Tuberculosis Complicated by Diabetes
Barbara J. Seaworth MD
April 7, 2016

Tuberculosis Intensive
April 5-8, 2016
San Antonio, TX

Barbara Seaworth, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
A Little Test Before We Begin

Which NBA player has won 1,000 games in his career?

A. Stephen Curry  
B. Michael Jordan  
C. Lebron James  
D. Tim Dunkin  
E. Kobe Bryant
The San Antonio Spurs are the best basketball team in the NBA?

A. True
B. False

TB Intensive is the best course I’ve ever attended?

A. True
B. False
Tuberculosis Complicated by Diabetes
Barbara J. Seaworth MD
Medical Director, Heartland NTBC
Professor of Medicine, UT Health Northeast

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Objectives

• Identify the impact of DM on the risk of LTBI and TB disease.

• Understand the impact of DM on treatment and case management practices

• Discuss the impact of DM on TB treatment outcomes

Does Diabetes Predispose to TB?

DOES TB INCREASE THE RISK OF DIABETES?
Relative Risk of Progressing to Active TB Disease for Diabetes:

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicosis</td>
<td>30 (37,38)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.0–4.1 (40–44)</td>
</tr>
<tr>
<td>Chronic renal failure/hemodialysis</td>
<td>10.0–25.3 (39–41)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>2–5 (45–47)</td>
</tr>
<tr>
<td>Jejunuleal bypass</td>
<td>27–53 (46–49)</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>20–74 (51,52)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>16 (53)</td>
</tr>
</tbody>
</table>

*Relative to control population: independent of tuberculin-test status.  
* Numbers in parentheses are reference numbers.

CDC, ATS, IDSA: Treatment of LTBI 2000

YES ! - Diabetes Predisposes to TB

- Hong Kong prospective study of 4661 close contacts of active TB cases
  - **RR 3.4** increase in diabetics for both:
    - **early** – primary progressive disease (3month)
    - **late**- reactivation (within 5 years) disease

Lee MS, Int J Tuberc Lung 2008
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2010

http://www.cdc.gov/diabetes/statistics

Figure 2. Prevalence of total confirmed diabetes and obesity.

Figure 1. Trends in the prevalence of diagnosed DM and undiagnosed DM (calibrated HA1c levels >6.5%), by age and race/ethnicity


Annals Internal Med, 2014

County-Level Diagnosed Diabetes Among Adults ≥ 20 Years – U.S. 2009

Age-adjusted ranks based on age-adjusted percentage of diabetes:
- Red: Above median rank
- Yellow: Below median rank
- Orange: Not above median rank or below median rank
Counties in the Top and Bottom Two Quintiles of Both Diabetes and Obesity, 2007

The Diabesity Epidemic!
Prevalence Adult Obesity 2011-2012

New obesity prevalence data show almost 35% of adults were obese in 2011-2012 – the same as in 2009-2010. Data in the report, *Prevalence of Obesity Among Adults in the United States, 2011-2012*, are based on measured height and weight obtained by the National Health and Nutrition Examination Survey.

In 2011-2012 the prevalence of obesity was **33.5% among males** and **36.1% in women**.

CDC’s National Center for Health Statistics

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Prevalence of diabetes in adults aged 25+
by WHO region and World Bank Income Group, 2008

### Graph

- **men**
- **women**
- **both sexes**

<table>
<thead>
<tr>
<th>Region</th>
<th>Low-income</th>
<th>Lower-middle-income</th>
<th>Upper-middle-income</th>
<th>High-income</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td></td>
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<tr>
<td>AMR</td>
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<td>EMR</td>
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<td>EUR</td>
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<td>SEAR</td>
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<tr>
<td>WPR</td>
<td></td>
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</tr>
</tbody>
</table>
Globally urbanization has fueled an increasing incidence of DM in Africa, India, Asia, South and Central America and the U.S.

- Many are areas with high rates of TB

By 2030 it is estimated that 80% of diabetes will be in areas of the world with the highest rates of TB

- Diabetes becoming more prominent in low and middle income countries
Global Rising Tide of Diabetes

- **WHO:**
  - Diabetes rises fourfold over last quarter-century

  - WHO reported:
    - 8.5% of the world population had DM two years ago, up from 108 million, or 4.7%, in 1980.
    - Blamed the growing consumption of food and beverages high in sugar.
    - DM grew around the world, but increased most in Africa, the Middle East and Asia.

