**Background**

The WHO recently recommended diabetes screening in people newly diagnosed with tuberculosis (TB) in high burden settings. However, the optimal implementation of this strategy is hampered by stress hyperglycemia, i.e. stress-induced insulin resistance resulting in hyperglycemia that is transient and subsides with TB treatment which may result in misdiagnosis of diabetes.

Early studies have shown a decrease in the proportion of TB cases with hyperglycemia diagnosed with oral glucose tolerance testing (OGTT) or fasting blood glucose (FBG) assay after initiation of TB treatment.

Since then, glycated hemoglobin (HbA1c) testing has been widely used for diabetes screening worldwide. In addition to being highly stable, HbA1c testing is operationally less challenging than OGTT and fasting blood glucose levels during the preceding 2.3 months, potentially serving as a screening tool for diabetes during the acute phase of TB.

We sought to characterise trends in HbA1c levels during TB treatment and its potential impact on diabetes screening from an ongoing cohort study of new adult TB pulmonary cases with and without diabetes in western India.

**Methods**

**Study population:**
Consecutively enrolled newly diagnosed adult (≥18 years) pulmonary TB cases referred from the Revised National Tuberculosis Control Program (RNTCP) clinics since December 2013 in Pune, India.

Those with rifampicin resistant TB, HIV co-infection, TB treatment exceeding seven days or a prior history of TB were excluded.

Pulmonary TB cases were diagnosed by the presence of acid-fast bacilli (AFB) on smear microscopy. Mycobacterium tuberculosis DNA on Xpert® MTB/RIF assay or M. tuberculosis growth on liquid culture.

**Definitions of diabetes:**
HbA1c testing was done by high-performance liquid chromatography (BioRad Laboratories, USA) at enrollment (TB treatment initiation), 3 months, 6 months (treatment completion) and 12 months.

Participants reporting current glucose-lowering medication use or a self-reported physician diagnosis at enrollment were classified as having known diabetes (KDM).

**Newly diagnosed diabetes (NOM):**
Defined as HbA1c≥6.5% in participants without prior diagnosis at enrollment.

Pre-diabetes was classified as having HbA1c levels between 5.7% and 6.5% in participants without KDM at enrollment.

**Results**

**Table 1. Participant characteristics by glycaemic status at enrolment**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Euglycemic</th>
<th>Pre-diabetes</th>
<th>NDM</th>
<th>KDM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>90 (47)</td>
<td>84 (43)</td>
<td>102 (52)</td>
<td>70 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>30 (16)</td>
<td>20 (10)</td>
<td>48 (24)</td>
<td>30 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c, median (IQR)</td>
<td>5.4 (5.2-5.6)</td>
<td>6.0 (5.8-6.1)</td>
<td>8.5 (7.6-11.5)</td>
<td>10.1 (8.8-11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years (median, IQR)</td>
<td>27 (22-36)</td>
<td>29 (23-40)</td>
<td>46 (38-50)</td>
<td>43 (35-53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>106 (56)</td>
<td>78 (42)</td>
<td>72 (38)</td>
<td>190 (79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²), median</td>
<td>17 (14-19)</td>
<td>17 (14-19)</td>
<td>19 (16-23)</td>
<td>18 (16-24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm), median</td>
<td>69 (63-75)</td>
<td>72 (66-78)</td>
<td>78 (72)</td>
<td>73 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regular alcohol use, n (%)</td>
<td>44 (23)</td>
<td>29 (15)</td>
<td>9 (4)</td>
<td>11 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes in 1st rel, n (%)</td>
<td>5 (3)</td>
<td>13 (7)</td>
<td>22 (11)</td>
<td>11 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MIGN TDD (days), median</td>
<td>10 (7-17)</td>
<td>10 (6-12)</td>
<td>10 (6-15)</td>
<td>9 (6-15)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Discussion**

**Key findings:**
- HbA1c levels declined significantly during TB treatment irrespective of glycaemic status at treatment initiation.
- Greatest reduction in HbA1c levels were observed during the first 3 months of TB treatment, with no significant change beyond TB treatment completion.
- Changes in glycaemic status were common during the first 3 months of TB treatment, with no significant change beyond TB treatment completion.
- Transient hyperglycemia was common despite the long half-life of HbA1c, with nearly 25% of participants with diabetes and 70% with pre-diabetes reverting their HbA1c levels to the non-diabetic and euglycemic range by TB treatment completion respectively.
- NDM had the greatest decline in HbA1c during TB treatment and were 5-times more likely to revert their HbA1c to the non-diabetic range by TB treatment completion compared to KDM (p<0.04).

**Implications:**
The WHO recommends screening for diabetes among adults newly diagnosed with TB. Our data suggests that a repeat HbA1c test at least 3 months, and ideally at 6 months, following TB treatment initiation, especially for NOM with HbA1c between 6.5 and 7.5% at TB treatment initiation, could reduce misdiagnosis of diabetes.

Participants with "transient diabetes" during TB might represent a distinct phenotype of individuals with episodic prediabetes to diabetes who are susceptible to unmasking of subclinical insulin resistance in response to stress. In contrast to gestational diabetes and stress-hyperglycaemia in hospitalised patients, whether transient diabetes in TB is associated with increased risk of subsequent diabetes and microvascular pathology needs further study.

**Conclusion**
- HbA1c levels declined significantly with TB treatment irrespective of glycaemic status at treatment initiation.
- Transient hyperglycemia was commonly seen in newly diagnosed adult pulmonary TB cases.
- Repeat HbA1c testing following the intensive phase of treatment or at treatment completion could reduce misdiagnosis of diabetes in TB.