to diminish the implications of our findings in real-world screening activities, reinforcing our conclusion that repeat HbA1c testing following anti-tuberculosis treatment should be undertaken to reduce the risk of misdiagnosis of DM in TB.

Despite these limitations, results from our study have several key implications. The WHO and the American Diabetes Association (Arlington, VA, USA) recommend confirming a HbA1c test result of $\geq 6.5\%$ within 2 weeks of the initial test.^{25,26} In our study, transient hyperglycemia was common despite the long half-life of HbA1c, and HbA1c levels declined significantly during anti-tuberculosis treatment in all participants, irrespective of glycemic status at treatment initiation. Our data suggest that repeat HbA1c testing should be delayed for at least 3 months from TB treatment initiation to confirm a diagnosis of DM. Second, reversion of HbA1c levels to a non-diabetic range was common in participants with NDM, highlighting the need to confirm a DM diagnosis following treatment, particularly in participants with NDM and an HbA1c level between 6.5% and 7.5%. Importantly, longitudinal studies investigating the risk of DM and microvascular disease among individuals with transient hyperglycemia during TB should be undertaken. Finally, emerging evidence suggests that medications such as metformin and statins, commonly prescribed in DM, may have antimycobacterial activity.^{27,28} The impact of transient hyperglycemia on the optimal timing of DM and pre-DM screening and glucose monitoring in TB is likely to gain importance in the near future if evidence from randomized clinical trials support adjuvant therapy and tighter glycemic control to improve clinical outcomes in TB and DM.

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Appendix

Figure A.1.

Pictorial representation of reversion and progression of glycemic status. Reversion was defined as individuals with an HbA1c level in the diabetic (or pre-diabetic) range at enrollment who then had an HbA1c level in the pre-diabetic or euglycemic range (only euglycemic range for individuals with pre-diabetes at enrollment) during follow-up. Progression was defined as individuals with an HbA1c level in the euglycemic (or pre-diabetic) range at enrollment who then had an HbA1c level in the pre-diabetic or diabetic range (only diabetic range for individuals with pre-diabetes at enrollment) during follow-up. HbA1c = glycated hemoglobin.

Figure A.2.

Enrollment schema. Consort diagram depicting analytic sample size and participant exclusion. PTB= pulmonary tuberculosis; HbA1c = glycated hemoglobin.

Table AGlycemic status by random or fasting blood glucose testing at enrollment ($n = 366$)

Characteristics	No diabetes ($n = 323$) n (%)	Diabetes ($n = 43$) n (%)	P value [*]
Fasting blood glucose test	111 (34)	13 (30)	0.73
HbA1c, %, median [IQR]	5.6 [5.3–6.0]	10.3 [8.9–12.3]	<0.001 [†]
HbA1c 6.5%	19 (6)	43 (100)	<0.001 [†]
Anti-diabetes medications	8 (3)	23 (53)	<0.001 [†]
Age, years, median [IQR]	29 [22–38]	48 [40–55]	<0.001 [†]
Male	194 (60)	33 (77)	0.4 [‡]
SMI, kg/m ² , median [IQR]	17 [15–19]	20 [18–23]	<0.001 [†]
Waist circumference, cm, median [IQR] [‡]	69 [63–77]	80 [73–90]	<0.001 [†]
Ever smoking	54 (17)	9 (21)	0.52
Regular alcohol consumption	76 (24)	12 (28)	0.57
Diabetes in first-degree relatives [§]	15 (5)	9 (23)	<0.001 [†]
Hemoglobin, g/dl, median [IQR]	12 [11–13]	13 [12–14]	0.003 [‡]
AFB smear			
Negative	104 (32)	10 (23)	0.08
1+	121 (38)	22 (51)	
2+	59 (18)	10 (23)	
3+	37 (12)	1 (2)	
MGIT TTD, days, median [IQR]	10 [7–13]	10 [8–14]	0.46

^{*} P values reported are by Fisher's exact test or for trends across groups defined by glycemic status using non-parametric tests.[†] Statistically significant.[‡] Measured at the upper margin of the lateral iliac crest.[§] Defined as parents, siblings or children.HbA1c = glycated hemoglobin; IQR = interquartile range; BMI = body mass index; AFB = acid fast bacilli; MGIT = mycobacterial growth indicator tube; TTD = time to (*M. tuberculosis*) detection.

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Figure 1.

Glycemic status assessed by HbA1c at enrollment. Consort diagram depicting participant enrollment and glycemic status by HbA1c assessments at enrollment. PTB = pulmonary tuberculosis, HbA1c = glycated hemoglobin.

Figure 2.

A) Change in HbA1c levels during anti-tuberculosis treatment by glycemic status at enrollment. Figure shows median (IQR) HbA1c levels during anti-tuberculosis treatment by glycemic status at enrollment. **B)** Change in HbA1c levels during anti-tuberculosis treatment by diabetes status at enrollment. Figure gives median (IQR) HbA1c levels during anti-tuberculosis treatment by type of diabetes (known and new) at enrollment. HbA1c = glycated hemoglobin; solid line = 6.5% threshold for diagnosing diabetes; dashed line = 5.7% threshold for diagnosing pre-diabetes; + = significant change since previous visit.

