Original Article

Higher risk of developing active TB among adult diabetics exposed to TB during childhood: A study from Kerala, India

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Abstract

Introduction: Factors associated with tuberculosis (TB) in Kerala, the southern Indian state that notifies approximately 33 microbiologically confirmed new cases per 100,000 population every year for the past two decades, are still unclear. We did a community-based case–control study in Kollam district, Kerala, to identify the individual-level risk factors for TB. **Methods:** Structured questionnaire was applied to 101 microbiologically confirmed new TB cases registered under Revised National Tuberculosis Control Program and 202 age- and gender-matched neighborhood controls without present or past TB. Information was sought on socioeconomic status (SES), smoking, consumption of alcohol, close contact with active TB during childhood or recent past, diabetes mellitus (DM), and other comorbid conditions. **Results:** Close contact with TB during childhood [odds ratio (OR) 15.88, 95% confidence interval (CI) 3.21–78.55], recent close contact with TB (OR 4.81, 95% CI 2.09–11.07), DM (OR 1.64, 95% CI 1.04–3.06), SES (OR 2.16, 95% CI 1.16–4.03), smoking more than 10 cigarettes/beedis per day (OR 3.32, 95% CI 1.27–8.96), consuming more than 10 standard drinks per week (OR 2.91, 95% CI 1.33–6.37), and the interaction term of having close contact with TB during childhood and DM at present (OR 7.37, 95% CI 1.18–50.29) were found to be associated with TB. **Conclusion:** Close contact with a case of TB, presence of DM, lower SES, smoking, and alcohol consumption were associated with active TB in Kollam. Having close contact with a case of TB during childhood and development of DM in later life together are significantly associated with active TB in the study population. The findings also direct further studies to confirm and explore mechanisms of interaction of diabetes with childhood exposure to TB.

Keywords: Diabetes, risk factors, tuberculosis

Introduction

Tuberculosis (TB) preserves its top position among the major killer diseases in spite of global strategies to control, end, and then eliminate TB. Annually, 10.4 million new cases are estimated to occur globally including 0.48 million multidrug resistant cases. India tops the high TB burden countries with an estimated annual incidence rate of 274 per 100,000.[1]

Kerala, the southern Indian state, notified 33 microbiologically confirmed new TB and 69 all types of TB per 100,000 in 2017.[2] However; since the implementation of Revised National Tuberculosis Control Program (RNTCP) in 1997, notification rate of new cases remains standstill. Age-specific notification rate of new cases was the highest among 45–64 years. Kerala

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has achieved near-universal literacy. Many of its maternal and child health indicators are comparable to that of countries with more advanced economies. Health coverage indicators of the state are promising. Health seeking and access to service are high.[3] Prevalence of HIV in adults is low (0.12%), but that of diabetes mellitus (DM) is high (20%).[4,5] Approximately half of the patients with TB in Kerala above the age of 15 years are diabetic.[6] There is evidence for a low level of transmission of TB infection in Kerala.[7]

The risk of infection after exposure to TB bacilli is primarily determined by a combination of factors such as infectiousness of the source case, proximity of contact, and social and behavioral risk factors including smoking, alcohol, and indoor air pollution. Factors that increase the progression of infection to disease are primarily host-related. Conditions like HIV, which alter the immune response, increase the risk of progression to disease. Diabetes, malnutrition, alcohol, tobacco smoke, and indoor air pollution also accelerate progression of infection to disease.[8] However; we are still unclear about the factors associated with TB in Kerala that continues to notify similar numbers every year for the past two decades. To further reduce the incidence of TB in the state, it may be necessary to identify and target the factors that increase individual's risk for TB. We did a community-based case–control study in Kollam district, Kerala, to identify the individual-level risk factors for TB.

