Tuberculosis, Diabetes, Serum Drug levels

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No disclosures

Overview

Diabetes increases the risk of progression to active TB disease
(odds 2.4-8.3 compared to non-diabetics) and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

Drug concentrations are suboptimal for most DM/TB patients
No “special insidiousness” of presentation
No difference in location of disease or lung cavitation

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Location</th>
<th>Participants</th>
<th>Lung less</th>
<th>More cavities</th>
<th>More diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In diabetes</td>
<td>involved?</td>
<td>in diabetes</td>
<td>involvement?</td>
</tr>
<tr>
<td>2000</td>
<td>USA</td>
<td>20</td>
<td>15</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>South Africa</td>
<td>9</td>
<td>47</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Spain</td>
<td>30</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2000</td>
<td>Texas, USA</td>
<td>30</td>
<td>20</td>
<td>No</td>
<td>No</td>
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<tr>
<td>2004</td>
<td>Turkey</td>
<td>37</td>
<td>27</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2004</td>
<td>Cameroon</td>
<td>-</td>
<td>23</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Saudi Arabia</td>
<td>30</td>
<td>20</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Tunisia</td>
<td>52</td>
<td>22</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2000</td>
<td>Mexico</td>
<td>102</td>
<td>130</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2000</td>
<td>Saudi Arabia</td>
<td>97</td>
<td>224</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Taiwan</td>
<td>90</td>
<td>262</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Taiwan</td>
<td>74</td>
<td>146</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2000</td>
<td>Saudi Arabia</td>
<td>57</td>
<td>170</td>
<td>No</td>
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</tr>
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</table>

Dooley et al. Lancet ID 2009

Attributable risk of TB from Diabetes > HIV in Texas/Mexico border


Diabetes is the leading identified risk factor for TB in Virginia (10-15%)


Table 15. Tuberculosis Cases by Selected Risk Factors: Virginia, 2008-2012
Screening for diabetes in new TB patients can be highly effective (India)

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Number of TB patients whose DM status was accelerated (%)</th>
<th>Number with previously known DM (%)</th>
<th>Number of DM newly diagnosed (%)</th>
<th>Additional Yield (if done with HbA1c) (%)</th>
<th>Number needed to screen (with HbA1c) to detect one new case of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New smear Positive Pulmonary TB</td>
<td>507</td>
<td>67</td>
<td>70</td>
<td>64%</td>
<td>3.7</td>
</tr>
<tr>
<td>New smear Negative Pulmonary TB</td>
<td>37</td>
<td>4</td>
<td>7</td>
<td>64%</td>
<td>4.7</td>
</tr>
<tr>
<td>New Extrapulmonary TB</td>
<td>138</td>
<td>15</td>
<td>21</td>
<td>58%</td>
<td>5.3</td>
</tr>
<tr>
<td>Miliary</td>
<td>35</td>
<td>12</td>
<td>8</td>
<td>41%</td>
<td>3.3</td>
</tr>
<tr>
<td>Treatment after Failure</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>22%</td>
<td>6.0</td>
</tr>
<tr>
<td>Treatment after Default</td>
<td>26</td>
<td>6</td>
<td>9</td>
<td>70%</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Overall, number of **TB patients needed to screen** (with HbA1c) in order to detect one new case of diabetes was just 4.

Balakrishnan et al. *PLoS ONE* 2012

Based on studies like this,

The national TB guidelines in India have changed to recommend screening for diabetes in all new TB cases

In the USA

LTBI

TB treatment

*MMAWs*

Standards of Medical Care in Diabetes - 2013
Overview

Diabetes increases the risk of progression to active TB disease (odds 2.4-8.3 compared to non-diabetics) and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w/ TB)

Drug concentrations are suboptimal for most DM/TB patients

Outcomes during treatment for TB

Most do well (>90%)  Some don't

Death < “slow response” = persistent symptoms/smear+

Many possible factors
- Extensive disease
- Drug resistance
- HIV
- Other comorbidities/smoking
- Low drug levels
- Diabetes

Diabetics in Indonesia more likely to be culture-positive at 6 months of treatment (22%)

Table 3: Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tuberculosis-positive (n = 546)</th>
<th>Without DM (n = 546)</th>
<th>Odds OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive disease</td>
<td>17 (17.9)</td>
<td>54 (9.9)</td>
<td>3.13 (1.5-6.4)</td>
<td>3.44 (1.7-7.0)</td>
</tr>
<tr>
<td>Drug resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other comorbidities/smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low drug levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Some don’t

- Death < “slow response” = persistent symptoms/smear+
- Many possible factors
  - Extensive disease
  - Drug resistance
  - HIV
  - Other comorbidities/smoking
  - Low drug levels
  - Diabetes

Diabetics in Indonesia more likely to be culture-positive at 6 months of treatment (22%)

- 14.8% prevalence of undiagnosed DM in new TB patients
- TB-DM had greater symptoms at time of diagnosis

In Maryland, odds of death were 6.5 times higher (p=0.039) for diabetics than non-diabetics with TB, even adjusting for HIV, age, weight, and foreign birth.

Time to sputum culture conversion was longer (49 days for diabetics vs 39 days for non-diabetics, p=0.09).

All cause mortality increased in diabetics during TB treatment

Slower culture conversion in diabetics (without cavitary disease)

>20% of diabetics with non-cavitary pulmonary TB remain sputum positive at 3 months of treatment.
Worse outcomes.....What can we do about it?

