Original Article

Co-morbidity of Diabetes and Tuberculosis can Affect the Results of Treatment; A Case Control Study in Iran

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Abstract

***Background and Purpose*:** Several evidences have shown some synergistic effect of diabetes co-morbidity on the tuberculosis (TB) treatment results, while some other studies have not found such associations. This study aimed to investigate the relationship between TB-diabetes co-morbidity and outcomes of TB treatment.

Materials and Methods :The research population in this case control study were patients with smear positive tuberculosis. The cases were 158 patients with TB and diabetes selected by consensus method, while controls were 316 patients randomly selected from TB patients without diabetes.

***Results*:** Frequency of unfavorable outcome among cases was higher than among controls (7.6% vs 7.3% respectively, p-value =0.901). Multivariate logistic regression models showed that the odds ratios for adverse treatment outcome, death, treatment failure, positive smear after the intensive phase of treatment and high grade positivity (2+ & 3+) were 0.97(0.45- 2.06), 0.97(0.42-2.24), 0.91(0.17-4.85), 1.39(0.79- 2.44) and 2.57(0.83-7.92) respectively. Moreover, treatment adverse outcomes among patients with drug complications (22.2% vs. 6.5%, p-value =0.010) and rural residents (10% vs 4.9% respectively, p-value=0.037) were significantly higher than those among patients without complication and urban residents respectively.

***Conclusion*:** Although we did not observe any significant association between TB-diabetes co-morbidity and treatment results, there was a significant effect measure regarding the effect of smear positivity at the end of the intensive phase of treatment, especially high grade of smear positivity. Because of probable bias in the classification of the exposure, screening of TB patients regarding diabetes mellitus at the beginning of the treatment is recommended.

Keywords: Tuberculosis; Diabetes; Death; Treatment Failure

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1. *Introduction*

During the recent years, tuberculosis (TB) has reduced in the high income countries; however, it has still a high burden in countries with high HIV infection, malnutrition, populated countries and those with poor control situation (1). Increasing trend of type 2 diabetes especially in the endemic regions, introduced diabetes as a newly emerged risk factor (2) and a new threat for the global public health (3). Diabetes is associated with immunodeficiency (4), so that incomplete response to the initial mycobacterial infection and consequently the delayed acquired immune response to the infection can increase the susceptibility of diabetic patients to tuberculosis (3). Diabetes is responsible for 15% of the TB burden and one of the main risk factors for unfavorable outcomes of the TB treatment (5). Recent evidences have reported that diabetes has the main role in developing adverse outcomes of the TB treatment, and it is associated with increased death during TB treatment. (6).

Most of the studies carried out regarding the interaction between tuberculosis and diabetes mellitus have focused on the effect of diabetes on developing tuberculosis and also on the results of the TB treatment. Different results have been reported from these studies in different countries. Results of a systematic review indicated that diabetes caused three folds increase in the risk of tuberculosis (7). The primary studies in this systematic review reported effect measures from no effect to eight folds increased risk. A meta-analysis study reported prevalence of diabetes among TB patients in Sub-Saharan Africa as of 9% (8), while another meta-analysis carried out in global setting including 2291571 population, estimated the prevalence of diabetes among TB patients as of 15.3% (95% confidence interval: 2.5- 36.1) in the world and 17.5% (95% confidence interval: 13.3- 22.1) in the Middle East and North Africa. The corresponding figure for 11 Iranian studies was estimated as of 17.85 (95% confidence interval: 12.5- 23.8) (9). In India, Sharma et al. found that 13.1% of the TB patients were diabetics (10). It should be noted that these primary studies had different definitions for diabetes.

There are a lot of controversies in the impact of diabetes on the results of TB treatment. Findings of a review study showed that diabetes increased the risk of treatment failure, death and relapse of tuberculosis (11). However, in the study carried out by Kazempour et al., the rate of death among TB patients with diabetes was the same as that of among non-diabetic TB patients (12). In the study conducted by Nandakumar et al. in India, the prevalence of unfavorable treatment outcomes among diabetic, non-diabetic and unknown diabetic TB patients was 17%, 13%, and 23%, respectively (13). In addition, Martínez-Rodríguez in Cuba reported that 5.4% of diabetic and 7.1% of non-diabetic TB patients experienced death during the treatment (p=0.79) (14).