Associated Press Published April 06, 2016
Growing Diabetic Epidemic Will Have a Significant Impact on TB Control

Case Study

• 36 yr old Latino woman with close exposure to an infectious individual with drug susceptible pulmonary TB

• She has a long history of poorly controlled diabetes
Compared to other contacts to the source case is she more at risk of developing LTBI?

A. Yes
B. No

Linkage Between Tuberculosis and Diabetes

- Patient diagnosed with Diabetes
- Immune Response is weakened
- Exposure to M. Tuberculosis
- No increased risk of LTBI
Does Diabetes or Pre-Diabetes Increase Risk of LTBI?

Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus

R. L. Hensel,* R. R. Kemper,** J. Tapia,† A. Oladele,† H. M. Blumberg,†* M. J. Magee†*

*School of Medicine, Emory University, Atlanta; †Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta; ‡DeKalb County Board of Health, Decatur; †Departments of Epidemiology and Global Health, Emory Rollins School of Public Health, Atlanta; †Division of Epidemiology and Biostatistics, Georgia State University, School of Public Health, Atlanta, Georgia, USA

SUMMARY

Setting: Although diabetes mellitus (DM) is an established risk factor for active tuberculosis (TB) disease, little is known about the association between pre-DM, DM, and latent tuberculous infection (LTBI).

Objective: To estimate the association between DM and LTBI.

Design: We conducted a cross-sectional study among recently arrived refugees seen at a health clinic in Atlanta, GA, USA, between 2013 and 2014. Patients were screened for DM using glycosylated-hemoglobin (HbA1c), and for LTBI using the Quantiferon®-TB QFT test. HbA1c and QFT results, demographic information, and medical history were abstracted from patient charts.

Results: Among 702 included patients, 681 (97.0%) had HbA1c and QFT results. Overall, 54 (7.8%) patients had DM and 235 (33.8%) had pre-DM. LTBI prevalence was significantly higher (P < 0.01) among patients with DM (43.4%) and pre-DM (39.1%) than in those without DM (25.9%). Refugees with DM (adjusted OR [aOR] 2.3, 95% CI 1.2–4.5) and pre-DM (aOR 1.7, 95% CI 1.1–2.4) were more likely to have LTBI than those without DM.

Conclusion: Refugees with DM or pre-DM from high TB burden countries were more likely to have LTBI than those without DM. Dyglycemia may impair the immune defenses involved in preventing Mycobacterium tuberculosiis infection.

KEY WORDS: hemoglobin A1c; QuantiFERON test; refugee; vitamin D
Does Diabetes or Pre-Diabetes Increase Risk of LTBI?

• Presumption that DM increases risk of LTBI –
  – Two small studies suggested more LTBI in diabetics
• Study of newly arrived refugees evaluated prevalence of DM with HBA1C;
  – DM ≥ 6.5%, pre-DM 5.7-6.4%, no DM < 5.7%
• 681 patients with both HBA1C and QFT results
  – 54 DM, 235 pre-DM,
  – LTBI prevalence 31.8%
• Also screened for low Vitamin D level

Int J TB and Lung Disease; Hensel 2016

Does Diabetes or Pre-Diabetes Increase Risk of LTBI?

• LTBI was significantly more common patients with DM
  – Noted in both those with prior DX of DM and new DX of DM
  – DM (43.4%) and pre-DM (39.1%) vs
  – No DM (25.9%)

• HBA1C higher in patients with LTBI
  – 5.7% vs 5.5 in those without LTBI
Association of Vitamin D and MTB

- Vitamin D deficiency is associated with:
  - Increased risk of active TB and
  - Increased risk of progression from LTBI to active TB disease

- Did not find that vitamin D deficiency was associated with LTBI,
  - Median 25OHD plasma level among patients with DM was significantly lower than in those without DM
  - Did note association between DM and LTBI in those with low Vitamin D levels
Compared to other contacts, is she more at risk of progressing to active TB disease if she develops LTBI?

A. Yes
B. No

WHO 2009

People with a weak immune system, as a result of chronic diseases such as diabetes, are at a higher risk of progressing from latent to active TB.

