Diabetes and Tuberculosis:
A Practical Approach to Diagnosis and Treatment

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Background
Epidemiology of Tuberculosis and Diabetes

Estimated Tuberculosis Incidence
WHO

Reported TB Cases
United States 1982-2014

Trends in TB Cases in Foreign-born Persons,
United States, 1993 – 2013*

*Updated as of June 11, 2014.
Age-Adjusted Percentage of Adults Diagnosed with Diabetes - 2014

Infections in Diabetics
Why the increased risk of infections?

Susceptibility to Infections in Diabetics:
- Peripheral Neuropathy
- Autonomic Neuropathy
- Hyperglycemia
- Poor tissue perfusion due to peripheral vascular disease

Immunity to *Mycobacterium tuberculosis* in Diabetes

Obesity and Lipotoxicity

Clinical Implications

Does Diabetes Effect the Risk of Infection and Persistence?

Relative Risk of LTBI in Patients with Diabetic versus Non-Diabetic Patients

- Has not been studied systematically in the last fifty years
- Bourcot in 1952 chest x-ray survey found abnormal films suggestive of TB in 8.4% diabetic contacts versus 4.3% of non-diabetics

Bourcot et al. Ann Rev Tuberc 1952

Does diabetes effect the performance of TST and the IGRA in diagnosing LTBI?

IGRAs and Diabetes

- The sensitivity of the interferon-gamma release assays (IGRAs) in the detection of Mycobacterium tuberculosis infection or disease may be affected by immune dysregulation in diabetes.
- As millions of type 2 diabetes patients are at risk for tuberculosis (TB) worldwide, it is important to determine if the sensitivity of IGRAs is compromised in this population.
- A prospective cohort study was designed to evaluate the sensitivity of the IGRAs QuantiFERON®-TB Gold (QFT-G) and T-SPOT®.TB among specimens from newly diagnosed adults with microbiologically confirmed TB with and without diabetes.
- Investigators also evaluated the association between QFT-G results and diabetes-associated conditions (dyslipidemia, obesity).


IGRAs and Diabetes

- QFT-G sensitivity was 70% among TB patients.
- Patients with diabetes, chronic hyperglycemia or overweight/obesity were more than twice as likely to have positive test results in multivariate models (P < 0.05).
- Low high-density lipoprotein cholesterol or high triglycerides were not associated with assay results.
- In a separate group of TB patients (n = 43), T-SPOT.TB was 93% sensitive, with similar performance in patients with and without diabetes.

CONCLUSION:
- IGRA sensitivity is not compromised by diabetes in TB patients. Accordingly, IGRA may also be suitable for diagnosing TB infection in diabetes patients, which is required to assess TB risk.


What is the impact of diabetes on the risk of progression to active TB?
Risk of Developing Disease
Normal Immune System

- Untreated, 5% of infected persons with normal immunity develop TB in first 1–2 years post infection, another 5% later in life
- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

Association Between Diabetes and Tuberculosis

- Investigators sought to determine the characteristics, prevalence and temporal trends of diabetes in US and foreign-born persons attending the San Francisco Tuberculosis Clinic.
- Investigators analyzed data from patients with the diagnosis of tuberculosis, latent infection, or not infected with Mycobacterium tuberculosis.
- They assessed the temporal trend and the characteristics of individuals with and without diabetes.
- Between 2005 and 2012, there were 4371 (19.0%) individuals without evidence of tuberculosis infection, 17,856 (77.6%) with latent tuberculosis, and 791 (3.4%) with tuberculosis. 66% were born in the United States, China, Mexico, and the Philippines.

Association Between Diabetes and Tuberculosis

- The prevalence of diabetes was the highest among individuals with tuberculosis and increased during the study period.
- Patients with tuberculosis and diabetes were more likely to be male, older than 45 years and born in the Philippines.
- There was a disproportionate association of TB and DM relative to LTBI and DM among Filipinos in individuals older than 45 years old.
- CONCLUSIONS:
  - The data suggest that Filipinos older than 45 years old are more likely to have tuberculosis probably due to a higher prevalence of diabetes.
  - In San Francisco, tuberculosis-screening programs in individuals with diabetes and latent tuberculosis may be beneficial in patients older than 45 years old especially from the Philippines.

How strong is the effect of diabetes on the risk of developing tuberculosis?

- In a study from Taiwan, researchers prospectively investigated the risk of tuberculosis among persons with diabetes stratified by severity.
- The prospective cohort study involved 17,715 Taiwanese persons on whom baseline data were collected during Taiwan’s 2001 National Health Interview Survey.
- Participants’ subsequent care was captured from the National Health Insurance database.

How strong is the effect of diabetes on the risk of developing tuberculosis?

- Diabetes was significantly associated with tuberculosis (adjusted hazard ratio, 2.09 [95% confidence interval (CI), 1.10–3.95] and 2.60 [95% CI, 1.34–5.03], respectively).
- Compared with persons without treated diabetes, participants’ risk of tuberculosis increased as the number of complications of diabetes mellitus increased (P = .0016), with >3-fold risk among those with ≥2 diabetes-related complications (odds ratio, 3.45; 95% CI, 1.59–7.50).
- Similarly, the risk increased among those with higher Diabetes Complications Severity Index scores (P = .0002).

- Conclusions. The risk of developing tuberculosis increased among those with increasing diabetes severity.