Methods

Kollam district, located in the south-west coast of Kerala, has a population of 2.6 million. We selected Kollam because it represents the state in terrain, population characteristics, and healthcare service delivery. It is one of the first districts to roll out RNTCP. The district tested 278 patients with symptoms of TB and notified 38 sputum smear-positive new cases per 100,000 population in 2016.[2]

The study was conducted during June–November 2016. Sample size was calculated with an alpha error of 5%, beta error of 20%, and anticipated odds ratio (OR) of 2. With assumed proportion of controls with diabetes as 20% and controls per case as two, the number of cases and controls was calculated as 100 and 200, respectively. An additional 10% was selected to deal with nonresponse. Cases were randomly picked from new microbiologically confirmed pulmonary TB registered in the district during June–September 2015. Previously treated cases were excluded. Two age- (±5) and gender-matched neighborhood controls without present or past history of TB were selected per case, from the house with the next serial number. If there were no eligible controls at the next door, houses were visited serially until eligible controls were obtained.

A structured questionnaire was developed based on literature review, group consensus, and expert opinions. It was translated to local language and back to check for consistency. Questionnaire was pilot-tested and interview techniques were standardized before initiation of data collection. Cases and controls were interviewed at their home, for information about sociodemographic, behavioral, and environmental factors and exposure to TB at home/workplace. Questions were repeated uniformly for cases and controls. Diabetes status was elicited with date of diagnosis, test reports, and medications. If screening was not done within a year, subjects were offered free diabetic testing and management by government-funded Non Communicable Disease Control Programme in the nearby facility.[9] Test results were collected on a later date. Privacy was ensured during the time of interview.

Socioeconomic status (SES) was estimated using Modified BD Prasad scale 2014.[10] Close contact was defined as living in the same household or in frequent contact with (family members, roommates or housemates, close friends, coworkers, classmates) or staying together in a closed room for at least 6 h, with a TB case. Recent close contact was defined as a close contact within the past 5 years, and exposure to TB during childhood was defined as exposure before the age of 12 years. Subjects with history of both childhood and recent contact were counted among those with recent contact. Current smokers (smoked at least one cigarette/beedi in the past 6 months) were classified further based on the usual number of cigarettes/beedis smoked per day which is less or more than 10. Current alcoholics (consumed alcohol in the past 6 months) were classified based on the usual standard drinks per week which is less or more than 10. Behavioral factors were elicited with reference to time period before the diagnosis of TB.

Double-data entry was done using Epi Info 3.5.1, and data were analyzed using Statistical Package for Social Sciences, version 15 (SPSS Inc., Chicago, IL, USA), for Microsoft Windows. Chi-square test was used to test difference between proportions. Univariate analysis was performed to look for any association between TB and factors such as SES, number of cigarettes/beedis per day (categorical), alcohol use (quantified and categorized), childhood exposure to TB, recent close contact with TB, diabetes, chronic respiratory illness, HIV, other comorbidity, and long-term steroid treatment. ORs with 95% confidence interval (CI) were calculated. Stratified analysis was done to identify confounding and interactions, and Mantel–Haenszel (MH) ORs were calculated. Variables were then entered into a backward conditional logistic regression model along with interaction terms and appropriate models were built.

Results

A total of 101 cases and 202 age-, gender-, and neighborhood-matched controls were interviewed. The majority of the cases were males (71.2%) and were in the age group of 45–64 years (50.5%). Of the cases, 28.7% (29/101) and of the controls 18.8% (38/101) belonged to the lower SES category (0.057). The details of the sociodemographic characteristics of the cases and controls are shown in Table 1.