People with diabetes have a 2-3 times higher risk of TB compared to people without diabetes.

About 10% of TB cases globally are linked to diabetes.
Latent TB Infection (LTBI) in Diabetic Patients

- Due to the increased risk for progression to active TB disease, the following should be done:
  - Diabetics who are at risk for TB exposure should be screened for TB with an IGRA or TST
  - The risk of progression to TB disease should be communicated to community physicians caring for diabetics
  - Diabetics with TB infection should be treated
    - 3 HP regimen
    - Rifampin for 4 months
    - INH for 9 months

Risk of TB Related to Degree of Diabetic Control

- Actuarial probability of developing TB was 24% in IDDM and 4.8% in NIDDM
  - 1592 diabetics in Chili followed prospectively from 1959-1982
    - Olmos, Rev Med Chil 1989

- 9.0% IDDM versus 2.7% NIDDM developed pulmonary TB
  - Prospective study in Tanzania, diabetic patients followed 1 – 7 years
    - Wild, Diabetes Care 2004
ORIGINAL RESEARCH

Type 2 Diabetes Mellitus Coincident with Pulmonary Tuberculosis Is Associated with Heightened Systemic Type 1, Type 17, and Other Proinflammatory Cytokines

Nathalia Pavan Kumar1,2, Rathiham Sridhar3, Vaithilingam V. Banurekha4, Mohideen S. Jawahar3, Michael P. Fay5, Thomas B. Nutman6, and Subash Babu1,5

1International Center for Excellence in Research, National Institutes of Health, 2National Institute for Research in Tuberculosis, and 1Government Stanley Medical Hospital, Chennai, India; and 5Epidemiology Research Branch and 6Laboratory of Parasitic Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Abstract

Rationale: Type 2 diabetes mellitus is a major risk factor for the development of active tuberculosis, although the biological basis underlying this susceptibility remains poorly characterized.

Conclusions: Our data reveal that tuberculosis with diabetes is characterized by heightened cytokine responsiveness, indicating that chronic inflammation underlying type 2 diabetes potentially contributes to increased immune pathology and poor control in tuberculosis infection.

Annals ATS Oct 2013

The Journal of Infectious Diseases Advancements

BRIEF REPORT

Impaired Cytokine but Enhanced Cytotoxic Marker Expression in Mycobacterium tuberculosis-Induced CD8+ T Cells in Individuals With Type 2 Diabetes and Latent Mycobacterium tuberculosis Infection

Nathalia Pavan Kumar,1 Kedar Moideen,1 Parakkal Jovian George,1 Chandrakumar Dolly,1,2 Paul Kumar,1,2 and Subash Babu1

1National Institutes of Health-National Institute for Research in Tuberculosis-International Center for Excellence in Research, and 1National Institute for Research in Tuberculosis, Chennai, India

Type 2 diabetes mellitus (DM) is a risk factor for tuberculosis among individuals with latent Mycobacterium tuberculosis infection. To explore the influence of DM on CD8+ T-cell responses during latent M. tuberculosis infection, we estimated the cytokine and cytotoxic marker expression pattern in individuals with latent M. tuberculosis infection with DM and those without DM. Among individuals with latent M. tuberculosis infection, those with DM had diminished frequencies of CD8+ T-helper type 1 (Th1), Th2, and Th17 cells following stimulation by M. tuberculosis antigen and enhanced frequencies of CD8+ T cells expressing cytotoxic markers, compared with those without DM. Thus, our results suggest that coincident DM modulates CD8+ T-cell function during latent M. tuberculosis infection.

Keywords: latent M. tuberculosis infection; diabetes mellitus; CD8+ T cells; cytokines.

November 2015
What additional evaluation or treatment should this patient have?

A. Medical History
B. TST or IGRA
C. CXR
D. Hb A1C
E. Start INH for LTBI
F. A and B

Case Study

– TST 20 mm

– Patient notes several weeks of dry cough but is otherwise well
  • Incidentally her HB A1C is > 8.9%

• Now What?
Case Study

- CXR was read as normal by radiologist
- Exam was normal
- Patient reported frequent allergies
- One sputum specimen was submitted
  - Smear negative for AFB
What else should be done?

