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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

The Effect of Smoking on Treatment Outcome of Multidrug-Resistant Tuberculosis

Çok İlaca Dirençli Tüberküloz Olgularında Sigara İçiciliğinin Tedavi Başarısı ile İlişkisi

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Abstract

OBJECTIVE: Smoking appears to be causally associated with active tuberculosis (TB). However, there is insufficient evidence linking passive or active tobacco smoking with certain important outcomes, such as treatment response in multidrug-resistant TB (MDR-TB).

MATERIAL AND METHODS: The present study is a retrospective study including seconder analysis of a cohort of hospitalised patients with MDR-TB treated in our clinic between February 2000 and March 2005. All patients were followed with monthly sputum smears for acid-fast bacilli, Löwenstein-Jensen cultures and a chest X-ray during treatment. The radiologic involvement of disease was categorised as extensive or limited.

RESULTS: Of 103 MDR-TB patients, 81 (78.6%) were male and the mean age was 40.50±13.50 years (range 14-72) and all were HIV-negative. Extensive radiologic involvement was evident in 22 cases (21.4%). Among the cohort, 34 (33%) were current smokers, and 27 (26.2%) were former smokers. In the group with a successful outcome, the mean cigarette consumption was 14.7±19.9 pack-years, whereas in the group with a poor outcome it was 40.5±44.4 and the difference was statistically significant (p=0.0001).

CONCLUSION: Prospective clinical studies are required to evaluate whether aggressive smoking cessation intervention, in addition to chemotherapy, will improve survival of patients with MDR-TB.

KEY WORDS: Smoking, tuberculosis, treatment success

Özet

AMAÇ: Sigara içiciliğinin aktif tüberküloz ile sebepsel ilişkili olduğu sonucu için yeterince kanıt var gibi görünüyor ancak aktif ya da pasif sigara içiciliğini, Çok İlaca Dirençli Tüberkülozun (ÇİD-TB) tedavi sonucu gibi bazı önemli durumlarla ilişkilendiren yeterince bilgi mevcut değildir.

GEREÇ VE YÖNTEMLER: Bu çalışma, Şubat 2000-Mart 2005 tarihleri arasında kliniğimizde yatarak tedavi edilen ÇİD-TB olgularından oluşan bir kohortun ikincil analizlerini içeren retrospektif bir çalışmadır. Tedavi boyunca tüm hastalar, her ay yapılan aside resistant basil için balgam yayma ve Löwenstein- Jensen kültür tetkiki ve ayrıca akciğer radyografisi (PA Grafi) ile takip edilmiştir. Hastalığın radyolojik tutulumu, PA grafideki görüntüye göre yaygın veya sınırlı olarak sınıflandırılmıştır.

BULGULAR: Yüz üç ÇİD-TB olgusunun %78,6'sı erkek (n=81); yaş ortalaması 40,5±13,5 (14-72) idi. Hepsi HIV (-) olgulardı. Olguların %21,4'ünde (n=22) yaygın hastalık mevcuttu. Olguların %33'ü (n=34) aktif içici, %26,2'si (n=27) eski-içiciydi. Tedavi başarısı sağlanan grupta sigara kullanımı, ortalama 14,7±19,9 paket-yıl; tedavi başarısızlığı grubunda 40,5±44,4 paket-yıldı; fark istatistiksel olarak anlamlıydı (p=0,0001).

SONUÇ: ÇİD-TB tedavisi ile birlikte ciddi sigara bırakma müdahalesinin hastaların yaşam olasılığı üzerindeki etkilerini inceleyen klinik çalışmalara gereksinim vardır.

ANAHTAR SÖZCÜKLER: Sigara, tüberküloz, tedavi başarısı

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) that leads to the transmission of resistant strains among the population is a contemporary weakness of TB control programmes [1]. Patients infected with multidrug-resistant strains are less likely to be cured [2]. The treatment is much more toxic and expensive (about 700 times the cost) than for patients with drug-sensitive organisms [3]. As these patients are difficult to treat, they can remain infectious for a prolonged period and are of great epidemiological importance.

A high prevalence of tobacco use has been noted since 1918 in studies looking at TB risk factors [4]. There appears to be sufficient evidence to conclude that smoking is causally associated with active TB. Taken together, smoking (both current and former, passive and active) appears to increase the risk of being infected with M. tuberculosis and of developing TB, as well as the severity of disease and the risk of death [5-8]. Feng et al., [9] recently showed in a physiologically-relevant animal model that cigarette smoke exposure increased the bacterial burden and inhibited the pulmonary T-cell response

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in mice infected with *M. tuberculosis*. Increased risk of TB associated with smoking has been reported to be more prominent among older adults, individuals with a lower education level and those with a history of alcohol consumption [10]. In a study by Wen and colleagues [11], the mortality rate of smokers was as much as nine times greater than that of people who had never smoked, and quitting lowered the risk substantially. To highlight the importance of smoking cessation in TB management, a recent mathematical modelling analysis projected the effects of tobacco smoking on TB control worldwide. The model estimated that aggressive tobacco control (achieving an annual 1% decrease in smoking prevalence until the point of eradication) would avert 27 million smoking-attributable deaths from TB by 2050 [12].