Among the study subjects, 20.8% of the cases (21/101) and 6.4% (13/202) of the controls reported staying with a TB case

Table 1: Sociodemographic characteristics of the study population

Characteristics	Categories	Cases (*n*=101)	Controls (*n*=202)	*P*
Age group	<14 years	0 (0%)	3 (1.5%)	0.660
	15-44 years	34 (33.7%)	67 (33.2%)	
	45-64 years	51 (50.5%)	98 (48.5%)	
	More than 65 years	16 (15.8%)	34 (16.8%)	
Gender	Male	72 (71.2%)	144 (71.2%)	0.549
	Female	29 (28.7%)	58 (28.7%)	
Educational status	<8th standard	63 (62.4%)	123 (60.9%)	0.451
	More than 8th standard	38 (37.6%)	79 (39.1%)	
Place of residence	Slums	3 (2.9%)	7 (3.4%)	0.670
	Colony	17 (16.8%)	35 (17.3%)	
	Residential area	79 (78.2%)	157 (77.7%)	
	Shelter home/old-age home	2 (1.9%)	3 (1.5%)	
State of origin	Kerala	98 (97%)	196 (97%)	0.626
	Other state	3 (3%)	6 (3%)	
Using kitchen As living room	Yes	18 (17.8%)	24 (11.9%)	0.110
	No	83 (82.2%)	178 (88.15)	
Roofing Material	Tile	22 (21.8%)	29 (14.4%)	0.102
	Concrete	57 (56.4%)	131 (64.9%)	
	Sheet (aluminium/asbestos)	19 (18.8%)	37 (18.3%)	
	Thatched	3 (2.9%)	5 (2.4%)	
SES (Modified BD Prasad 2014)	Upper class	9 (8.9%)	24 (11.9%)	
	Upper middle class	18 (17.8%)	34 (16.8%)	
	Middle class	21 (20.8%)	56 (27.7%)	
	Lower middle class	24 (23.8%)	50 (24.8%)	
	Lower class	29 (28.7%)	38 (18.8%)	0.057

SES: Socioeconomic status

in the household during their childhood (OR 3.81, 95% CI 1.82–7.99). Among the cases, 18.8% (19/101) and among the controls 5.4% (11/202) reported close contact with a person with TB within the past 5 years (OR 4.02, 95% CI 1.83–8.83). Five (5%) and 8 (7.9%) of the cases gave a history of close contact with a case of TB within the past 2 years at house and workplace, respectively. Forty-one (40.6%) cases and 48 (23.8%) controls had DM (OR 2.19, 95% CI 1.31–3.66). Thirty-six cases (35.6%) and 28 (18.8%) controls reported smoking more than 10 cigarettes/beedis per day (OR 2.36, 95% CI 1.36–4.10). Twenty-eight (27.7%) cases and 32 (15.8%) controls reported consuming more than 10 standard drinks per week (OR 1.89, 95% CI 1.02–3.49). One of the cases and four of the controls were on long-term steroids ($P = 0.460$). One each in the case group had HIV and chronic kidney disease, whereas none in the control group had these conditions. Four of the cases and six of the controls were treated for a cancer ($P = 0.649$). The details of univariate analysis are shown in Table 2.

Stratified analysis was done for association between TB and history of close contact with a person with TB, by diabetes, smoking, age, and consumption of alcohol. Association between childhood exposure to TB and development of TB, stratified by diabetes status, is shown in Table 3. Among those who had DM, stratum-specific OR for association between exposure to TB during childhood and later development of TB was 11.93 (95% CI 2.51–56.52), whereas the same was 1.71 (95% CI 0.63–4.66) among those without DM. MH OR for association between household exposure to TB during childhood and development of TB stratified by diabetes status was 3.57 ($P = 0.001$).

The variables age group, gender, SES, childhood exposure to TB, recent close contact with a case of TB, smoking (categorical), consumption of alcohol (categorical), and diabetes status were entered into a backward conditional logistic regression model. The results are shown in Table 4. Another model was built by adding an interaction term diabetes × childhood exposure to TB along with the other variables. The final logistic regression model is shown in Table 5.

In the final model, close contact with a case of TB during childhood (OR 15.88, 95% CI 3.21–78.55), recent close contact with a person with TB (OR 4.81, 95% CI 2.09–11.07), presence of DM (OR 1.64, 95% CI 1.04–3.06), SES (OR 2.16, 95% CI 1.16–4.03), smoking more than 10 cigarettes/beedis per day (OR 3.32, 95% CI 1.27–8.96), consuming more than 10 standard drinks per week (OR 2.91, 95% CI 1.33–6.37), and the interaction term of having close contact with a case of TB during childhood and DM at present (OR 7.37, 95% CI 1.18–50.29) were found to be associated with TB.