A. Sputum for smear & culture x 3
B. Bronchoscopy with BAL?
C. Start treatment for LTBI
D. Start treatment for active TB disease (RIPE)
E. A and C
F. A and D

Presentation of TB in Diabetics

• Various reports of more severe disease

• Varying findings as to the radiographic presentation
  — ? More cavities
  — ? Isolated lower lung involvement
Classic Article Prior to Availability of TB Medications
Howard Root MD, Deaconess Hospital, Boston
NEJM, 1934

- No pathological findings unique to “the tubercular diabetic”
  Autopsy series of 126 patients
  Review of 245 TB cases in diabetic patients

TB developed most frequently in patients with poor diabetic control
  Dooley, & Chaisson, Lancet ID, Dec, 2009

TB and Diabetes, CXR Findings

<table>
<thead>
<tr>
<th>Year</th>
<th>Study location</th>
<th>Participants (n)</th>
<th>With diabetes</th>
<th>Without diabetes</th>
<th>Lower lung more commonly involved</th>
<th>More cavitation lesions?</th>
<th>More diffuse involvement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1924</td>
<td>USA</td>
<td>20 182</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>1980</td>
<td>South Africa</td>
<td>9 427</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>1992</td>
<td>Japan</td>
<td>311 71</td>
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<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>1992</td>
<td>Taiwan, USA</td>
<td>20 20</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
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<tr>
<td>1984</td>
<td>Turkey</td>
<td>37 37</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>1996</td>
<td>Cameroon</td>
<td>2731</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>1997</td>
<td>Saudi Arabia</td>
<td>28 38</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
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<tr>
<td>2001</td>
<td>Turkey</td>
<td>92 92</td>
<td>No5</td>
<td>No5</td>
<td>No5</td>
<td>No5</td>
<td>No5</td>
</tr>
<tr>
<td>2000</td>
<td>Mexico</td>
<td>192 430</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2003</td>
<td>Saudi Arabia</td>
<td>182 506</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2005</td>
<td>Taiwan</td>
<td>99 362</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2008</td>
<td>Taiwan</td>
<td>74 143</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2009</td>
<td>Saudi Arabia</td>
<td>57 78</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
</tbody>
</table>

*Apart from the study by Iwase et al., in which computed tomography was used. Patients with diabetes mellitus or who were immunocompromised. Patients with tuberculosis, of whom 28 had lower lung disease. Insulin-dependent diabetes mellitus had more cardiac disease than non-insulin-dependent diabetes mellitus, in subgroup analysis, diabetes mellitus was a risk factor for lower lung disease in patients aged >60 years. – not reported.

Table 2: Studies assessing chest radiographic findings in patients with tuberculosis, comparing diabetic to non-diabetic patients

Dooley, & Chaisson, Lancet ID, Dec, 2009
40 yr old DM with HBA1C 9.3%
2 ½ mo history of cough, night sweats, weight loss
DX as CAP; treated with levaquin

Increased symptoms, returned to ER
Treated with Levaquin/Vancomycin
BAL showed AFB +
RIPE started 10/29/15
First negative culture 1/4/2016
Treatment Outcomes of TB Disease Among Patients with and without Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with positive sputum at end of treatment (%)</th>
<th>Patients with negative results at end of treatment (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>7 (100.0)</td>
<td>85 (100.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetics☆</td>
<td>7 (100.0)</td>
<td>41 (48.2)</td>
<td></td>
</tr>
<tr>
<td>Male sex*</td>
<td>6 (85.7)</td>
<td>77 (90.6)</td>
<td>0.526</td>
</tr>
<tr>
<td>Non-sero-conversion at end of intensive phase*</td>
<td>2 (28.6)</td>
<td>1 (1.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Smoker*</td>
<td>4 (57.1)</td>
<td>54 (63.5)</td>
<td>0.707</td>
</tr>
<tr>
<td>Alcohol user*</td>
<td>4 (57.1)</td>
<td>58 (68.2)</td>
<td>0.679</td>
</tr>
<tr>
<td>Interruption of treatment (median days)**</td>
<td>10 days</td>
<td>11 days</td>
<td>0.631</td>
</tr>
<tr>
<td>Age (median years)**</td>
<td>34 years</td>
<td>49 years</td>
<td>0.274</td>
</tr>
</tbody>
</table>

