

Tuberculosis, Diabetes, Serum Drug levels

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No disclosures



Overview

Diabetes increases the risk of progression to active TB disease
(odds 2.4-8.3 compared to non-diabetics)
and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

Drug concentrations are suboptimal for most DM/TB patients

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THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*
Epidemiology, Pathology, Treatment and Prognosis
BY HOWARD F. SOOY, M.D.†

(a) The development of pulmonary tuberculosis in juvenile diabetics occurred more than ten times as frequently as among non-diabetic Massachusetts grade and high school children.

No "special insidiousness" of signs and symptoms in the "tuberculous diabetic"

(b) Pulmonary tuberculosis developed in 8 per cent of diabetic patients within three years of recovery from coma.

TB more frequent in those with poor diabetes control

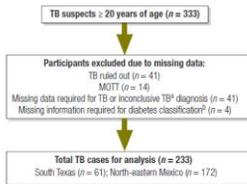
(c) The incidence of pulmonary tuberculosis in adult diabetics is increasing despite the general decrease of tuberculosis mortality with consequent reduction of contacts in the community.

No "special insidiousness" of presentation
No difference in location of disease or lung cavitation

Year	Study location	Participants (n)		Lower lung more commonly involved?	More cavitary lesions?	More diffuse involvement?
		With diabetes	Without diabetes			
Weaver ⁶⁶	1974 USA	20	182	Yes	--	--
Marais ⁶⁷	1980 South Africa	9	427	Yes	--	--
Rezoze et al ⁶⁸	1992 Japan	311	71	No	Yes	Yes
Morris et al ⁶⁹	1992 Texas, USA	20	20	No	No	No
Umit et al ⁷⁰	1994 Turkey	37	37	No	Yes	Yes
Kusban et al ⁷¹	1996 Cameroon	--	2721	Yes	--	--
al-Wabel et al ⁷²	1997 Saudi Arabia	28	28	No	--	--
Bacakoglu et al ⁷³	2001 Turkey	92	92	No/5	No/5	No
Perez-Guzman et al ⁷⁴	2000-01 Mexico	192	130	Yes	Yes	Yes
Shaikh et al ⁷⁵	2003 Saudi Arabia	187	505	Yes	--	--
Wang et al ⁷⁶	2005 Taiwan	99	362	No	Yes	--
Wang et al ⁷⁷	2008 Taiwan	74	143	Yes	Yes	--
Al-Tawfiq et al ⁷⁸	2009 Saudi Arabia	57	78	--	No	--

Dooley et al. *Lancet ID* 2009

Attributable risk of TB from Diabetes > HIV in Texas/Mexico border



Age (years)	Diabetes			HIV infection		
	RR (95% CI)	AR _{exposed} (%) ^a	AR _{population} (%) ^b	RR (95% CI)	AR _{exposed} (%) ^a	AR _{population} (%) ^b
South Texas						
20+ (n=61)	2.7 (1.6-4.4)	63	26	17.8 (6.5-9.0)	94	5
20-34 (n=20)	0.9 (0.1-6.8)	-9	1	34.4 (8.0-147.7)	97	6
35-64 (n=32)	5.1 (2.6-10.2)	80	48	12.2 (2.9-50.9)	92	5
65+ (n=9)	1.7 (0.5-5.8)	41	22	0 ^c	NA	NA
NE Mexico						
20+ (n=172)	3.1 (2.3-4.2)	68	24	16.0 (7.5-34.0)	94	3

Restrepo et al. *Bull WHO* 2011

Diabetes is the leading identified risk factor for TB in Virginia (10-15%)

http://www.vdh.state.va.us/epidemiology/diseaseprevention/programs/tuberculosis/documents/annual_final_8_16_2013_revised.pdf

Table 15. Tuberculosis Cases by Selected Risk Factors: Virginia, 2008-2012

Total Cases	2008		2009		2010		2011		2012	
	No.	%								
Total Cases	292		273		268		221		235	
Occupation										
Health Care	6	2.1	11	4.0	12	4.5	7	3.2	8	3.4
Migrant	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4
Corrections	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Type of Residence										
Long Term Care	5	1.7	3	1.1	8	3.0	5	2.3	2	0.9
Prison/Jail	5	1.7	4	1.5	8	3.0	8	3.6	6	2.6
Homeless	4	1.4	9	3.3	12	4.5	1	0.5	10	4.3
Disability										
Diabetes	40	13.7	37	13.6	37	13.8	31	14.0	27	11.5
HIV	9	3.1	18	6.6	8	3.0	9	4.1	12	5.1
Substance Use										
Alcohol	19	6.5	21	7.7	23	8.6	17	7.7	21	8.9
IDU	0	0.0	6	2.2	1	0.4	0	0.0	2	0.9
Non-IDU	6	2.1	6	2.2	4	1.5	13	5.9	15	6.4