Clinical Characteristics of TB Associated with Diabetes

- Investigators from Spain sought to analyze the prevalence of DM and its associated factors among adults with TB in a large city in an industrialized country.
- A population-based study in adults diagnosed with TB between 2000 and 2013 in Barcelona.
- They studied potentially associated sociodemographic and clinical/epidemiological factors.
- Logistic regression was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs).
- Of 5849 TB patients, 349 (5.9%) had DM.
- The annual prevalence of DM ranged from 4.0% to 7.2%.

Factors associated with DM were:
- being Spanish-born (OR 1.46, 95%CI 1.11-1.96),
- age ≥40 years (OR 6.08, 95%CI 4.36-8.66),
- cavitary patterns on chest X-ray (OR 1.42, 95%CI 1.08-1.86),
- experiencing more side effects due to anti-tuberculosis treatment (OR 1.86, 95%CI 1.28-2.64)
- and hospitalization at the time of diagnosis (OR 1.8, 95%CI 1.40-2.31).
- Human immunodeficiency virus infection was associated with a lower probability of DM in both subjects with a history of injection drug use (OR 0.27, 95%CI 0.10-0.57) and those without (OR 0.04, 95%CI 0.002-0.19).

CONCLUSIONS: DM prevalence among adults with TB in Barcelona is low and remained stable over the 14-year study period. However, TB patients with DM were potentially more infectious and their clinical management was more complicated.


Do chest radiographs appear differently in diabetic TB patients?

- To assess radiological images of pulmonary tuberculosis in a large population of diabetic patients.
- Radiographs from in-patients admitted with pulmonary tuberculosis and diabetes (TBDM group, n = 192) were reviewed and compared with a control group of patients with pulmonary tuberculosis alone (TB group, n = 130).
- Both TB patients with DM and those without DM had a similar evolution time of tuberculosis (approximately 2 years).
- Statistical differences were observed as follows: TBDM patients were older (51.3+/-0.9 vs. TB group 44.9+/-1.8 years, mean +/- SEM), and had a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs. 7%) and upper + lower (64% vs. 36%) lung field lesions.
- More TBDM patients developed:
  - cavitations (82% vs. 59%)
  - more often in the lower lung fields (29% vs. 3%)
  - more multiple cavities were seen in TBDM patients (25% vs. 2%).
  - had a lower total leukocyte count (9836.7 +/- 219.5 vs. 10013.1 +/- 345.2 cells/mm3), mainly due to a lower number of non-lymphocyte cells (8836.7 +/- 221.8 vs. 8095.7 +/- 321.9 cells/mm3).
- Multiple logistic regression showed that being a diabetic patient was the most important factor determining lower lung field lesions and cavities.
- CONCLUSIONS: This study in a large number of diabetics with pulmonary tuberculosis confirmed that their chest X-ray images significantly depart from the typical presentation. Clinicians must keep this in mind to avoid misdiagnosis.


Clinical and Radiographic Features of TB Associated with Diabetes

- Investigators sought to study the clinical and radiological features of lower lung field tuberculosis (LLFTB) in relation to the patients of nonlower lung field tuberculosis (non-LLFTB) in India.
- All the patients of lower lung field tuberculosis defined by the lesions below an arbitrary line across the hila in their chest X-rays were included in the study.
- Their sputum for acid fast bacilli, HIV, blood sugar, and other relevant investigations were performed.
- 2136 cases of pulmonary tuberculosis were studied.
- Among them 215 (10%) cases of patients were diagnosed as the case of lower lung field tuberculosis.
- Females (62%) were more commonly affected.
- The relative risk of having the LLFTB in diabetes patients, HIV seropositive patients, end stage renal disease patients, and patients on corticosteroid therapy was high.
- In diabetes the relative risk (RR) was 4.95 similar to that found in HIV (5.17)
Does diabetes treatment effect treatment outcomes?

Clinical Outcomes in TB Associated with Diabetes

- The prevalence of DM among 1262 patients with pulmonary TB was 29.63% (n=374).
- Patients with DM and pulmonary TB had:
  - more severe clinical manifestations (cavities of any size on the chest x-ray, adjusted OR (aOR) 1.80, 95% CI 1.35 to 2.41),
  - delayed sputum conversion (aOR 1.91, 95% CI 1.09 to 2.10),
  - a higher probability of treatment failure (aOR 2.93, 95% CI 1.18 to 7.23),
  - recurrence (adjusted HR (aHR) 1.76, 95% CI 1.11 to 2.79) and relapse (aHR 1.83, 95% CI 1.04 to 3.23),
- Most of the second episodes among patients with DM were caused by bacteria with the same genotype but, in 5/26 instances (19.23%), reinfection with a different strain occurred.

Jimenez-Corona et al. Thorax 2012
Mortality due to Infections in Diabetics

Risk of TB relapse for TB patients with diabetes compared with TB patients without diabetes

Question
- Which x-ray is more likely to be from a patient that has diabetes?

X-ray 1 Mediastinal adenopathy
X-ray 2 Upper lobe infiltrates

Is extra-pulmonary disease more likely as it is in other immunosuppressed patients?
Tuberculosis of the Spine

Is diabetes related tuberculosis more infectious than non-diabetes related tuberculosis?

Probability TB Will Be Transmitted

- Susceptibility of the exposed person
- Infectiousness of person with TB (i.e., number of bacilli TB patient expels into the air)
- Environmental factors that affect the concentration of M. tb organisms
- Proximity, frequency, and duration of exposure (e.g., close contacts)
- Can be transmitted from children, though less likely
There are no incurable diseases — only the lack of will.

Avicenna