*Fisher's exact test, **Unpaired-t-test

Effect of Type II DM on Treatment Outcomes of TB Viswanathan & Gawde Lung India 2014
**TB and Diabetes - Clinical Presentation**

- **My clinical experience**
  - Unless long term insulin dependent
    - More likely to have higher BMI
    - Nearly all have poor diabetic control
    - Most not particularly interested in diabetes
    - Often have had > 2 medical evaluations that did not diagnose TB
    - Most have not had routine screening for TB risk factors or testing for TB

**Case Study – Back to Patient Exposed to TB and Treated for LTBI**

- 3 months later:
  - Fever
  - Productive cough
  - Hemoptysis
August 26, 2011

Case Study

• Smear + for AFB

• CXR notes bilateral upper lobe opacifications and cavitation
**What now?**

A. Start RIPE
B. Stop INH continue RPE
C. Stop INH, start RPE and add fluroquinolone

---

**Case Study**

- Culture grows M TB
  - Later found resistant to INH
Are outcomes different than for other TB patients?

A. Slower sputum conversion
B. Increased risk of failure
C. Increased risk of death
D. Increased risk of relapse
E. All of above

Does Diabetes Impact TB Treatment Outcomes?

• Previously thought not to affect treatment outcomes

• Four studies from Baltimore, Texas, Taiwan and Indonesia reveal:
  – Delayed culture conversion
  – Higher mortality
    – Dooly, 2009; Restrepo 2008; Wang 2008; Alisahlanda, 2007
Response to Treatment

• Relapse may be more frequent
  – Recent Shanghai study - 203 diabetics with TB followed for 2 years after standard treatment
    • 20% relapse rate in patients with DM (most Type 2)
    • 5% relapse rate in patients without DM

Zhang et al. Jpn J Infect Dis, 2009
TB Treatment Outcomes in those with/without Diabetes

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Diabetics yes (%)</th>
<th>Not diabetics yes (%)</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>41 (46.1)</td>
<td>43 (35.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>39 (43.8)</td>
<td>72 (60.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>7 (7.9)</td>
<td>9 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Default</td>
<td>1 (1.1)</td>
<td>4 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.1)</td>
<td>1 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful treatment (all patients)</td>
<td>80 (89.9)</td>
<td>115 (95.8)</td>
<td>0.386 (0.125-1.196)</td>
<td>0.110 (0.017-1.662)</td>
</tr>
<tr>
<td>Successful treatment (pulmonary TB) n = 182</td>
<td>75 (89.3)</td>
<td>99 (84.9)</td>
<td>0.448 (0.144-1.394)</td>
<td>0.191* (0.046-0.900)</td>
</tr>
<tr>
<td>Successful treatment (cavity positive TB) n = 109</td>
<td>44 (83.0)</td>
<td>51 (91.1)</td>
<td>0.479 (0.140-1.537)</td>
<td>0.098* (0.013-0.761)</td>
</tr>
</tbody>
</table>

*P<0.05

Effect of Type II DM on Treatment Outcomes of TB Viswanathan & Gawde Lung India 2014

Impact of Diabetes on Tuberculosis Treatment Outcomes

- A Systematic Review of 33 studies:
  - Diabetes is associated with an increased risk of failure and death during TB treatment.

  » Baker et al. Bio Med Central, Medicine, 2011
Relative Risk (DM)

Failure & Death: 1.69
Death (4 studies death): 4.95
Relapse: 3.89

TB and DM Outcomes:
Death During TB Treatment

Baker, BMC Medicine 2011
TB and DM Outcomes: Relapse

- Prospective study in Veracruz, MX of persons with AFB + or MTB culture + between 1995-2010
  - Cultures on AFB+ 1995-2000
  - Cultures on all sputum samples of those presenting with cough > 15 days
  - CXR assessed by blinded radiologists
  - All tested for HIV
  - 1126/1262 had serum glucose (≥ 126 fasting or ≥200 for random sample)

- 374/1262 (29%) had prior diagnosis of diabetes
  - More likely to be older, female, and from higher socioeconomic status.
  - Less likely to be homeless, abuse alcohol or drugs, be HIV +.
  - More cavitary disease