Discussion

Many previous researchers have proved the causal association of close contact with a case of TB, with subsequent development of active disease.[11] We have observations agreeing with it. However,

Table 2: Univariate analysis of factors associated with TB

Characteristics	Categories	Case (*n*=101)	Control (*n*=202)	Odds ratio (95% CI)
Close contact with	Yes	21 (20.8%)	13 (6.4%)	3.81 (1.82-7.99)*
A case of TB during childhood	No	80 (79.2%)	189 (93.6%)	
Recent close	Yes	19 (18.8%)	11 (5.4%)	4.02 (1.83-8.83)*
Contact with a case of TB	No	82 (81.2%)	191 (94.6%)	
Chronic respiratory	Yes	9 (11.8%)	18 (12.9%)	0.91 (0.38-2.13)
Disease	No	67 (88.2%)	122 (87.1%)	
Diabetes mellitus	Yes	41 (40.6%)	48 (23.8%)	2.19 (1.31-3.66)*
	No	60 (59.4%)	154 (76.2%)	
No. of cigarettes per day	1-10/day	10 (9.9%)	27 (13.4%)	0.92 (0.41-2.03)
	More than 10/day	36 (35.6%)	28 (18.8%)	2.36 (1.36-4.10)*
	Not current smoker	55 (54.5%)	137 (67.8%)	1
Alcohol consumption	More than 10 standard drinks/week	28 (27.7%)	32 (15.8%)	1.89 (1.02-3.49)*
	<10 standard drinks/week	25 (24.8%)	66 (32.7%)	0.82 (0.46-1.45)
	Not current alcoholic	48 (47.5%)	104 (51.5%)	1

*P<0.05. TB: Tuberculosis; CI: Confidence interval

Table 3: Stratified analysis of household contacts as a risk factor for TB by presence or absence of diabetes mellitus

Diabetes mellitus	Close contact with a case of TB during childhood	Cases (*n*=101)	Controls (*n*=202)	Stratum-specific odds ratio
Present	Yes	14 (34.1)	2 (4.2%)	11.93 (2.51-56.52)
	No	27 (65.9%)	46 (95.8%)	
	Total	41 (100%)	48 (100%)	
Absent	Yes	7 (11.7%)	11 (7.1%)	1.71 (0.63-4.66)
	No	53 (88.3%)	143 (92.9%)	
	Total	60 (100%)	154 (100%)	

TB: Tuberculosis. Mantel-Haenszel odds: 3.57 (1.65-7.65)

Table 4: Logistic regression model showing factors associated with TB

Characteristics	Categories	Adjusted odds ratio (95% confidence interval)
Close contact with a case of TB during childhood		4.52 (2.02-10.11)*
Recent close contact with a case of TB	Yes	4.83 (2.08-11.20)*
Diabetes mellitus	Present	2.12 (1.19-3.77)*
Socioeconomic status	Lower	2.13 (1.14-3.92)*
Cigarette smoking	More than 10 cigarettes/day	3.47 (1.29-9.34)*
	<10 cigarettes/day	1.96 (0.88-5.37)
	Not current smoker	1
Alcohol consumption	More than 10 standard drinks/week	2.94 (1.35-6.43)*
	<10 standard drinks/week	1.36 (0.67-2.78)
	Not current alcoholic	1

*P<0.05. TB: Tuberculosis

we also observed that half of the cases reporting history of contact reveal that their contact dates back to childhood, not recent past. In the study sample with approximately 65% of the subjects being above 45 years, "childhood contact" is too far temporally, but it is significantly associated with active disease. Recall after long time may be challenging, but that applies to the cases and controls equally. Smoking, consumption of alcohol, and low socioeconomic status were also significantly associated with active TB. There was a qualitative interaction between diabetes and close contact with a TB case during childhood.

