DM and TB Double Burden

Anil Kapur
The association between DM and TB was known to ancient Roman and Indian physicians.

In 1883, Bouchardt stated ‘at autopsy every case of diabetes had tubercles in the lungs’.

Global Burden of DM and TB

Diabetes Mellitus: 2011
366 M People Affected
7 M New Cases
4.6 M Deaths

Tuberculosis: 2011
[WHO- Global TB Control 2012]
12.0 M Cases
8.7 M New Cases
1.4 M Deaths
Global Distribution of DM and TB

**Diabetes Mellitus: 2011**
- South East Asia 19.5%
- Western Pacific 36%
- Africa 5%
- 79% in LIC and MIC

**Tuberculosis: 2011**
[WHO- Global TB Control 2012]
- South East Asia 41.6%
- Western Pacific 20.8%
- Africa 20.8%
- 95% in LIC and MIC
### Studies on DM and TB Association

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jeon CY, Murray MB. PLoS Medicine 2008; 5: e152</strong></td>
<td>Systematic review of 13 observational studies with 1,786,212 participants and 17,698 TB cases - DM associated with increased risk of TB. Cohort studies: RR 3.1, 95% CI (2.3 – 4.3). Case control studies: OR 1.2 – 7.8. Higher risks in young people and communities with high background TB incidence.</td>
</tr>
<tr>
<td><strong>Stevenson et al (Chronic Illn, 2007):</strong></td>
<td>Medline search for studies after 1995 - Diabetes Mellitus increases risk of active tuberculosis. Increased RR or OR of 1.5 – 7.8. Risk higher in younger people.</td>
</tr>
<tr>
<td><strong>Stevenson et al BMC Public Health 2007</strong></td>
<td>Epidemiological model based on 21M adults with DM and 900,000 new TB cases in 2000 in India - DM accounted for 15% PTB (CI 7% - 23%). 20% smear +ve PTB (CI 8% - 42%). Diabetes mellitus contributes substantially to new TB burden in India. Urban areas more affected than rural areas.</td>
</tr>
</tbody>
</table>
Association between TB and DM

Not in doubt
  • Biologically plausible

Limitations:-
  • Most studies from industrialised countries; almost none from Africa
  • Many are health facility-based and are secondary analyses of routine data sources
  • Many critical unanswered questions
WHO, The Union, and WDF met in Geneva early 2009 to identify scope of work, funds mobilized from WDF

Outsourcing of a systematic review to Harvard School of Public Health

Expert meeting in Paris, November 2009 (Researchers, TB and DM technical experts and agencies, practitioners, programme managers)

Symposium in The Union conference, Cancun, December 2009

Series of papers published

Framework developed by writing committee, endorsed by the WHO TB Departments external Strategic and Technical Advisory Group, and the WHO Guideline Review Committee.


List of Publications based on Systematic Review
Key finding in the Systematic Review

Diabetes increases the risk of active TB about 3-fold, risk seems to increase with poor glucose control.

Diabetes increases the risk of adverse TB treatment outcomes:
- Delayed sputum conversion
- Higher relapse rate
- Higher death rate

No trials on the efficacy of alternative TB treatment regimens in people with diabetes.
In some settings the DM prevalence among TB patients is 40-50% (e.g. Mexico, Pacific Islands, and growing number of middle income countries). The number of TB cases needed to screen to find one diabetes case is generally low (<10). If TB prevalence is less than 25 per 100,000 persons, at least 1000 people with DM would need to be screened to diagnose one case of TB, whereas in high TB burden countries the number needed to screen is about 100-300. Appropriateness of TB screening in people with diabetes depends on local TB burden. Some drug-drug interactions may complicate treatment. Very little evidence on the effectiveness of preventive TB treatment (e.g. isoniazid) in people with diabetes suspected.
Diabetes prevalence was higher in patients with TB than in the comparisons where available.