Jimenez-Corona et al; Thorax Vol 68; 2013
Diabetes and TB Treatment Outcomes

Sputum conversion ≥ 60 days
- 45.86 vs. 37.22 days P = 0.014; OR 1.51

• Failure 4.68% vs. 2.24%; OR 2.93

• Death during treatment similar
• Death from other causes was more common in diabetics

- Jimenez-Corona et al; Thorax Vol 68; 2013

Diabetes and TB Treatment Outcomes

• Recurrent disease 11.6% vs. 8.14%; OR 1.76

  – Diabetic patients were more likely to have new isolate of TB (by genotype)
    • Identical strains in 1st and 2nd samples 80.77% vs. 89.47%; OR 1.8

  – Retreated diabetics more likely to have INH and rifampin resistant isolate

   Jimenez-Corona et al; Thorax Vol 68; 2013
Should Treatment of Diabetics with TB be Different?

• No data to make comprehensive recommendations on diabetics
  – But we should treat aggressively and monitor carefully

• Case by case decision:
  – Intensity of dosing, most if not all should have daily dosing
  – Duration of therapy
  – Monitoring during treatment
    • Drug levels if slow to convert

Impact of Diabetes Epidemic on TB Incidence

• “In India, HIV accounts for 3.4% of adult tuberculosis incidence, the proportion we estimate to be attributable to diabetes is 14.8%”

• “The current diabetes epidemic may lead to a resurgence of tuberculosis in endemic regions, especially in urban areas”

» Stevenson et al, BMC Public Health, 2007
Association of DM and TB Impact on TB Outcomes

- Prospective study Southern Mexico 1995-2010
  - Prevalence of DM among 1262 patients 29.63%
- Presentation: More severe clinical manifestation
  - Cavities aOR 1.82
- Outcomes:
  - Delayed sputum conversion aOR 1.52
  - Higher probability of treatment failure aOR 2.93
  - Recurrence: aHR 1.76
  - Relapse: aHR 1.83
    - Genotyping of both isolates showed 19.23% due to a new strain
What Complicates Her TB Treatment?

What should be considered when deciding on future management?

Case Study

• Slow conversion of cultures and smears after > 2 1/2 months of therapy

• Slow radiographic improvement

• HB A1C remains > 9%

• Nausea and some vomiting after TB meds

• Rifampin level (900 mg qd) - trace - (nl 8 – 24)
What Would You Do?

- Add extra drugs
- Request weekly sputum smear
- Request more frequent LFTs
- Follow CXR in one month
- Advocate for good diabetic control.
Low Blood Levels of Rifampin in Diabetics: Indonesia

- 17 Patients with Diabetes and Tuberculosis

- Rifampin levels decreased 50%
  - Perhaps related to higher BMI in diabetics

- Is a different dose of rifampin needed?
  - Mg/kg?
    - Hanneke M. J. Nijland Clinical Infectious Diseases, 43 2006

Pharmacokinetics of TB Drugs in Pulmonary TB in Type 2 DM

- 18 diabetic patients in intensive phase of treatment matched with 18 gender and weight matched non-DM patients

  - Earlier study found peak levels and mean exposure over time to Rifampin was 2 fold lower in patients with DM
    - Higher body weight and higher blood sugar found in these patients
      - Ruslami, Antimicrob Ag and Chemother, Mar 2010
Rifampin Levels in Diabetics and Non Diabetics Matched by Weight

Antimicrob Agents Chemotherapy 2010

Slow Response To TB Treatment

- Retrospective study of slow responders (42/311) ≥ 30 days of treatment

- Slow response ≥ 2 of following:
  - Smear still positive
  - Symptoms present and not improved
  - CXR shows no improvement

- All had serum therapeutic drug level done
  - Low INH 23/39 (39%)
  - Low rifampin 22/42 (52%)
  - Low INH and rifampin 13/39 (33%)

Heysel, EID October 2010
**Slow Response to Treatment**

- Diabetes was only independent predictor of low rifampin level: 5.8 times greater risk, \( p = 0.01 \)

- Only independent significant predictor of slow response was diabetes: \( \text{6.9 OR, } p < 0.001 \)
  
  - 90% of those with low initial rifampin level were therapeutic with increase dose from 600 to 900 mg
    
