Concurrent Tuberculosis and Diabetes Mellitus
Unraveling the causal link, and improving care

TANDEM

The challenge of tuberculosis and diabetes mellitus comorbidity

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• We hope that we may be able control TB- but things do not look good for diabetes which is increasing worldwide
• The number of people with diabetes rose from 153 million in 1980 to 347 million in 2008 and is expected to rise to 592 million by 2035
• 80% of those with diabetes currently live in low or middle income countries, where there is a lot of tuberculosis
• Does co-morbidity with TB and diabetes matter?
Diabetes can increase the risk of tuberculosis 3-fold, and many TB patients have diabetes.

The Indian State of Kerala has reported that 44% of its TB patients have diabetes – another study by Nandakumar et al. (PlosOne 2013) found 24% of the TB patients had type 2 DM.
Morbidity for hypertension, HIV, Type 2 diabetes and TB in Khayelitsha, Cape Town

(based on prescriptions given to 32,474 patients over 9 months)

Oni et al, BMC Infect Dis, 2015
Projected diabetes changes from 2010-2030
data from WHO and International Diabetes Association (Lancet Infect Dis 2009, 9:737)
The impact of diabetes on tuberculosis infection

- Immunocompetent
  - Exposure to Mtb
  - 90%
  - 10% annual risk

- Immunocompromised
  - Host Susceptibility
  - 10-20% lifetime risk
  - Reactivation
  - Active infection
  - 90%
  - 10%

Clinical Features

- Non-diabetic
  - Lower lung: 15%
  - Cavitary lesions: 31%
  - Extrapulmonary: 16%
  - Relapse: 5%
  - Death: 8%

- Diabetic
  - Lower lung: 27%
  - Cavitary lesions: 46%
  - Extrapulmonary: 29%
  - Relapse: 20%
  - Death: 18%

Hodgson et al, Immunology 2014, 144:171
WHO and the International Union against Tuberculosis and Lung Diseases Collaborative Framework

Collaborative Framework for Care and Control of Tuberculosis and Diabetes

Key research questions | Priority | Study design and methodology
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Screening for Disease: 
- Screening patients with DM for active TB 
- Screening patients with TB for DM | High | Prospective observational cohort studies of DM patients routinely attending diabetic clinics and screened for TB, and TB patients starting anti-TB treatment and screened for diabetes
TB treatment outcomes in patients with DM, including mortality and more detailed assessment of death during anti-TB treatment | High | Prospective observational cohort studies using standardized TB regimens and standardized treatment outcomes and focusing on defined primary outcomes
Implementing and evaluating the "DOTS" model for standardized case management of DM | High | Operational research including quarterly cohort reporting of new cases, treatment outcomes of cumulative cases including frequency of co-morbidities such as TB, and survival analysis
Development and evaluation of a point of care glycated haemoglobin test (HbA1c) | High | Developmental work to develop a dipstick for measuring HbA1c for use in rural areas, which then needs to be tested for efficacy and feasibility in the field
Rates of hospitalization and additional medical costs associated with diagnosis and management of dual disease | Medium | Cross-sectional studies
Use of the community to improve management and care of patients with DM and TB | Medium | Operational research
Household contact tracing of adult patients with smear-positive pulmonary TB | Medium | Prospective observational studies to determine the yield of screening household contacts for TB infection, active TB, HIV, and DM, and to assess whether DM influences the establishment of TB infection
Radiographic findings in DM patients with TB | Medium | Systematic review of the literature and prospective cross-sectional studies if further evidence is required to determine the common radiographic patterns
Modelling the effect of the DM epidemic on the TB epidemic | Medium | Mathematical modeling studies
TB preventive therapy in patients with DM | Low | Randomized controlled trial assessing efficacy and safety of isoniazid preventive therapy in reducing risk of active TB in patients with DM
“The TANDEM Consortium brings together partners with complementary skills in clinical studies, epidemiology, health economics, human genetics and immunology.”
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What needs to be done?

The Facts...

• 15% TB also with DM
• TB-DM: Poor outcome
• Little is known about why worse outcome of TB in DM
• Even less known about basic mechanism for susceptibility

Questions...