Figure 3.
Proportion of participants with hyperglycemia during anti-tuberculosis treatment by glycemic status at enrollment

Table 1

Participant characteristics according to glycemic status at enrollment

Characteristics	Englycemia (<i>n</i> = 191) median [IQR]	Pre-diabetes (<i>n</i> = 126) median [IQR]	New DM (<i>n</i> = 30) median [IQR]	Known DM (<i>n</i> = 45) median [IQR]	<i>P</i> value [*]
HbA1c, %	5.4 [5.2–5.6]	6.0 [5.8–6.1]	8.5 [6.7–11.5]	10.1 [8.3–11.6]	<0.001 [†]
Duration of diabetes, years	—	—	—	2 [1–5]	—
Glucose-lowering medications, <i>n</i> (%)	—	—	—	37 (82)	—
Age, years	27 [22–35]	29 [23–40]	46 [38–50]	50 [43–55]	<0.001 [†]
Male, <i>n</i> (%)	106 (56)	78 (62)	27 (90)	35 (78)	<0.001 [†]
BMI, kg/m ²	17 [15–19]	17 [15–19]	19 [16–22]	21 [18–24]	<0.001 [†]
Waist circumference, cm [‡]	69 [63–75]	71 [64–78]	78 [71–85]	81 [73–89]	<0.001 [†]
Ever smoker, <i>n</i> (%)	34 (18)	20 (16)	6 (20)	10 (22)	0.79
Regular alcohol consumption, <i>n</i> (%)	44 (23)	29 (23)	9 (30)	15 (33)	0.43
Diabetes in first-degree relatives, <i>n</i> (%) [§]	5 (3)	13 (11)	2 (7)	11 (26)	<0.001 [†]
Hemoglobin, g/dl	11.9 [10.7–13.2]	11.6 [10.5–13]	12.3 [10.6–13.2]	12.8 [11.8–13.9]	0.01 [†]
AFB smear, <i>n</i> (%)					
Negative	67 (35)	37 (30)	3 (10)	14 (31)	0.05 [†]
1+	67 (35)	52 (42)	19 (63)	21 (47)	
2+	36 (19)	24 (19)	4 (13)	8 (18)	
3+	21 (11)	11 (9)	4 (13)	2 (4)	
MGTTTDD, days	10 [7–13]	10 [7–12]	8 [6–11]	10 [8–12]	0.87

^{*} *P* values reported are by Fisher's exact test or for trends across groups defined by glycemic status using non-parametric tests.[†] Statistically significant.[‡] Measured at the upper margin of the lateral iliac crest.[§] Defined as parents, siblings or children.IQR = interquartile range; DM = diabetes mellitus; HbA1c = glycated hemoglobin; BMI = body mass index; AFB = acid fast bacilli; MGIT = Mycobacterial Growth Indicator Tube; TTD = time to (*M.* tuberculosis) detection.

Table 2

Change in glycemic status during anti-tuberculosis treatment *

Glycemic status at enrollment	Euglycemia (<i>n</i> = 191)			Pre-diabetes (<i>n</i> = 126)			New diabetes (<i>n</i> = 30)			Known diabetes (<i>n</i> = 45)		
	3 months <i>n</i> (%)	6 months <i>n</i> (%)		3 months <i>n</i> (%)	6 months <i>n</i> (%)		3 months <i>n</i> (%)	6 months <i>n</i> (%)		3 months <i>n</i> (%)	6 months <i>n</i> (%)	
Glycemic status during follow-up												
Euglycemia, <i>n</i> (%)	180 (94)	185 (97)		98 (78)	85 (67)		6(20)	7(23)		3(7)	C	
<i>P</i> value [†]	—	—		<0.001 [‡]	<0.001 [‡]		0.03 [‡]	0.31		0.25	—	
Pre-diabetes, <i>n</i> (%)	11 (6)	6(3)		28 (22)	39 (31)		5(17)	6(20)		2(4)	7(16)	
<i>P</i> value [†]	<0.001 [‡]	0.04 [‡]		—	—		0.06	0.31		0.50	0.25	
Diabetes, <i>n</i> (%)	0	0		C	2(2)		19 (63)	17 (57)		40 (89)	38 (84)	
<i>P</i> value [†]	—	—		—	0.31		—	—		—	—	
Percentage change in HbA1c since previous visit												
% (95%CI)	-3 (-4 to -2)	1 (-1 to 2)		-9 (-10 to -8)	3 (1 to 5)		-12 (-18 to -7)	0 (-6 to 6)		-6 (-12 to 1)	0 (-5 to 6)	
<i>P</i> value	<0.001 [‡]	0.10		<0.001 [‡]	0.01 [‡]		<0.001 [‡]	0.98		0.06	0.91	

* Progression and reversion was defined as change in diagnostic classification towards the diabetic and euglycemic end of the glycemic spectrum, respectively.

[†]McNemar's χ^2 test for the proportion of participants progressing/reverting since the previous visit.[‡]Statistically significant.

TB = tuberculosis, CI = confidence interval; HbA1c = glycated hemoglobin.