It seems that different methodological limitations, especially definition criteria, play a main role in the controversies in the results of different studies regarding co-morbidity of diabetes and tuberculosis, and the treatment results. This study aimed to investigate the association between diabetes mellitus and treatment outcomes among smear positive TB patients in North of Iran. The other

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objective was to focus on the importance of the screening of diabetes among TB patients.

2. *Materials and Methods*

This case control study was carried out among patients with smear positive tuberculosis diagnosed and treated from 2005 to 2017 in Mazandaran University of Medical Sciences, Sari, Iran. The cases were all TB patients with history of diabetes mellitus entered into the study by census method. Controls were randomly selected from TB patients without history of diabetes mellitus. The number of controls (316) was twice the number of cases (158). Controls were matched with cases based on age group, year of beginning the treatment and the treatment center.

Required data for the current study was collected from TB registry software of Mazandaran University of Medical Sciences in excel format. The first outcome was favorability of the treatment results. Favorable outcome referred to patients with negative sputum smear at the end of the treatment (successive treatment), while patients with treatment failure or death were considered as unfavorable outcome. The second outcome investigated in this study was the conversion (results of the sputum smear test at the end of the intensive treatment phase).

All collected data were refined before statistical analysis. Data analysis was performed using SPSS Software, version 24. Conversion, treatment success, treatment failure, and death during the treatment were described by percent frequency. Comparing these indicators between cases and controls was performed using Chi square test. Crude and adjusted odds ratios for these factors were also estimated based on univariate and multivariate logistic regression models. P value less than 0.05 was considered statistically significant.

3. *Results*

Of 2075 TB patients during the study period, 239 patients were excluded from the research population due to unknown status of the treatment outcome (including 29 transferred out, 135 under treatment, 63 treatment absence, and 12 other cases). In addition, 212 patients were excluded due to unknown status of diabetes mellitus. Finally, 1624 smear positive TB patients were remained in the study including 158 TB patients with diabetes (cases). Of patients without history of diabetes mellitus, 316 patients were randomly selected as controls.

Frequency of unfavorable outcome among cases was higher than among controls (7.6% vs. 7.3% respectively, p-value =0.901). However, the difference was not statistically significant. These differences were also non-significant in the subgroups, such as gender (p-value =0.263), history of previous treatment (p-value =0.236), and nationality (p-value =0.265). Frequency of unfavorable outcomes was also higher among patients with adverse drug reactions (22.2% vs 6.5%, respectively, p-value=0.010), and rural residents (10% vs. 4.9%, respectively, p-value=0.037) (Table 1). Crude and adjusted odds ratios (95% confidence intervals) for unfavorable outcomes were 1.06 (0.51- 2.19) and 0.97 (0.45- 2.06), respectively (Table 2).

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Table 1. Treatment results among different subgroups

Variables		n(total)	Result of treatment		P-value
			Favorable; n(%)	Unfavorable; n(%)	
Exposed with diabetes	No	316	293(92.7%)	23(7.3)	0.901
	Yes	158	146(92.4)	12(7.6)	
Gender	Male	299	280(93.6)	19(6.4)	0.263
	Female	175	159(90.9)	16(9.1)	
Drug complications	No	447	418(93.5)	29(6.5)	0.010
	Yes	27	21(77.8)	6(22.2)	
Residence area	Urban	243	231(95.1)	12(4.9)	0.037
	Rural	231	208(90)	23(10)	
History of anti-TB treatment	No	451	419(92.9)	32(7.1)	0.236
	Yes	23	20(87)	3(13)	
Nationality	Iranian	470	436(92.8)	34(7.2)	0.265
	Non-Iranian	4	3(75)	1(25)	

Table 2. Impact of diabetes on treatment results of smear positive tuberculosis in present and other studies (univariate and multiple logistic regression models)