**TB disease:**
- Extrapulmonary TB
- Extensive lung cavities
- Delayed presentation to care

**Host factors:**
- HIV
- Diabetes
- Malnutrition
- Silicosis

**M. tuberculosis strain:**
- Drug resistance
- Virulence?

![Diagram showing TB disease, host factors, and drug resistance](image)

Low plasma drug levels?

- Start TB treatment
- Delayed culture conversion
- Death
- Acquired drug resistance
- Relapse

**Outcomes during treatment for Tb**

- Most do well (>90%)
- Some don’t
- Death < “slow response” = persistent symptoms/smear+

*We have been routinely checking serum anti-TB drug concentrations in “slow responders” since ~2007 (thanks to some add’l funding)

•~14% of all Tb patients, defined as no improvement in sx or persistent smear +

•Diabetics were **6.3 times more likely to be slow responders** (p<0.001) adjusted for age, gender, foreign birth, prior TB episodes, cavitary disease, HIV, alcohol and tobacco use.

•~40% of diabetics

•Among slow responders, **diabetics had significantly lower serum rifampin levels** (estimated peak C2h)

Heysell et al. Emerg Infect Dis 2010
Majority of slow responders had low $C_{2hr}$ levels of INH and rifampin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low</th>
<th>Within Target</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>59%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>RMP</td>
<td>52%</td>
<td>46%</td>
<td>2%</td>
</tr>
<tr>
<td>EM0</td>
<td>31%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

82% had low levels to one of INH or RMP, hard to predict which one

Heysell et al, Emerg Infect Dis, 2010

Drug levels usually correct after first dose adjustment

Drug levels can vary depending on the dose and frequency of administration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH daily</td>
<td>300 mg</td>
<td>450 mg</td>
</tr>
<tr>
<td>INH biweekly</td>
<td>900 mg</td>
<td>1200 mg</td>
</tr>
<tr>
<td>RMP daily/biweekly</td>
<td>600 mg</td>
<td>900 mg</td>
</tr>
</tbody>
</table>

$\pm$ spans $C_{2hr}$ expected range

Heysell et al, Emerg Infect Dis, 2010

Determinants of anti-TB drug pharmacokinetics:

1. mg/kg dosing (weight categories, poor availability of drug in fixed-dose combinations in some settings)
2. Adherence
3. Drug interactions
4. Gastroenteritis
5. Malabsorption
6. Diabetes
7. Poor solubility
8. Cystic Fibrosis
9. Host genetics
10. Poor solubility

Heysell et al, Emerg Infect Dis, 2010

What is the right* dose of rifampin?

*In 1971 the dose of 10 mg/kg was arbitrarily chosen without a maximum tolerated dose study.

In 2011, an initiative was started to measure isoniazid and rifampin levels (these 2 drugs only, PZA usually fine, EMB usually dropped) in all diabetics at 2 weeks of TB therapy (instead of waiting for ~40% to be slow responders).
The Virginia Algorithm


Instead of only self-report and prior DM diagnoses, we now recommend checking HbA1C on all >6.5: education/resource packet, referral <6.5: education/resource packet

Implementation of early TDM in diabetics was operationally feasible

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetic (early TDM)</th>
<th>Slow response (standard TDM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ±SD</td>
<td>57 ±17</td>
<td>46 ±12</td>
<td>P=0.04</td>
</tr>
<tr>
<td>Gender, male (%N)</td>
<td>15 (71)</td>
<td>11 (79)</td>
<td>P=0.69</td>
</tr>
<tr>
<td>Prior episode of TB, n (%N)</td>
<td>0</td>
<td>2 (14)</td>
<td>P=0.17</td>
</tr>
<tr>
<td>Pulmonary TB only, n (%N)</td>
<td>17 (81)</td>
<td>8 (57)</td>
<td>P=0.65</td>
</tr>
<tr>
<td>Foreign born (%N with confirmed status)</td>
<td>15 (79)</td>
<td>12 (92)</td>
<td>P=0.63</td>
</tr>
<tr>
<td>HIV infected (%N with confirmed status)</td>
<td>0</td>
<td>1 (11)</td>
<td>P=0.43</td>
</tr>
<tr>
<td>Insulin dependence, n (%N)</td>
<td>10 (48)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Days to TDM from treatment initiation, median days (IQR)</td>
<td>21 ±10</td>
<td>88 ±54</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

Heyssel et al. NTCA 2013

Early TDM in diabetics corrected low drug concentrations in the majority and may limit slow response

• Of the 21 diabetics, 16 (76%) had a \( C_{2hr} \) value below the expected range for isoniazid (mean 2.1±1.5 μg/ml; expected 3-5), rifampin (mean 6.6±4.3 μg/ml; expected 8-24) or both

A proper target population

• 15 patients had follow-up concentrations after dose adjustment, all increased and 12 to the expected range (including all for rifampin).

• In practice, what our algorithm does is shunt most diabetics to at least 3x weekly therapy during continuation phase, with INH 900/RIF 900, while keeping to a 6 month total duration

No major toxicities reported

• 88% of diabetics with early TDM and pulmonary TB had sputum culture conversion <2 mos.

Better than expected norms for diabetes/TB

• Total statewide burden of slow response decreased from 1.6 patients/mo (40% diabetic) to 1.2 patients/mo (12.5% diabetic)

May limit the need for prolonged treatment and program resources

Heyssel et al. NTCA 2013
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  – Scott Heysell, Tania Thomas, Dorothy Bunyan, Suzanne Stroup

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  – Jane Moore, Suzanne Keller, Debbie Staley, Denise Dodge

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