TUBERCULOSIS AND DIABETES
The 21st Century Pandemic

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Catastrophic collision of two ancient diseases

Egyptian papyrus describing a ‘rare disease causing rapid loss of weight and frequent urination’
c 1550 BC

The first report of diabetes dates to 1550 BC
TB MAY BE MORE ANCIENT STILL

Egyptian mummy 1550-1080 BC

- Extensive pleural adhesions,
- Left lung collapsed.
- Severe anterior destruction of lumbar vertebral bodies

113 bp sequence of *mycobacterium, tuberculosis* detected

TB DNA detected in a 900 year old pre-Columbian mummy.

97 bp sequence of IS6110 specific for *mycobacterium tuberculosis* detected

V. Morell. Science:1994;263:1686

So TB was in the Americas before Europeans arrived

Did it cross the Bering straits thousands of years ago???
3. There were four common causes of death. These were:
(a) Coma with or without a terminal infection; (b) sepsis; (c) cardiovascular renal disease, including gangrene; (d) pulmonary tuberculosis.

Coma and pulmonary tuberculosis tended to occur more frequently in the younger patients; cardiovascular renal disease,
DIABETES IS A CHRONIC METABOLIC DISEASE

- Named in the 2\textsuperscript{nd} Century AD by Araetus of Cappadocia after the Greek word for syphon.

- Diabetes is better understood as a continuum of impaired glucose metabolism rather than a discrete disease.

- This impairment ranges from pre-diabetes to diabetes.

- The severity of diabetes is usually measured by the level of fasting blood glucose and of glycated hemoglobin (HbA1c)

- The more severe the diabetes the more common the many complications—one of which is tuberculosis.
American Diabetes Association: 2010  
Criteria for diagnosis of diabetes

1. Glycated hemoglobin (HbA1c) ≥ 6.5%  
   OR
2. Fasting blood glucose ≥ 126 mg/dl  
   OR
3. Oral Glucose Tolerance Test (OGTT) 2 hour post glucose load of ≥ 200 mg/dl  
   OR
4. In a patient with classical symptoms, random blood glucose of ≥ 200 mg/dl

**HbA1c = glycated hemoglobin or AIC**

Percent of hemoglobin molecules in red blood cells with glucose molecules attached. Since the life of red blood cells is about 120 days, this is a measure of glucose control over the preceding three months.
THERE ARE THREE MAJOR TYPES OF DIABETES

- Type 1 diabetes (also known as juvenile onset involving pancreatic β-cell destruction usually leading to absolute insulin deficiency). Usually immune mediated.

- Type 2 diabetes (also known as adult onset). Often associated with obesity.

- Other types of diabetes: a very long list!

TODAY MORE THAN 95% OF DIABETES IS TYPE 2. DIABETES IS PART OF THE CURRENT MASSIVE PANDEMIC OF NON-COMMUNICABLE DISEASES (NCDS).
A continuum of metabolic impairment

Several studies have shown that prediabetes (impaired glucose tolerance) also significantly increases risk of tuberculosis.

<table>
<thead>
<tr>
<th>Types</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal glucose regulation</td>
<td>Impaired Glucose Tolerance or Impaired Fasting Glucose (Pre-Diabetes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Specific Types**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Diabetes **</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PRACTICAL TIP

- In a TB clinic it is reasonable to screen by using the random blood glucose (RBG).
- If the RBG is $\geq 200$ mg/dl you can assume diabetes, or at least impaired glucose metabolism.
- This tells you the patient may have problems with TB medication and is at increased risk of poor outcome.
- Confirmation of diabetes can be done later and the patient referred for diabetes management.

PROBLEM

Diabetes and TB health care systems do not talk to each other.
TOTAL DEATHS BY BROAD CAUSE BY WHO REGION/WORLD BANK INCOME 2008.

80% of diabetes is in the LMICs where there is most TB.

World Bank Income levels
L=Low
L/M=low middle
U/M=upper middle
H=high

<table>
<thead>
<tr>
<th>Region</th>
<th>Non-Communiqueable Diseases</th>
<th>Communicable, Maternal, Perinatal and Nutritional Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Americas</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>EM</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>ER</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>SEA</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>WP</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Injuries

AF=Africa, AM=Americas, EM=Eastern Mediterranean, ER=European Region, SEA=South East Asia, WP=Western Pacific
Data from the seven high burden tuberculosis countries with the highest numbers of people with diabetes showing rates of tuberculosis and prevalence and numbers with diabetes in 2013. (Data from WHO and IDF)

<table>
<thead>
<tr>
<th>Country</th>
<th>Tuberculosis</th>
<th>Diabetes Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reported cases</td>
<td>Reported Prevalence</td>
</tr>
<tr>
<td></td>
<td>Rate/100,000</td>
<td>%</td>
</tr>
<tr>
<td>China</td>
<td>99</td>
<td>9.6</td>
</tr>
<tr>
<td>India</td>
<td>230</td>
<td>8.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>59</td>
<td>9.0</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>121</td>
<td>10.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>185</td>
<td>5.6</td>
</tr>
<tr>
<td>Pakistan</td>
<td>376</td>
<td>6.8</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>434</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Total estimate with diabetes in just 7 high burden countries: 206.7 million