First author	Study type	Country	Death (OR/RR/HR)		Failure (OR/RR/HR)		Unfavorable result (failure and death), (OR/RR/HR)		Diabetes criteria
			crud	Adjusted	Crud	Adjusted	crud	Adjusted	
Present study*	Case-control	Iran	1.11(0.50-2.48)	0.97(0.42-2.24)	0.80(0.15-4.19	0.91(0.17-4.85)	1.06(0.51-2.19)	0.97(0.45-2.06)	History of diabetes(self-reported)
Dooley, 2009 (15)	Retrospective cohort	Maryland	2(0.74-5.2)	6.5(1.1-38)	-	-	-	-	History of diabetes, taking oral hypoglycemic, or had a non-fasting glucose measurement of greater than 200
Jumaev, 2016 (16)	Retrospective cohort	Uzbekistan	3.2(1.9-5.5)	-	3.7(2-6.8	-	1.5(1.1-1.9)	-	Clinical screening for symptoms and signs
Kazempour Dizaji, 2018 (12)	Retrospective cohort	Iran	1(0.6-1.7)	3(1-8.3)	-	-	-	-	Unknown
Nandakumar, 2013 (13)	Retrospective	India	-	-	-	-	1.25(1.02-1.53)	0.99(0.81-1.21)	Screening for DM
Martínez-Rodríguez, 2016 (14)	Retrospective cohort	Cuba	0.82(0.26-2.60)	-	-	-	-	-	Unknown
Mukhtar, 2018 (17)	Prospective cohort	Pakistan	-	-	-	-	2.60(1.48-4.56)	2.70(1.30-5.59)	Self-report and screening with a Random blood glucose test
Satung, 2016 (18)	Retrospective cohort	Thailand	-	-	-	-	1.09(0.99-1.20)	1.04(0.89-1.20)	Mostly based on a medical history of having an abnormal fasting blood sugar level

***Adjusted based on gender, Adverse drug reactions, Residence area, History of anti-TB treatment and Nationality, OR: Odds ratio. RR: Risk Ratio, HR: Hazard Ratio**

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Frequency of treatment failure among cases and controls was found to be 1.3% and 1.6%, respectively (p-value =0.794). Death rate among cases and controls was 6.3% and 5.7%, respectively (p-value =0.789). Meanwhile, crude and adjusted odds ratios (95% confidence intervals) for death were 1.11(0.50-2.48) and 0.97(0.42-2.24), respectively. Corresponding odds ratios for failure rate were 0.80(0.15- 4.19) and 0.91(0.17-4.85), respectively (Table 2).

Positive conversion rates among cases and controls were 15.2% and 13%, respectively (p-value =0.509). Crude and adjusted odds ratios for being positive sputum smear after the intensive treatment phase were 1.20(0.70- 2.07) and 1.39(0.79-2.44), respectively. Moreover, crude and adjusted odds ratios for being high grade (2^+ or 3^+) sputum smear at this phase were 2.39(0.79- 7.26) and 2.57(0.83- 7.92), respectively.

4. *Discussion*

Our results showed that although co-morbidity of TB and diabetes mellitus caused 3%, 9% and 3% decreased chance of unfavorable treatment results, death and treatment failure, respectively, these observed associations were not statistically significant. In addition, 39% and 2.57 folds increased odds of conversion rate, and the remaining high grade smear positivity after the intensive phase of treatment was also, respectively, non-significant.

Similar to our results, in a study carried out by Dooley et al. among 255 TB/diabetes and non-diabetic TB patients, the observed odds ratios for death were not statistically significant. History of having diabetes mellitus, taking drugs or having blood sugar more than 200 were considered as diagnostic criteria for diabetes mellitus in that study (15). There was low misclassification of exposure in the mentioned study due to appropriate and acceptable diagnostic criteria.

Jumaev et al. found lower success rate among TB patients with diabetes than those without diabetes. They applied clinical screening for symptoms and signs as diagnostic criteria (16). Similarly, Mukhtar et al. in Pakistan showed significantly 2.70 folds higher risk of unfavorable treatment results among diabetic TB patients. The diagnostic criteria in the study of Mukhtar were self-reporting as well as random screening with FBS test (17). Results of these two studies were in contrast to our findings. It should be noted that both studies had used larger sample sizes (176 cases and 1643 controls in Jumaev study and 113 cases and 501 controls in Mukhtar study).