Community studies have shown that diabetes is highly prevalent in Kerala.[4,5] In an earlier study, we have reported that approximately 44% of the patients with TB in Kerala are diabetic.[6] In this study also we observed that more than 40% of the cases are diabetic. *Mycobacterium tuberculosis* may remain dormant in human body for years following a primary infection and may get reactivated under favorable conditions. Pathogenesis of latent TB infection (LTBI) and reactivation TB have been explained by science. The role of diabetes in reactivation has also been explained.[12-14] Our study has proved that in Kollam district, diabetes plays an important role in the development of TB among those exposed to TB in the childhood.

Annual risk of tuberculosis infection in Kerala has been estimated to be at low levels.[7] Notification of microbiologically confirmed TB cases in the state is among the lowest in the country. Childhood TB notification is also very low, of which the confirmed segment is negligible.[2] Age distribution of the confirmed new TB cases among the notified shows a right

Table 5: Final logistic regression model showing factors associated with TB

Characteristics	Categories	Adjusted odds ratio (95% confidence interval)
Close contact with a case of TB during childhood	Yes	15.88 (3.21-78.55)*
Recent close contact with a case of TB	Yes	4.81 (2.09-11.07)*
Diabetes mellitus	Present	1.64 (1.04-3.06)*
Close contact with a case of TB during childhood × diabetes mellitus	Interaction term	7.37 (1.18-50.29)*
Socioeconomic status	Lower	2.16 (1.16-4.03)*
Cigarette smoking	More than 10 cigarettes/day	3.32 (1.27-8.96)*
	<10 cigarettes/day	1.87 (0.76-5.87)
	Not current smoker	1
Alcohol consumption	More than 10 standard drinks/week	2.91 (1.33-6.37)*
	<10 standard drinks/week	1.52 (0.73-3.10)
	Not current alcoholic	1

*P<0.05. TB: Tuberculosis

skewing, the peak moving from 35 to 44 years to 55 to 64 years over a period of 20 years. In Kollam district, apart from risk factors such as smoking, consumption of alcohol, and low SES, TB may also be identified as a disease of middle-aged diabetics particularly exposed to TB during their childhood.

Many studies have shown that diabetics appear to have alterations in innate immunity with reduction in *Mycobacterium tuberculosis* phagocytosis, expression of genes that contribute to *Mycobacterium tuberculosis* containment or antigen presentation, and secretion of antimycobacterial peptides. Peripheral blood monocytes may also have defects in cell trafficking.[15,16] While DM may first induce immune defects and then predispose to TB, diabetics with TB may also share similar genetic or acquired deficiencies that simultaneously predispose them to both diseases.

The majority of those who developed TB had their childhood in an era where chemoprophylaxis for household childhood contacts of TB did not exist. This study highlights the importance of treating LTBI among children who are household contacts of TB. Kerala is treating, as guided by RNTCP, the childhood household contacts of pulmonary TB for the past one and a half decade.

Diabetes epidemic poses a serious challenge to the health system all over the world. Epidemiology of TB could be redefined by diabetes, like what HIV did a few decades ago. To curtail this menace, we suggest the state should think of a few policy revisions. First, all diabetics should be screened periodically for history of contact with TB and for TB symptoms, and those with symptoms should be subjected to a high sensitivity confirmation test. Second, diabetics with history of exposure to TB but without current symptoms may be screened for latent TB infection and those who are positive may be offered treatment for LTBI. We agree that more evidences may be generated to support our hypothesis, and cost-effectiveness of these interventions needs to be studied further.

The findings of our study highlight the importance of primary care practitioners eliciting the history of household contact with a case of TB, including that occurred during childhood in high TB-prevalent communities. This practice is especially important for primary care physicians detecting and manging diabetes in settings where there is considerable prevalence of diabetes and TB. Equally important is testing for diabetes among those with TB. Bidirectional screening in primary care settings may offer an early opportunity to control the dual epidemic due to diabetes and TB.