Overview

Diabetes increases the risk of progression to active TB disease (odds **2.4-8.3** compared to non-diabetics) and likely higher for poorly controlled diabetics

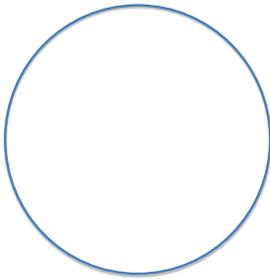
Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

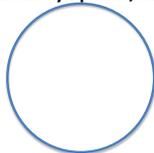
Drug concentrations are suboptimal for most DM/TB patients

Outcomes during treatment for Tb

Most do well (>90%)



Some don't
Death < "slow response" = persistent symptoms/smear+



Many potential factors
Extensive disease
Drug resistance
HIV
Other comorbidities/smoking
Low drug levels
Diabetes
.....



Diabetics in Indonesia more likely to be culture-positive at 6 months of treatment (22%)

Table 3. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

Period, variable	No. (%) of patients with TB		Crude OR (95% CI)	Adjusted OR (95% CI)
	With DM (n = 94)	Without DM (n = 540)		
Intensive phase				
AFB negative ^a	67 (71.3)	455 (84.3)
AFB positive	17 (18.1)	54 (10.0)	2.14 (1.17-3.9)	1.90 (0.92-4.42)
No sputum sample available, hospital transfer, and/or study default	8 (8.5)	31 (5.7)
Death	2 (2.1)	0 (0)
Culture result positive for <i>Mycobacterium tuberculosis</i>	7 (41 (17.1)	68 (372 (18.3)	0.92 (0.39-2.16)	0.90 (0.30-2.68)
End of treatment				
AFB negative ^a	70 (74.5)	455 (80.6)
AFB positive	4 (4.3)	17 (3.1)	1.46 (0.48-4.47)	1.06 (0.17-6.60)
No sputum sample available, hospital transfer, and or study default	18 (19.1)	88 (16.3)
Death	2 (2.1)	0 (0)
Culture result positive for <i>M. tuberculosis</i> ^b	6 (27 (22.2)	32 (333 (9.6)	2.69 (1.01-7.14)	7.65 (1.89-30.95)

NOTE. The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.

- 14.8% prevalence of undiagnosed DM in new TB patients
- TB-DM had greater symptoms at time of diagnosis

Alisjahbana et al. *Clin Infect Dis* 2007



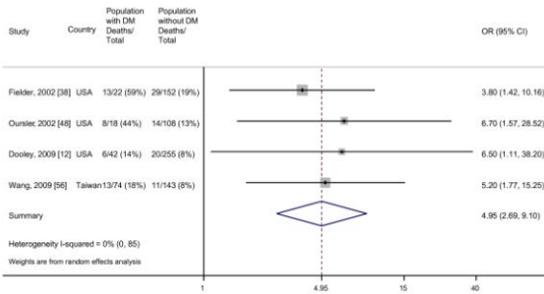
• In Maryland, odds of death were 6.5 times higher ($p=0.039$) for diabetics than non-diabetics with TB, even adjusting for HIV, age, weight, and foreign birth

★ % of deaths were not TB related

• Time to sputum culture conversion was longer (49 days for diabetics vs 39 days for non-diabetics, $p=0.09$)

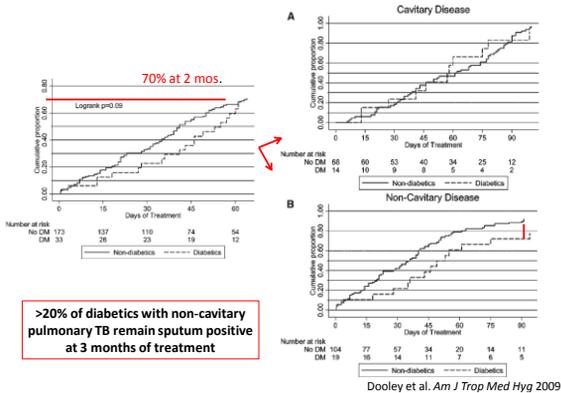
Dooley et al. *Am J Trop Med Hyg* 2009

All cause mortality increased in diabetics during TB treatment

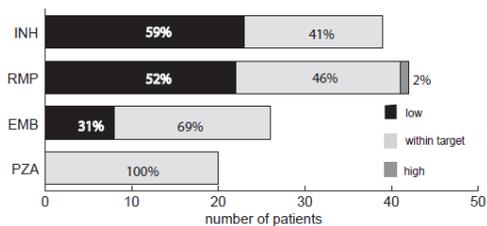


Baker et al. *BMC Med* 2011

Slower culture conversion in diabetics (without cavitary disease)