    - No associated toxicity
    
    - Good treatment outcomes

*Heysel, EID October 2010*

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**Early Therapeutic Drug Monitoring (TDM) for Diabetes**

- TDM started in 2007 at 2 weeks in all diabetics and at 4 – 6 weeks in slow responders

  - Low rifampin concentration in 12/21 (60%) diabetics
  
  - Low INH concentration in 11/17 (65%) diabetics

  - Low rifampin concentrations in 5/14 (40%) slow responders
  
  - Low INH concentrations in 5/8 (63%) slow responders

- 14/16 (88%) converted sputum in < 2 months
  
  - Better than the earlier study where diabetics had slow response

  
  - *Heysel, TB Research and Treatment, 2013*
Hyperglycemia in Patients with TB

- High glucose at TB diagnosis may not be diabetes

- Blood glucose control may worsen while patients are taking Rifampin
  - Rifampin augments intestinal absorption of glucose
  - Does so in both diabetics and non-diabetics

- Infections impair glucose tolerance early in disease in both diabetics and non-diabetics
  - Independent of rifampin, infection can lead to poor glucose control

Treatment Issues – Rifampin Effect on Anti-diabetic Medications

- Rifampin induces CYP450 enzyme system increasing production of enzymes that metabolize many drugs

  - Increased metabolism results in lower blood levels of drug (20 – 40+%)

  - Affects many classes of diabetic medications

  - Insulin is a better alternative
What happened to your patient?

Month 5 of treatment
Case Study

- Month 5 of therapy
  - New positive culture

Approach to Treatment Failure

Gene Xpert assay for Rifampin resistance – Positive

CDC Molecular Detection of Drug Resistance (MDDR)
- Mutation at rpoB locus: Asp516Val
  - Confirms rifampin resistance. Patient is new MDR case!
  - Consistent with rifabutin susceptibility (later confirmed)

- No mutations for ethambutol and PZA noted
**TB and Diabetes - Treatment Issues**

- **Gastroparesis**
  - Vomiting and slow emptying could prevent good drug levels

- **Diabetic neuropathy at baseline complicates therapy due to risk of INH-related neuropathy**
  - Baseline assessment of neuropathy
  - Vitamin B6 to all diabetics on INH or ethionamide

- **Renal insufficiency** is associated with diabetes, especially long standing or poorly controlled DM
  - Adjust dose and dosing interval of EMB & PZA (Cr Cl < 30)

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**TABLE 15. Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt;30 ml/min or for patients receiving hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg three times per week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1,000 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose three times per week*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250–500 mg/dose daily</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
</tbody>
</table>
TB and Diabetes - Treatment Issues

• Diabetics have an increased risk of hepatotoxicity
  – Multiple medications
  – Fatty liver

• Monitoring and education are very important
  – Baseline and monthly liver enzymes
  – Educate regarding risk of liver toxicity, symptoms to watch for, and what to do should these occur
    • Hold TB medications until liver injury excluded

Case Study

- Patient started on treatment with an MDR regimen
  - Amikacin
  - Moxifloxacin
  - Ethambutol
  - PZA
  - Rifabutin

- Month 5
  - Rash developed on abdomen -----NOOOOOOOOOO!!!!
Drug rash - Typical maculopapular rash

Rash is raised, reddish pin or salmon colored
Begins on trunk and spreads to arms and legs

Diabetic Skin Rashes

- Diabetics have more vulnerability to skin infections
  - Yeast infections
  - Bacterial infections such as cellulitis

- Encourage patients to examine the feet to look for fungus (athlete’s foot), small cuts that may get infected and fungus that may be growing around the nails.
  - Stress that because of diabetic neuropathy they may not feel pain
Diabetic Skin Rashes

- **Eczema**
  - Dry itching which has dry flakey patches

- **Diabetic Dermopathy**
  - Most common skin change for diabetic patients (>30%)
  - Depressed darkened spots found on the legs and other parts of the body. This can mix with eczema patches (dermatitis).
  - Steroid creams and moisturizers are important. If necessary, anti-histamines can be taken as well.

- **Reactions to insulin or Medication**
  - Certain brands of insulin may cause an allergy so have this checked out.
  - Patients can get a skin test for an allergy to insulin.

