Diabetes and Tuberculosis

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Disclosure

I have no conflict of interest to declare
Learning Objectives

• Learn about the risk of TB associated with diabetes
• Understand the implications of diabetes on management of patients with TB
• Be aware of current screening recommendations for diabetes in TB/ TB in diabetes
Presentation overview

1. Introduction

2. TB risk associated with diabetes
   - The role of glycaemic control
   - Screening recommendations for TB in patients with diabetes
   - Performance of screening tests in patients with diabetes

3. Impact of diabetes on treatment of patients with TB
   - Clinical management
   - Screening recommendations for diabetes in patients with TB
Introduction
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015

Introduction: Bidirectional association between TB and DM

- Diabetes as risk factor for TB
- Effect of DM on:
  - clinical characteristics of TB
  - radiological characteristics of TB
  - TB treatment response
- TB as risk factor for DM
- Effect of TB on DM

Screening for LTBI/TB in patients with diabetes

Screening for diabetes in patients with TB
TB risk associated with diabetes
Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

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Abstract

Background

Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. We conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies.

Methods and Findings

We searched the PubMed and EMBASE databases to identify observational studies that had reported an age-adjusted quantitative estimate of the association between DM and active TB disease. The search yielded 13 observational studies (n = 1,786,212 participants) with 17,698 TB cases. Random effects meta-analysis of cohort studies showed that DM was associated with an increased risk of TB (relative risk = 3.11, 95% CI 2.27–4.26). Case-control studies were heterogeneous and odds ratios ranged from 1.16 to 7.83. Subgroup analyses showed that effect estimates were higher in non-North American studies.

- Only 3 cohort studies (2 in renal transplant recipients)
- Case-control studies mostly not corrected for confounders
Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study

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ABSTRACT
Objective: Previous studies that have found an increased risk for tuberculosis (TB) in people with diabetes mellitus (DM) have been conducted in segments of the population and have not adjusted for important potential confounders. We sought to determine the RR for TB in the presence of DM in a national population with data on confounding factors in order to inform the decision-making process about latent tuberculosis infection (LTBI) screening in people with diabetes.

Design: Whole population historical cohort study.
Setting: All Australian States and Territories with a mean TB incidence of 5.8/100 000.
Participants: Cases of TB in people with DM were identified by record linkage using the National Diabetes Services Scheme Database and TB notification databases for the years 2001–2006.

ARTICLE SUMMARY

Article focus
National, general population-based, historical cohort study to estimate the risk of tuberculosis (TB) among people with diabetes mellitus (DM).

Adjustment for important potentially confounding risk factors including age, sex, indigenous status and TB incidence in country of birth.

Key messages
Overall, people with DM have a 1.5-fold increased risk of developing TB.
The risk for TB is higher among people who are using insulin for DM.
DM accounts for a small proportion of cases of TB in a low TB incidence setting.

Strengths and limitations of this study
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crude RR univariate analysis (95% CI)</th>
<th>p Value</th>
<th>Adjusted RR* multivariate analysis (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TB</td>
<td>1.78 (1.17 to 2.73)</td>
<td>0.008</td>
<td><strong>1.48 (1.04 to 2.10)</strong></td>
<td>0.03</td>
</tr>
<tr>
<td>Culture-positive TB</td>
<td>1.83 (1.19 to 2.81)</td>
<td>0.006</td>
<td><strong>1.49 (1.05 to 2.11)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>All TB in insulin users</td>
<td>2.16 (1.19 to 3.93)</td>
<td>0.01</td>
<td><strong>2.27 (1.41 to 3.66)</strong></td>
<td>0.0008</td>
</tr>
<tr>
<td>Culture-positive TB in insulin users</td>
<td>2.44 (1.37 to 4.34)</td>
<td>0.002</td>
<td><strong>2.55 (1.62 to 4.01)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, indigenous status and TB incidence in country of birth. TB, tuberculosis.
Relative risks of TB compared to the general population:

• Patients with diabetes:  
  RR 1.48 (95% CI 1.04-2.10)  
  RR 3.11 (95% CI 2.27-4.26) 
  *Dobler et al., BMJ Open 2011, Jeon et al., PLOS Medicine 2008*

• TB contacts: RR 46.6 (IQR 3.2-68)  *Fox GJ et al, Eur Respir J, 2013*

• patients with HIV infection: RR 70 (range 41-77)  
  *Corbett EL, Arch Intern Med, 2003*

• patients on TNF-alpha inhibitors: RR 1.8-29.3  
  *Dobler CC, Microbiol Spectrum, 2016*

• patients with renal failure: RR 7.8 (95% CI 3.3-18.7)  
  *Dobler CC et al., PLoS One 2011*
Age-Adjusted Prevalence of Diagnosed Diabetes Among US Adults

2015

<table>
<thead>
<tr>
<th>Prevalence Range</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.5%</td>
<td>White</td>
</tr>
<tr>
<td>4.5%–5.9%</td>
<td>Light Orange</td>
</tr>
<tr>
<td>6.0%–7.4%</td>
<td>Orange</td>
</tr>
<tr>
<td>7.5%–8.9%</td>
<td>Dark Orange</td>
</tr>
<tr>
<td>≥9.0%</td>
<td>Red</td>
</tr>
</tbody>
</table>

CDC’s Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data
Should we screen patients with DM for LTBI/TB?