Contrary to our expectation, Satung et al. in Thailand (18) and Martínez-Rodríguez in Cuba (14) found lower death rates among TB patients with diabetes compared to control groups. However, the observed differences were not statistically significant. Chance of unfavorable treatment outcomes among diabetic and non-diabetic TB patients in Nandakumar study was the same. They randomly tested the study samples to provide an estimate of diabetes mellitus among cases and controls (13).

Of studies carried out in Iran regarding the role of TB/diabetes co-morbidity in treatment results, Kazempour Dizaji (12) and Shahrezaei et al. (19) did not find any difference between the cases and controls regarding death rate. It should be noted that the unknown diagnostic criteria was one of the main challenges in the methodology of many of the studies.

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Therefore, any comparison between the results of different studies can be very difficult. The results of a meta-analysis conducted by Baker showed that diabetes caused 69% increased risk of death and failure rate among TB patients. However, the primary studies used in this meta-analysis had applied different definitions of diabetic patient (11).

Although some of the above evidences did not find significant associations between diabetes and TB treatment outcomes, the role of diabetes in the results of anti-TB treatment is undeniable. This association is very strong, so that it can affect the incidence of tuberculosis. For example, the results of a meta-analysis showed that diabetes mellitus increased the risk of tuberculosis as of 3.59 (2.25- 5.73) folds in case control studies and 2.09 (1.71- 2.55) folds in cohort studies (20). It has also reported that having diabetes mellitus can significantly increase the risk of anti-TB drug resistance (21).

Although Dooley et al. (15) and Satung et al. (18) found that the conversion rate among TB patients with and without diabetes mellitus was the same, Shariff and Safian in Malaysia showed that diabetes increased the risk of sputum smear positivity rate after the intensive phase of treatment more than four folds indicating that diabetes can be an independent risk factor for remaining positive smear two months after beginning anti-TB treatment (22).

In the study carried out by Viswanatha et al., mean duration of sputum smear conversion was compared between TB patients with and without diabetes. They found that diabetic patients had longer conversion time than non-diabetic ones (23), the result which was in contrast to our results.

Probable misclassification of exposure for specifying case/control groups was one of the limitations of the current study. Because in the national TB control program in Iran, TB patients are not screened for diabetes mellitus. While screening of all TB patients for diabetes at the beginning of the treatment has been strongly recommended by World Health Organization (24).

Limitation

In the present study, the diagnostic criteria were applied for classification of cases and controls, and it was suggested to screen all TB patients for diabetes mellitus at the beginning of treatment based on WHO recommendations.

5. Conclusion

In conclusion, the results of our study showed that co-morbidity of diabetes and tuberculosis had no effect on the treatment results. Considering the findings of the previous evidences mentioned, the negative role of diabetes on TB treatment outcomes and also methodological limitations of the present study, such as diagnostic criteria applied for classification of cases and controls, it is suggested to screen all TB patients for diabetes mellitus at the beginning of treatment based on WHO recommendations.

Abbreviations

TB: Tuberculosis

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Authors' contributions

M Kh amd M M were involved in concept of the study. M A, M A, A N analysed the data.

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K H, M Z, F R and M KH were involved in writing the article.

Availability of data and materials
Required data for the current study was collected from TB registry Software of Mazandaran University of Medical Sciences

Declarations

Ethics approval and consent to participate
(IR.MAZUMS.REC.1397.1563)

Consent to publications
Not applicable

Conflicts of Interest
The authors declare that there is not conflict of interest.