Cellulitis – Bacterial Infection
Impetigo - Infection Due to Streptococcus or Staphylococcus

“Shingles” - Herpes Zoster Infection

Blistering rash in a dermatomal distribution
Cellulitis due to Candida

www.life123.com/question/Atlas-Dermatology

Does Diabetes Increase the Risk of TB?

DOES TB INCREASE THE RISK OF DIABETES?
No evidence to suggest that having tuberculosis or taking medications for tuberculosis increases the risk for diabetes

Increased hyperglycemia with active disease and with rifampin-induced medicine interactions, does not lead to development of diabetes

Impact of Diabetes on TB Incidence: Mexico

- Risk of TB in diabetics was increased 7 times
- Risk was increased in both reactivation and new infection
- Increased risk due to diabetes is comparable to that found in other studies attributable to HIV
- Tuberculosis-attributable risk due to HIV was 2% compared with 25% due to diabetes

Authors concluded that:

Ponce-de-Leon, 2004 "TB and Diabetes in Southern Mexico", Diabetes Care
Prevalence of DM and Pre-diabetes and Associated Risk Factors in India

- Nationwide study in 2011 reported prevalence of diabetes & pre-diabetes 10.4% and 8.3% in general population of Tamil Nadu, South India
- 5 TB units in state studied adults treated by DOT in 2011
  - Evaluated for history of DM, BMI, 2 hour Glucose tolerance test, FBS, postprandial glucose and HBA1C
- 25.3% had diabetes, 24.5% pre-diabetes
  - Diabetics: higher BMI (19.3 vs 18.4), AFB + (55.% vs 42.5%), older (49.3 vs 35.6 years)

Viswanathan et al., PLoS one July 2012

India - Screening for TB in Diabetics

- After national stakeholder agreement in 2011, implemented in 2012
- Screening occurred in 26% of 7218, 52% of 12,237, and 48% of 11,691 in 3 different sectors
  - 254 persons identified with TB
  - TB case rates were 859, 956, and 642 per 100,000
- Demonstrated feasibility of screening

Trop Med International Health May 2013
WHO 2009

• Three Action Areas
  – Establish mechanisms for collaboration
  – Detect and manage TB in patients with diabetes
  – Detect and manage diabetes in patients with TB

FEATURE

MULTIMORBIDITY

Why India should worry about a co-epidemic of diabetes and tuberculosis

More collaboration may be needed between lung and diabetes control programmes, finds Talha Burki.

Talha Burki, journalist, London, UK

Diabetes is fuelling the spread of tuberculosis warns a report published in October 2014 from the International Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation.

The report warns of a “looming co-epidemic,” which could have catastrophic consequences for healthcare systems in affected countries. With the world’s highest burden of tuberculosis—an estimated 65 million cases—India is especially vulnerable.

According to WHO, India’s tuberculosis prevalence dropped from 217/100,000 population in 1990 to around 171/100,000 population in 2013, the most recent year for which records are available. But patients with tuberculosis and diabetes are already thought to outnumber those infected with tuberculosis and HIV. In India, tuberculosis rates are around 150-900/100,000 in people with diabetes.

Moreover, only 40-50% of people with diabetes in India are known to have been identified, and only half of patients with diabetes receiving antidiabetic agents are able to keep their blood glucose levels under control. And normal a patient could remain at heightened risk of diabetes (something similar may happen in gestational diabetes).

Certainly, it makes it trickier to treat existing diabetes.
WHO LTBI Guidelines 2014

• Recommended against treatment of LTBI in: **diabetics**, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in prior risk group recommended for treatment.
  — *(Conditional recommendation, very low quality of evidence)*

What Can We Offer in TB Clinics?

• Include glucose or HB A1C on blood work.
• Educate on need to follow a healthy eating plan.
• Encourage physical activity for 30 to 60 minutes/day.
• Stress the importance of taking medicines as directed.
• Encourage patients to quit smoking.
• Refer for regular physician visits
• Educate on need for daily foot check for cuts, blisters, sores, swelling, redness, or sore toenails.
41 yr. old legal assistant with 8 months of dry cough, weight loss and decreased energy. DM x 10 yrs. HbA1C 12.9%

End of treatment CXR 4/4/2016