The strengths of the study are its design, a community-based setting, and rigorous standardized method for data collection. The study selected age- and gender-matched neighborhood controls. By selecting neighborhood controls, many attributes including environmental exposure and access to health services are also likely to get matched. However, the results might have been biased by recall and reporting by subjects. There is a possibility of misclassification of diabetes status, since we did not use laboratory tests to diagnose DM, but relied on previous records and self reports, but we believe that this would be nondifferential. Residual confounding may remain. We also recommend further studies investigating how TB risk varies by type, duration, and severity of DM, for a more thorough understanding of the association. The bacterial factors associated with the immunopathogenesis of TB and DM need to be explored in further studies. The interaction of diabetes with childhood exposure to TB provides opportunity for scientists to gain further insights into the pathogenesis of TB.

Conclusion

Close contact with a case of TB, presence of DM, lower SES, smoking, and alcohol consumption were associated with active TB in Kollam. Having close contact with a case of TB during childhood and development of DM in later life together are significantly associated with active TB in the study population. The study calls for a few policy decisions regarding active screening of TB among people with diabetes in the state. The findings also direct further studies to confirm and explore mechanisms of interaction of diabetes with childhood exposure to TB.

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Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Global Tuberculosis Report. Geneva: WHO. 2018.
2. Central TB Division. TB India 2018. Revised National TB Control Programme Annual Status Report Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Available from: http://www.tbcindia.nic.in/pdfs/RNTCP%20TB%20India%202011.pdf. [Last accessed on 2018 Oct 09].
3. Raman Kutty V. Historical analysis of the development of health care facilities in Kerala State, India. Health Policy Plan 2000;15:103-9.
4. Raman Kutty V, Joseph A, Soman CR. High prevalence of type 2 diabetes in an urban settlement in Kerala, India. Ethn Health 1999;4:231-9.
5. Menon VU, Kumar KV, Gilchrist A, Sugathan TN, Sundaram KR, Nair V, *et al.* Prevalence of known and undetected diabetes and associated risk factors in central Kerala–ADEPS. Diabetes Res Clin Pract 2006;74:289-94.
6. Balakrishnan S, Vijayan S, Nair S, Subramoniapillai J, Mrithyunjayan S, Wilson N, *et al.* High diabetes prevalence among tuberculosis cases in Kerala, India. PLoS One 2012;7: e46502.
7. Kumar S, Radhakrishnan, Chadha VK, Jeetendra R, Kumar P, Chauhan LS, *et al.* Prevalence of tuberculosis infection among school children in Kerala. Indian J Tuberc 2009;56:10-6.
8. Narasimhan P, Wood J, MacIntyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med 2013; doi: 10.1155/2013/828939.
9. Directorate of Health Services Kerala state (2011). Non-communicable diseases Available from: http://arogyakeralam.gov.in/index.php/programmes/ncd. [Last accessed on 2018 Oct 23].
10. Mangal A, Kumar V, Panesar S, Talwar R, Raut D, Singh S. Updated BG Prasad socioeconomic classification, 2014: A commentary. Indian J Public Health 2015;59:42-4.
11. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: A systematic review and meta-analysis. Eur Respir J 2013;41:140-56.
12. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. Diabetes Res Clin Pract 2014;106:191-9.
13. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Med 2008;5:e152.
14. Restrepo BI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis (Edinb) 2013;93:S10-4.
15. Restrepo BI, Twahirwa M, Rahbar MH, Schlesinger LS. Phagocytosis via complement or Fc-Gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. PLoS One 2014;9:e92977.
16. Gomez DI, Twahirwa M, Schlesinger LS, Restrepo BI. Reduced *Mycobacterium tuberculosis* association with monocytes from diabetes patients that have poor glucose control. Tuberculosis (Edinb) 2013;93:192-7.