References

1. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. The Lancet Infectious Disease. 2009;9(12):737-46.
2. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. Diabetes Research and Clinical Practice. 2014;106(2):191-9.
3. Martinez N, Kornfeld H. Diabetes and immunity to tuberculosis. Eurpean Journal of Immunolgy. 2014;4 26-617:3)4.
4. Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. Immunology. 2017;152(1):13-24.
5. Shewade HD, Jeyashree K, Mahajan P, Kumar AMV. National guidelines on screening for diabetes among patients with tuberculosis in India: Need for clarity and change in screening cut off?. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017;11 Suppl 2:929-30.
6. Workneh MH, Bjune GA, Yimer SA. Diabetes mellitus is associated with increased mortality duringtuberculosis treatment: a prospective cohort study among tuberculosis patients in South-Eastern Amahra Region, Ethiopia. Infectious Diseases of Poverty. 2016;5:22.
7. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Medicine. 2008;5(7):e152.
8. Alebel A, Wondemagegn AT, Tesema C, Kibret GD, Wagnew F, Petrucka P, et al. Prevalence of diabetes mellitus among tuberculosis patients in Sub-Saharan Africa: a systematic review and meta-analysis of observational studies. BMC Infectious Disease. 2019;19(1):254.
9. Noubiap JJ, Nansseu JR, Nyaga UF, Nkeck JR, Endomba FT, Kaze AD, et al. Global prevalence of diabetes in active tube rculosis: a systematic review and meta-analysis of data from2·3 million patients wi th tuberculosis. Lancet Global Health. 2019;7(4): e448-e460.
10. Sharma D, Goel NK, Sharma MK, Walia DK, Thakare MM, Khaneja R. Prevalence of Diabetes Mellitus and its Predictors among Tuberculosis Patients Currently on Treatment. Indian journal of community medicine. 2018;43(4):302-306.
11. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Medicine. 2011;9:81.
12. KazempourDizaji M, Kazemnejad A, Tabarsi P, Zayeri F.Risk Factors Associated with Survival of Pulmo nary Tuberculosis. Iranian Journal of Public Health. 2018;47(7):980-987.
13. NandakumarK V, Duraisamy K, Balakrishnan S, M S, S JS, Sagili KD, et al.Outcome of tuberculosis treatment in pat ients with diabetes mellitus treated in the revised national tuberculosis control pro gramme in Malappuram District, Kerala, In dia. PLoS One. 2013 ;8(10):e76275.
14. Martínez-Rodríguez A, Gonzalez-Díaz A, Armas L Sanchez L, Martínez-Morales MA, González-Ochoa E. Survival of Cuban Patients with Pulmonary Tuberculosis (2009–2010). Medicc Review. 2016; 18 (1–2):22-27.
15. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatmentoutcomes of patients with active tuberculosis. The American Journal of tropical medicine and hygene. 2009;80(4):634-9.
16. Jumaev G, Tillashaykhov M, Muazzamov B, Radjabov B, Gadoev J, Alikhanova N, et al. Prevalence, characteristics and treatment outcomes of all patients with new tuberculosis and diabetes mellitus in 2011–

[DOI: 10.18502/jhs.v10i3.10519]

2013, Bukhara, Uzbekistan. Public health panorama. 2016;02 (01), 40 - 47.
17. Mukhtar F, Butt ZA. Risk ofadverse treatment outcomes among newpulmonary TB patients co-infected with diabetes inPakistan: A prospective cohort study. PLoS ONE. 2018; 13(11): e0207148.
18. Satung J, Kaewkungwal J, Silachamroon U, Pokaew P, Rattanajiamrangsree S, Kasetjareon Y, et al. Treatment outcomes among diabetic patients with tuberculosis in Thailand. The Southeast Asian journal of tropical medicine and public health. 2016;47(6):1209-20.
19. Shahrezaei M, Maracy MR, Farid F. Factors affecting mortality and treatment completion of tuberculosis patients in Isfahan Province from 2006 to 2011. International Journal of Preventive Medicine. 2015;6:91.
20. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ (2017) Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. PLoS ONE. 12(11): e0187967.
21. Perez-Navarro LM, Fuentes-Dominguez FJ, Zenteno-Cuevas R. Type 2 diabetes mellitus and its influence in the development of multidrug resistance tuberculosis in patients from southeastern Mexico. Journal of Diabetes and its Complications. 2015;29(1):77-82.
22. Shariff NM, SafianN. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmon ary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. International journal of mycobacteriology. 2015;4(4):323-9.
23. Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis--a report from South India. Journal of diabetes and its complication. 2014;28(2): 162-5.
24. Adepoyibi T, Weigl B, Greb H, Neogi T, McGuire H. New screening technologies for type 2 diabetes mellitus appropriate for use in tuberculosis patients. Public Health Action. 2013;3(Suppl. 1):S10–17.

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