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>DM Prevalence Gen Pop</th>
<th>DM Prevalence TB Cases</th>
<th>Preval Ratio</th>
<th>OR</th>
<th>% Newly detected</th>
<th>Method Used</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Chennai</td>
<td>10.4%</td>
<td>25.3%</td>
<td>2.4</td>
<td>3.1</td>
<td>37%</td>
<td>OGTT</td>
<td>Vishwanathan V et al</td>
</tr>
<tr>
<td></td>
<td>Kerala</td>
<td>18.0%</td>
<td>44.0%</td>
<td>2.4</td>
<td></td>
<td>48%</td>
<td>HbA1c</td>
<td>Balakrishnan S et al</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>13.0%</td>
<td></td>
<td></td>
<td></td>
<td>38%</td>
<td>FPG</td>
<td>India TB DM Group</td>
</tr>
<tr>
<td>China</td>
<td>Various</td>
<td>9.7%</td>
<td>12.4%</td>
<td>1.3</td>
<td>22%</td>
<td>22%</td>
<td>FPG</td>
<td>Liang L et al</td>
</tr>
<tr>
<td></td>
<td>Linyi (rural)</td>
<td>4.7%</td>
<td>6.3%</td>
<td>1.3</td>
<td>3.2</td>
<td>43%</td>
<td>FPG</td>
<td>Wang Q et al</td>
</tr>
<tr>
<td>Pakistan</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lagos</td>
<td>7.0%</td>
<td>16.0%</td>
<td>2.3</td>
<td>3.6</td>
<td></td>
<td>HbA1c</td>
<td>Coldin A et al</td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td>5.6%</td>
<td>12.0%</td>
<td>2.1</td>
<td></td>
<td>67%</td>
<td>FPG/RPG</td>
<td>Ogbera A et al</td>
</tr>
<tr>
<td>USA</td>
<td>South Texas</td>
<td>19.5%</td>
<td>39.0%</td>
<td>2.0</td>
<td></td>
<td>10%</td>
<td>FPG/RPG</td>
<td>Resterpro BI et al</td>
</tr>
<tr>
<td>Mexico</td>
<td>North East</td>
<td>15.0%</td>
<td>36.0%</td>
<td>2.4</td>
<td></td>
<td>53%</td>
<td>FPG/RPG</td>
<td>Resterpro BI et al</td>
</tr>
<tr>
<td></td>
<td>South Mexico</td>
<td>15.0%</td>
<td>30.0%</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td>Jimnez-Carona et al</td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td>9.4%</td>
<td>16.7%</td>
<td>1.8</td>
<td>2.2</td>
<td></td>
<td>OGTT</td>
<td>Faurholt - Jepsen et al</td>
</tr>
<tr>
<td>Uganda</td>
<td></td>
<td>6.4%</td>
<td>8.5%</td>
<td>1.3</td>
<td></td>
<td></td>
<td>RBS</td>
<td>Kibirige D et al</td>
</tr>
</tbody>
</table>
In 12 studies prevalence of active TB among people with DM varied widely based on the country and time of study; the annual incidence ranged from 280 / 100,000 people with DM in Korea to 488 / 100,000 people with DM in Ethiopia. Five of the 12 studies provided an estimate of the TB prevalence in the population that gave rise to the study group. Prevalence ratios ranged from 2.0 in Hungary and United States to 5.1 in Korea.

In China screening 11331 DM cases over three quarters identified 55 cases of TB, the average case notification rates of TB among DM patients was 423/100,000 compared to 77/100,000 in general population. The prevalence ratio was about 5.5.


In India screening 13068 DM cases over three quarters identified 254 cases of TB, the average TB case notification rate was 810/100,000 DM cases compared to about 110 /100,000 in the general population. Prevalence ratio was about 7.4

India Diabetes Mellitus--Tuberculosis Study Group. Screening of patients with diabetes mellitus for tuberculosis in India. Trop Med Int Health. 2013;18:646-54
DM delays sputum culture conversion at 2-3 months

8 studies comparing DM with non-DM
Relative risks from 0.8 – 3.2
Five of eight studies had RR > 2

Baker et al.
BMC Medicine 2011, 9:81
## Increased risk of TB relapse

### Study, Country, and RR (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cases/Population (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wada, 2000</td>
<td>Japan</td>
<td>7/61 (11%)</td>
<td>8.15 (2.46, 26.97)</td>
</tr>
<tr>
<td>Mboussa, 2003</td>
<td>Congo</td>
<td>6/17 (35%)</td>
<td>3.02 (1.24, 7.35)</td>
</tr>
<tr>
<td>Singla, 2006</td>
<td>Saudi Arabia</td>
<td>2/130 (2%)</td>
<td>1.88 (0.32, 11.14)</td>
</tr>
<tr>
<td>Maalej, 2009</td>
<td>Tunisia</td>
<td>4/55 (7%)</td>
<td>5.96 (0.68, 51.95)</td>
</tr>
<tr>
<td>Zhang, 2009</td>
<td>China</td>
<td>33/165 (20%)</td>
<td>3.78 (1.87, 7.65)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td><strong>3.89 (2.43, 6.23)</strong></td>
</tr>
</tbody>
</table>

### Heterogeneity

- I-squared = 0% (0.79)
- Weights are from random effects analysis

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For Relapse, pooled RR = 3.89 (95% CI, 2.1 – 7.5)

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Baker et al.
BMC Medicine 2011, 9:81
DM increases risk of death in TB

- Pooled RR = 1.85 (95% CI, 1.5 – 2.3)

4 studies adjusted for age / other confounders: pooled OR = 4.95 (95% CI, 2.7 – 9.1)

23 studies comparing risk of death in DM and non-DM patients
In Mwanza, Tanzania within 100 days of TB treatment DM was associated with a five fold increased risk of death among HiV uninfected and a two fold increased risk among HiV co infected patients.