In India diabetes estimated to have increased TB cases 46%. 
FATAL OVERLAP

New TB cases

Deaths/100,000 from Diabetes and CVD
From the US perspective, immigrants may come from places where diabetes is common and is a major driver of TB and also of MDR-TB. Tourists also visit these places in increasing numbers, and like to shop in the bazaar!
THE LOOMING CO-EPIDEMIC OF TB–DIABETES: A CALL TO ACTION

Report issued on November 20th 2014 at the Barcelona 45th Union World Conference on Lung Health by the World Diabetes Federation


Knut Lönnroth, WHO

Diabetes is rampant in low- and middle-income countries, affecting the poor and rich alike, and increasing the risk of TB across all population segments.

If we fail to act, the consequences could prove catastrophic for healthcare systems in areas that are impacted.
<table>
<thead>
<tr>
<th>Region</th>
<th>TB Patients w/Diabetes</th>
<th>Year Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnataka State, India</td>
<td>32%</td>
<td>2011</td>
</tr>
<tr>
<td>Kerala State, India</td>
<td>44%</td>
<td>2012</td>
</tr>
<tr>
<td>Tamil Nadu State, India</td>
<td>25%</td>
<td>2012</td>
</tr>
<tr>
<td>Texas, USA</td>
<td>39%</td>
<td>2011</td>
</tr>
<tr>
<td>Mexico</td>
<td>36%</td>
<td>2011</td>
</tr>
<tr>
<td>Tanzania</td>
<td>17%</td>
<td>2011</td>
</tr>
<tr>
<td>Pakistan</td>
<td>16%</td>
<td>2012</td>
</tr>
<tr>
<td>South Pacific</td>
<td>40-45%</td>
<td>2013</td>
</tr>
</tbody>
</table>
TODAY DIABETES THREATENS TUBERCULOSIS CONTROL GLOBALLY

- Diabetes increases risk of tuberculosis three fold
- Diabetes increases and can spread MDR-TB
- Diabetes is a greater threat at the population level than AIDS

- 382 million people globally have diabetes
  - 25.5 million in the US

- An estimated 34 million globally have AIDS.
  - 1.5 million in the US
# Ratio of diabetes to AIDS

<table>
<thead>
<tr>
<th></th>
<th>Globally</th>
<th>In US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>14:1</td>
<td>22:1</td>
</tr>
<tr>
<td><strong>AIDS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## THE ISSUE IS NUMBERS AND EXPOSURE

- The threat of diabetes to tuberculosis control is much higher than that of AIDS.
- This is because of the sheer number of people with diabetes far outstrips those with AIDS.

The Population Attributable Fractions (PAF)* globally are:

<table>
<thead>
<tr>
<th>Disease</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>14.4%</td>
</tr>
<tr>
<td>AIDS</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

* PAF = percent of cases directly attributable to this underlying disease
We were among the first, but not the first

MPH student

Nuevo Santander Tuberculosis Trackers
Third annual meeting
November 2004
Reynosa, Mexico
WE WERE SLOW TO SEE THE WARNING SIGNS


### Characteristics of TB patients in the Texas-Mexico border

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients</td>
<td>3,506</td>
<td>1,543</td>
</tr>
<tr>
<td>Average number patients/year</td>
<td>584</td>
<td>220</td>
</tr>
<tr>
<td>Total male</td>
<td>2,439 (69.6%)</td>
<td>1,055 (68.4%)</td>
</tr>
<tr>
<td>Median age (IQR) (years)</td>
<td>39(26)</td>
<td>47(29)</td>
</tr>
<tr>
<td>Alcohol use¹</td>
<td>63 (1.9%)</td>
<td>292 (20.3%)</td>
</tr>
<tr>
<td>Use of illegal drugs¹</td>
<td>84 (2.5%)</td>
<td>152 (10.6%)</td>
</tr>
<tr>
<td>HIV-positive¹</td>
<td>69 (2%)</td>
<td>85 (5.9%)</td>
</tr>
<tr>
<td>Diabetes mellitus¹</td>
<td>607 (17.8%)</td>
<td>401 (27.8%)</td>
</tr>
</tbody>
</table>

TEXAS- Public Health Region 11
Tuberculosis patients 1998-2002

Risk profile without diabetes:
• Infants
• Young adults with:
  homelessness
  incarceration
  Drug and alcohol use
  HIV-positive
• Elderly homeless

Risk profile in diabetes:
• 40 years or older
• Type 2 diabetes
• No other social or demographic risk factor