1. How to screen?
2. How to manage?
3. What is the basis for the poor outcome?
4. What is basic mechanism for susceptibility?
Objectives:

1. Feasible, accurate & cost-effective ways of screening TB ↔ DM

2. DM management during and after TB treatment
   • effect of glucose control on TB treatment outcome.

3. Pathways that enhance susceptibility to, and poorer treatment outcomes of TB-DM

4. Cellular & molecular basis for the causal link between DM & TB
   • the effect of hyperglycemia and genetic variation on the host protective response to \textit{Mtb}.
1. Screening and management of DM among TB patients can be greatly improved and simplified with a major impact on control of TB-DM co-morbidity.

2. The effect of DM on TB susceptibility and outcome is regulated, at least partly, by hyperglycemia, which dysregulates the cellular response to *M. tuberculosis* (*Mtb*), and by genetic variation common to both diseases.
Methodology

- Patients with diabetes
- Patients with tuberculosis
- Screening
  - Diabetes
  - Diabetes and tuberculosis
  - Tuberculosis
    - Treatment and active follow-up
    - Passive follow-up

- 2000
- 350
- 2000

- Bioarchive and database
- Mycobacterium tuberculosis genotyping
- Cost-effectiveness studies
- Pharmacokinetic studies
- Gene expression studies
- Patient DNA genotyping

- In-vitro studies
  - Stimulation and M. tuberculosis infection of macrophages and adipocytes
  - Functional genomics
Screening TB patients for DM and DM patients for TB

All newly diagnosed TB patients (N=2000)
- history of DM
- HbA1c (gold standard)
- POC HbA1c, rcg, fpg, urine dipstick, diabetes risk score (alone/combination)

➔ Feasibility, accuracy, and cost of those modalities

Previously known DM patients (N=2000)
- Symptom screen
- CXR
- and followed by sputum examination

• Most DM identified in TB patients is pre-existing not newly diagnosed DM
Screening diabetes patients for active and latent TB...

Data from 4 sites (n: 807)
- History of TB: 6.4 – 25.5%
- Very low prevalence of active TB
- ...

Data from Indonesia (n: 375)
- IGRA test
- Prevalence: 38%
- ...

Ruslami/TANDEM consortium, unpub. data
Pragmatic trial in TANDEM

• **Objective:**
  • To evaluate the effect of enhanced glycemic monitoring of DM during TB treatment on clinical & microbiological outcomes.

• **Study design:**
  • 350 TB-DM patients across the sites (Romania, Peru and Indonesia)
  • Randomization for the clinical monitoring strategies
    • Normal practice (*standard*)
    • More intensive monitoring (*intensive*)
Gene expression changes occurring during tuberculosis treatment: will these be different in TB-DM?

4,151 gene entities >2-fold between time-points, P<0.05

Marked changes in gene expression (Affymetrix) early and late during treatment (Cliff et al J Infect. Dis, 20123, 207:18)
Diabetes affects different tissues and cells....

For example, can Mtb infect adipocytes?
Immune mechanisms that might contribute to the greater susceptibility of diabetes patients to Mtb

Hodgson et al, Immunology 2014, 144:171
T cell and macrophages interactions in TB: Impact of type 2 diabetes mellitus and HIV

Ronacher, Joosten, van Crevel, Dockrell, Walzl, Ottenhoff Immunological Reviews 2015, 264: 121–137
Effect of hyperglycaemia on macrophages infected with M.tbc

Graphs showing cytokine production (IL-6 and IL-10) and phagocytosis in M0 and M2 macrophages under different glucose concentrations.
Comorbidity with TB and diabetes does matter:

- Patients with type 2 diabetes mellitus have a 3-fold increased risk of developing TB
- Diabetes may alter the clinical presentation of tuberculosis
- Diabetes may make TB harder to treat successfully
- Diabetes may increase the rates of TB relapse following apparently successful treatment
- Hopefully our ongoing studies will help identify the most effective ways of bidirectional screening, of managing TB-DM patients and bring greater insights into the mechanisms underlying these interactions
Thank you...

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