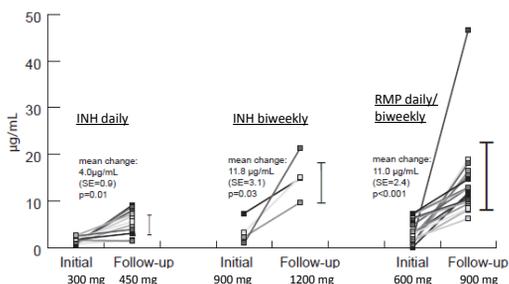
Majority of slow responders had low C_{2hr} levels of INH and rifampin



82% had low levels to one of INH or RMP, hard to predict which one

Heysell et al, *Emerg Infect Dis*, 2010

Drug levels usually correct after first dose adjustment



└ spans C_{2hr} expected range

Heysell et al, *Emerg Infect Dis* 2010

Determinants of anti-TB drug pharmacokinetics:

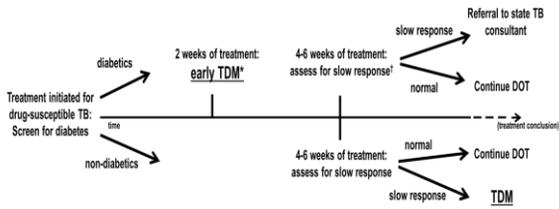
1. mg/kg dosing (weight categories, poor availability of drug in fixed-dose combinations in some settings)
2. Adherence
3. Drug interactions
4. Gastroenteritis
5. Malabsorption
 - HIV
 - Diabetes
 - Cystic Fibrosis
6. Poor solubility¹
7. Host genetics
 - Genetic polymorphism of gut xenobiotic transport
 - Metabolism
8. Age
9. Gender



1. Ashokraj et al. *Clin Res Reg Affairs* 2008

The Virginia Algorithm

http://www.vdh.state.va.us/epidemiology/diseaseprevention/programs/tuberculosis/documents/TDMRecommendationsandProceduresRevised082013Final.pdf



Instead of only self-report and prior DM diagnoses, we now recommend checking HbA1C on all >6.5: education/resource packet, referral <6.5: education/resource packet

Implementation of early TDM in diabetics was operationally feasible

Characteristic	Diabetes (early TDM) N= 21	Slow response (standard TDM) N= 14	P value
Age, mean years ±SD	57 ±17	46 ±12	P=0.04
Gender, male (%N)	15 (71)	11 (79)	P=0.69
Prior episode of TB, n (%N)	0	2 (14)	P=0.17
Pulmonary TB only, n (%N)	17 (81)	8 (57)	P=0.65
Foreign born (%N with confirmed status)	15 (79)	12 (92)	P=0.63
HIV infected (%N with confirmed status)	0	1 (11)	P=0.43
Insulin dependence, n (%N)	10 (48)	N/A	N/A
Days to TDM from treatment initiation, median days (IQR)	23 ±16	88 ±54	P=0.003

Heysell et al. NTCA 2013

Early TDM in diabetics corrected low drug concentrations in the majority and may limit slow response

•Of the 21 diabetics, **16 (76%)** had a C_{2h} value below the expected range for isoniazid (mean 2.1±1.5 µg/ml; expected 3-5), rifampin (mean 6.6 ±4.3 µg/ml; expected 8-24) or both

A proper target population

•15 patients had follow-up concentrations after dose adjustment, all increased and 12 to the expected range (including all for rifampin).

•In practice, what our algorithm does is shunt most diabetics to at least 3x weekly therapy during continuation phase, with INH 900/RIF 900, while keeping to a 6 month total duration

No major toxicities reported

•**88%** of diabetics with early TDM and pulmonary TB had sputum culture conversion <2 mos.

Better than expected norms for diabetes/TB

•total statewide burden of slow response decreased from 1.6 patients/mo (40% diabetic) to 1.2 patients/mo (12.5% diabetic)

May limit the need for prolonged treatment and program resources

Heysell et al. NTCA 2013

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