Diabetes
No Diabetes

Smear results during the course of treatment
Mexico

% positive smear

Month of Treatment

Diabetes
No Diabetes

# Association between MDR-TB and Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th></th>
<th>No diabetes</th>
<th></th>
<th>p value</th>
<th>adjOR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TEXAS</strong></td>
<td>n=401</td>
<td></td>
<td>n=1041</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>18</td>
<td>4.5</td>
<td>31</td>
<td>3</td>
<td>0.02</td>
<td>1.1 (1.2-4.4)</td>
</tr>
<tr>
<td><strong>MEXICO</strong></td>
<td>n=343</td>
<td></td>
<td>n=1384</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>59</td>
<td>17.2</td>
<td>173</td>
<td>12.5</td>
<td>0.04</td>
<td>1.5 (1.0-2.1)</td>
</tr>
</tbody>
</table>

Odds Ratio adjusted for age and gender

**Conclusion:** MDR-TB is more frequent in TB-DM

## Treatment compliance

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Alcohol use</th>
<th>Drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Texas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed therapy</td>
<td>317 (81.3)</td>
<td>1.5 (1.1-2.0)</td>
<td>210 (73.4)</td>
</tr>
<tr>
<td>Refused or incomplete therapy</td>
<td>1 (0.3)</td>
<td>0.3 (0.1, 0.6)</td>
<td>25 (8.7)</td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed therapy</td>
<td>445 (73.3)</td>
<td>1.2 (1.0-1.4)</td>
<td>37 (58.7)</td>
</tr>
<tr>
<td>Refused or incomplete therapy</td>
<td>55 (9)</td>
<td>0.8 (0.7, 1)</td>
<td>16 (25.4)</td>
</tr>
</tbody>
</table>

**Diabetes patients are more likely to adhere to treatment even after adjusting for age and gender**

The Chronic Inflammatory Syndrome in Diabetes is at the root of the susceptibility to infections, particularly TB.

Scientific Evidence shows:

- **CYTOKINES:** Cytokines (e.g. TNF alpha and Interferon gamma) that are critical for combating TB are *UPREGULATED* but **ineffective in killing Mtb**.

- **GENE EXPRESSION:** Patients with diabetes have *REDUCED EXPRESSION* of genes critical in controlling TB and are **ineffective in killing Mtb**.

- **NEUTROPHILS:** Patients with diabetes have neutrophils which *OVERREACT TO ANTIGENS* but are again **ineffective in killing Mtb**.

- **ANTIBODY RESPONSES:** These are *ALTERED IN DIABETES* and again **less effective in producing protection** after vaccination.
Viewpoint

Defining the research agenda to reduce the joint burden of disease from Diabetes mellitus and Tuberculosis

Anthony D. Harries¹,², Megan B. Murray³,⁴, Christie Y. Jeon³, Salah-Eddine Ottmani⁵, Knut Lonnroth⁵, Mauricio L. Barreto⁶, Nils Billo¹, Richard Brostrom⁷, Ib Christian Bygbjerg⁸, Susan Fisher-Hoch⁹, Toru Mori¹⁰, Kaushik Ramaiya¹¹,¹², Gojka Roglic¹³, Hanne Strandgaard¹⁴, Nigel Unwin¹⁵, Vijay Viswanathan¹⁶, David Whiting¹⁷ and Anil Kapur¹⁴

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⁶ Instituto de Saúde Coletiva, Universidade Federal da Bahia, Bahia, Brazil
⁷ Tuberculosis Control Programme, CNMI Division of Public Health, Saipan
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¹² Department of Medicine, Muhimbili University of Health and Allied Sciences, Dar Es Salaam, Tanzania
¹³ Department of Chronic Diseases and Health Promotion, World Health Organization, Geneva, Switzerland
¹⁴ World Diabetes Foundation, Lyngby, Denmark
¹⁵ Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK
¹⁶ M.V. Hospital for Diabetes and Research Centre, Royapuram, Chennai, India
¹⁷ International Diabetes Federation, Brussels, Belgium
CONCLUSION:

**Diabetes Threatens Tuberculosis Control Globally**

- Diabetes increases risk of tuberculosis three fold
- 382 million people globally have diabetes, more than tenfold more than those with AIDS.
- Diabetes threatens to spread MDR-TB
- The populations most at risk are Low and Middle Income
- Diabetes patients with TB are documented to have:
  - Increased drug resistance
  - Delayed clearance of Mtb from sputum
  - Intolerance of TB medication and drug interactions
  - Increased morbidity
  - Increased relapse rates
  - Increased deaths
Needs and questions?

- Screen TB patients for diabetes. Should now be routine.
- Screen DM patients for TB. Where, how and when??
- Better, cheaper and safer diagnostic techniques needed for both diseases
- Encourage TB and DM programs to work together
- Model DM diagnosis and care on TB control programs
- Develop specific treatment regimens for DM-TB
- Develop registries for diabetes
- Educate patients, health care professionals and communities
- Resources for implementation and research sorely needed
- Political will
CDC officials say diabetes cases in the U.S. reached 29 million in 2012, while another 86 million people were at an increased risk of diabetes. Researchers also found that diabetes and related complications were associated with a total of $245 billion in health costs and lost work and wages in 2012. (Reuters)