- Population attributable fraction in Iowa
- Proportion of TB cases in Iowa that can be attributed to diabetes
  \[
  \frac{(Pe \times (RR-1))}{(Pe \times (RR-1)+1)}
  \]
  \(Pe = \) population exposed = prevalence of DM in population
- Prevalence of diabetes in Iowa: 7.7% (CDC data 2015)
  - If RR of TB is 1.5: \(\frac{0.077 \times 0.5}{0.077 \times 0.5+1}=3.7\%\)
  - If RR of TB is 3.0: \(\frac{0.077 \times 2}{0.077 \times 2+1}=13.3\%\)
Should we screen patients with DM for LTBI/TB?

- Relative risk of TB in DM and absolute risk of TB in the population
- Performance of LTBI diagnostics tests (TST, IGRAs) in patients with DM (risk of false positive/false negative test results)
- Effectiveness of interventions (treatment for latent TB) to reduce risk of TB
Screening recommendations for TB in DM

- No systematic screening recommended by the CDC or WHO
- Decision needs to be made on an individual case basis, e.g. patients with diabetes and born in high incidence country for TB
Impact of diabetes on treatment of patients with TB (and vice versa)
Effect of diabetes on:

- **clinical** characteristics of TB
  - Extra-pulmonary TB less common among patients with diabetes compared to patients without diabetes
  - Rate of positive smears:
    - studies show conflicting results

- **radiological** characteristics of TB
  - Higher incidence of involvement
  - of the lower lung lobes in DM?
  - Cavitary lesions more common
Effect of diabetes on:

- TB treatment responses
  - increased time to sputum conversion rate of positive smears: conflicting study results
  - worse outcomes? probably
    - higher rates of drug resistance, impaired cellular immunity, delay in sputum conversion, and lower plasma levels of anti TB drugs
    - higher risk of treatment failure, death and relapse (Baker MA, BMC Med 201)
Implications for clinical practice

- TB treatment in patients with diabetes does not differ from TB treatment in other patients
- Extension of treatment (similar to HIV) has been considered, but not formal studies
- Beware toxic effects possibly more common because of add-on effect from diabetes complications:
  - peripheral neuropathy (isoniazid)
  - optic neuritis (ethambutol)
Effect of TB on diabetes

- **Glucose intolerance** among 16.5% to 49% of patients with active TB
- **control of hyperglycaemia is more difficult** during the active phase of TB

- **cause of hyperglycaemia associated with TB:**
  - Inflammation leading to increase in insulin resistance and decreased insulin production
  - isoniazid and rifampicin have hyperglycaemic effects
Should we screen TB patients for DM?

- The number of TB patients needed to screen for detection of one extra case of DM ranged from 4 to 54 in several studies\(^1\)
- Screening of DM among TB cases more cost-effective than screening of TB among DM cases.

1) Jeon CY et al, Trop Med Int Health, 2010
Screening TB patients for DM

• Preferred method of screening:
  – 2 hour postprandial glucose (2hPG), more sensitive than fasting blood glucose (FBG) and random blood glucose (RBG)
  – HbA1C: expensive, role as stand alone test controversial

• Pragmatic approach of RBG screening in TB clinic is acceptable

• If RGB > 200 mg/dl, diabetes (or at least impaired glucose tolerance) is likely
Screening TB patients for DM

- Best time for screening:
  - At time of TB diagnosis: risk of over-diagnosing DM (transient hyperglycaemia), but early intervention possible
  - Consider test at start of TB treatment and after 3 months
  - As hyperglycaemia may regress after treatment of TB, verification of glucose intolerance after cure of TB is necessary.
Take home messages

• Patients with diabetes have an increased risk for TB and patients with TB have an increased risk for diabetes

• The relative risk of TB in patients with diabetes is approximately 1.5-3. Poor blood glucose control seems to increase the risk.

• The relative risk of TB in diabetes is insufficient to warrant systematic screening in all patients with diabetes. Decisions are case-by-case.
Take home messages

- Diabetes can *complicate the management of active TB*
- TB can *complicate the management of diabetes*
- Screening TB patients for diabetes with an easy random blood glucose (taken at the time of any other blood test) should be considered.
Test your knowledge

• Patients with diabetes have a higher relative risk of developing TB than patients with chronic renal failure true/false

• Every patient with diabetes must be screened for TB true/false

• Many patients with TB have glucose intolerance (pre-diabetes) or diabetes true/false

• Patients with TB can be screened for diabetes with a random glucose test, although the test has to be interpreted with caution true/false
Thanks!

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