Faurholt-Jepsen D., Diabetes is a strong predictor of mortality during TB treatment: a prospective cohort study among TB patients from Mwanza, Tanzania. PhD thesis Faculty of Science university of Copenhagen 2012
Does TB present differently in patients with DM?

Pulmonary TB more common than Extra Pulmonary TB

“infiltrates more common in lower lung fields”

- Turkey [Bacakoglu et al, 2001]
- Saudi Arabia [Shaikh et al, 2003]
- Pakistan [Jabbar et al 2006]
- Taiwan [Wang et al, 2008]
Why an increased risk of adverse outcomes?

Drug-drug interactions between oral hypoglycaemic drugs and rifampicin (*decreased RF concentrations and poor glycaemic control*)

DM is a risk factor for hepatic toxicity with TB drugs

DM is associated with co morbid conditions (renal insufficiency)

Immune-suppressive effects of DM
China: Background prevalence of TB 77/100,000; prevalence ratio 5.5. Screening 250 people with DM will yield 1 case of active TB.

India – Chennai. Background prevalence of DM 10.4%; prevalence ratio 2.43. Screening 8 to 10 TB patients will identify one new case of DM.

Determining number of patients to be screened to detect one new case of tuberculosis or diabetes.

Number of people with diabetes to screen to detect one additional case of tuberculosis by varying baseline tuberculosis prevalence, given prevalence ratios found in screening studies.

Number of patients with tuberculosis to screen to detect one additional case of diabetes by varying baseline diabetes prevalence, given prevalence ratios found in screening studies.

Circulated to the WHO and The Union networks, and other partners in TB control

Presented at the UN Summit on NCDs
- NCD Alliance 17th September 2011
- PAHO Partners Forum 20th September 2011

Presentations in The Union conference in Lille

Field testing in countries:
- Sri Lanka
- Mexico
- China
- India etc...

Research, including operational research linked to field testing

## The recommendations

### A. Establish mechanisms for collaboration

<table>
<thead>
<tr>
<th></th>
<th>ESTABLISH MECHANISMS FOR COLLABORATION</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Set up a means of coordinating diabetes and TB activities</td>
</tr>
<tr>
<td>2</td>
<td>Conduct surveillance of TB disease prevalence among people with diabetes in medium and high-TB burden settings</td>
</tr>
<tr>
<td>3</td>
<td>Conduct surveillance of diabetes prevalence in TB patients in all countries</td>
</tr>
<tr>
<td>4</td>
<td>Conduct monitoring and evaluation of collaborate diabetes and TB activities</td>
</tr>
</tbody>
</table>

### B. Detect and manage TB in patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>DETECT AND MANAGE TB IN PATIENTS WITH DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intensify detection of TB among people with diabetes</td>
</tr>
<tr>
<td>2</td>
<td>Ensure TB infection control in health-care settings where diabetes is managed</td>
</tr>
<tr>
<td>3</td>
<td>Ensure high-quality TB treatment and management in people with diabetes</td>
</tr>
</tbody>
</table>

### C. Detect and manage diabetes in patients with TB

<table>
<thead>
<tr>
<th></th>
<th>DETECT AND MANAGE DIABETES IN PATIENTS WITH TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Screen TB patients for diabetes</td>
</tr>
<tr>
<td>2</td>
<td>Ensure high-quality diabetes management among TB patients</td>
</tr>
</tbody>
</table>

The TB/DM Framework, building on the TB/HIV policy

**TB control need**
- TB screening in risk groups, for early and comprehensive TB diagnosis
- Quality care for TB comorbidities to improved health outcomes among people with TB
- Better prevention of TB by reducing population prevalence of TB risk factors
- Health Systems Strengthening through synergistic collaboration

**TB/HIV Approach**
- Screening people living with HIV for TB
- HIV screening among people with TB, quality treatment and care, including ARV
- Scale up quality HIV treatment and care, and reduce HIV prevalence
- Collaborative structure, sensible integration

**DM/TB Approach**
- Screen people with DM for TB, in high TB burden settings
- Screen TB patients for DM, provide high quality DM treatment, adapt "DOTS" model
- Broad DM prevention and care efforts, TB programmes can help advocate
- Collaborative structure, sensible integration

The TB/DM Framework, building on the TB/HIV policy
In two recent large studies in China using FBG to screen for DM amongst cases of PTB (Liang Li et al TMIH 2012 and Wang Q et al PLoS ONE 2013) 2.9% and 2.8% patients had previously undetected diabetes and 7.8% and 7.4% had IFG.

If DM screening was scaled up nationwide and implemented at the level of performance achieved in these pilot projects, a prevalence of approx. 3% undetected DM among 1 million patients with TB will translate to 30,000 new DM cases diagnosed each year - an important contribution to case finding of DM and identification of approx. 75000 cases of people at risk of DM.

Only a third of all cases with diabetes in China are diagnosed and 50% of adult population has pre diabetes. (Xu Y et al JAMA 2013)
In three recent studies in India using various methods to screen for DM amongst cases of PTB 5% (FPG); 9.4% (OGTT) and 21% (HbA1c) patients had previously undetected diabetes. These constituted 38%, 37% and 48% cases of TB and DM.

If DM screening was scaled up nationwide and implemented at the level of performance achieved in these pilot projects, a prevalence of approx. 6-9% undetected DM among 2.2 million patients with TB will translate to 132,000 to 198,000 new DM cases diagnosed each year - an important contribution to case finding of DM.

Only a half of all cases with diabetes in India are diagnosed.
New TB case notification rate amongst people with DM in China have been reported to vary between 335 to 595 per 100,000 known DM cases screened for TB. (Lin Y et al TMIH 2012)

There are 40 million (3.5% of 114 million) people with known DM in China (Xu Y et al JAMA 2013)

If the TB screening protocol used in the pilot project was implemented nationally this would translate to between 134,000 to 238,000 new cases of TB detected amongst people with known DM.
Implementing the DM-TB Collaborative Framework – public health implications

<table>
<thead>
<tr>
<th>New TB case notification rate amongst people with DM in India have been reported to vary between 642 to 956 per 100,000 known DM cases screened for TB. (India DM TB Study Group TMIH 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are approx. 32 million people with known DM in India</td>
</tr>
<tr>
<td>If the TB screening protocol used in the pilot project was implemented nationally this would translate to between 205,000 to 306,000 new cases of TB detected amongst people with known DM.</td>
</tr>
</tbody>
</table>
During the study period, both female (standardized incidence ratio (SIR): 1.40, p<0.01) and male (SIR: 1.48, p<0.01) patients with type 2 diabetes were found to have a significantly higher rate of incident tuberculosis than the control group. Type 2 diabetes (HR:1.31, 1.23–1.39, p<0.001) was significantly associated with tuberculosis after adjusting sex, age, bronchiectasis, asthma and chronic obstructive lung disease.

In lower income countries, individuals with DM are more likely than non-DM to have TB [univariable OR: 2.39; 95% CI: 1.84–3.10; multivariable OR: 1.81; 95% CI: 1.37–2.39].

Increases in TB prevalence and incidence over time were more likely to occur when diabetes prevalence also increased (OR: 4.7; 95% CI: 1.0–22.5; OR: 8.6; 95% CI: 1.9–40.4).

Over 10 years, TB was more likely to increase in low and middle income countries where diabetes prevalence increased. Given the association between TB and DM this requires serious reconsideration in health policies to tackle the double burden in high TB burden countries with increasing rates of DM.

Diabetes And Tuberculosis – the converging pandemics

- DM increases the risk of active TB about 3-fold
- DM increases the risk of adverse TB treatment outcomes
  - Delayed sputum conversion
  - Higher relapse rate
  - Higher death rate
- Drug-drug interactions may complicate treatment

TB “high burden” by WHO (n=22)
80% of TB cases in 2008

China
India
Brazil
Bangladesh
Indonesia
Pakistan
Russia

Diabetes
Ten Countries with highest number of people with diabetes in 2010

WHO (n=22) reported 80% of TB cases in 2008.
Global Diabetes Burden

People with diabetes live in the Middle and Low Income Countries

Deaths attributable to diabetes occur in the same regions

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>% Population</th>
<th>2030</th>
<th>% Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>366,00</td>
<td>8,3%</td>
<td>552,00</td>
<td>9,9%</td>
</tr>
<tr>
<td>IGT</td>
<td>280,00</td>
<td>6,4%</td>
<td>398,00</td>
<td>6,7%</td>
</tr>
</tbody>
</table>

79%

Deaths attributable to diabetes occur in the same regions

88%
Undiagnosed, inadequately treated and poorly controlled Diabetes Mellitus is a bigger threat to TB prevention and control in high TB burden countries than previously realised.

Continuing to underplay and ignore this association will undo decades of painstaking gains in TB control and prove disastrous both in terms of health and economics.