As reviewed by Slama et al., [5] there are two cohort studies, six case-control studies and two cross-sectional studies, all of high scientific quality, that have each shown at least one statistically significant relationship between TB and active exposure to tobacco smoke. However, there is insufficient evidence from this body of literature for accurately measuring the effect of passive or active tobacco smoking on the outcome of drug-resistant TB, and additional studies are necessary to gauge the influence of this important factor on the disease process. Therefore, the present study was conducted to explore the impact of smoking on the radiological and clinical manifestations, as well as the outcome, of MDR-TB.

MATERIAL AND METHODS

Setting and Participants

This was a retrospective study of a cohort that has previously been described [13]. Briefly, participants were hospitalised MDR-TB patients treated in our clinic between February 2000 and March 2005. The hospital is located in Istanbul, an area with the highest TB incidence of all cities in its region and it is one of the main referral hospitals for difficult cases from all regions in Turkey.

Diagnosis and Treatment

The patients in this study could be classified into three groups according to their diagnosis and treatment, and all met the criteria for diagnosis of MDR-TB [14].

1. New cases of TB who received 'first-line' drugs under direct observation at the hospital. These medications, as specified by the National TB Control Programme, included isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E) or streptomycin (S) during the initial phase, and H and R during the continuation phase. Patients had a positive smear in the fifth month after initiation of treatment (considered as failure) and resistance against H and R revealed with a drug susceptibility test.

2. New cases of TB who received first-line drugs without direct observation, and whose treatment was considered a failure after a positive smear following an eight month re-treatment regimen (2HRZES+1HRZE+5HRE) and due to resistance to at least H and R demonstrated with the initial drug susceptibility test.

3. Patients with history of previous infections (relapse or defaulter) whose treatment was considered a failure after a positive smear following an eight month re-treatment regimen (2HRZES+1HRZE+5HRE) and due to resistance to at least H and R demonstrated with the initial drug susceptibility test.

Some MDR-TB patients were treated with second-line drugs including aminoglycosides (amikacin, capreomycin), quinolone derivatives (ofloxacin, ciprofloxacin), prothionamide or cycloserine, and first-line drugs (for example, Z and E) were occasionally included in the new regimen if susceptibility was suspected. If quinolone derivatives and prothionamide had already been used in a previous regimen, drugs such as clofazimine, para-aminosalicylic acid (PAS), thioacetazone, amoxicillin-clavulanic acid and capreomycin were included in the regimen [15,16]. Aminoglycosides were administered five days a week until three months after culture conversion. All patients were hospitalised during aminoglycoside administration and received drugs under direct observation.

The duration of treatment for MDR-TB cases was 18 months after achieving culture conversion, but this was extended to 24 months if there was no major drug in the regimen. All patients were followed monthly with a sputum smear for acid-fast bacilli, Lowenstein-Jensen cultures and a chest X-ray (CXR). At the end of the treatment, all patients were evaluated with cultures to evaluate the results. CXRs were reviewed by two pulmonary specialists, and if there was a discrepancy in the interpretation, the case was further reviewed by another chest specialist blinded to the results. The location of lesions and the presence of cavities were recorded.

All patients were given an informed consent document describing the drugs in use, possible adverse affects and the duration of treatment, and they were asked to sign before the initiation of treatment. The study was approved by the local Education and Training Programme Committee of the hospital. HIV serology was performed for every patient.

Definitions

Primary resistance was defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, denied having received any prior anti-tuberculous treatment (for as long as one month). Acquired resistance was defined as the presence of resistant isolates in those who admitted having been treated for TB for one month or more [17]. Radiologic involvement of disease was categorised as extensive or limited according to CXRs. Extensive involvement was defined as one or both of the following; a sum of cavity diameters totalling 15 cm or dense infiltrates involving more than 75% of lung fields [18].

Treatment outcome was classified as successful (cure) or poor (treatment failure, defaulter or death), and the classification was performed according to the recommendations of the World Health Organization [19]. Cure was defined as a negative smear and cultures throughout at least 18 months of treatment (or 24 months, in the absence of first-line drugs). If only one positive culture was reported during that time, and there was no concomitant evidence of deterioration, a patient was still considered cured if the positive culture was followed by a minimum of three consecutive negative cultures. Treatment failure was defined as persistence of a positive smear and culture despite treatment for 18-24 months. Defaulter was defined as a failure to complete treatment for any

reason. Death could be for any reason, including TB. Relapse was defined as recurrence of a positive smear or culture after a cure.

In this study, ever-smokers included current smokers and ex-smokers. A current smoker was defined as a person who smoked daily or occasionally during the treatment, an ex-smoker as a person who had quited before visiting the hospital, and a never-smoker as a person who had never smoked. Tobacco smoke exposure was measured according to duration and frequency of exposure and reported in 'pack-years'.

Statistical Analysis

Data were analyzed using SPSS for Windows v15.0 statistics program. Differences were evaluated using a Student's t-test for variables with normal distribution and using a Mann-Whitney U test for those without. Nominal variables were assessed by the chi-square test, and for all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Among 103 MDR-TB patients evaluated, 81 were male and 22 were female. The mean age of patients was 40.5±13.5 (14-72) years. All were HIV-negative. Most patients had only a primary school education (78.6%) and were married (81.6%). Nearly half of the cohort (45.6%) resided outside of Istanbul. A family history of TB was present in 14.6% of cases, and 9.7% had a family member with MDR-TB. Primary multidrug resistance was observed in more than one third of cases (39.8%). 28.8% of patients had at least one concomitant disease (Table 1), most commonly diabetes mellitus or chronic obstructive pulmonary disease (COPD).

Table 1. Demographic information and characteristics of subjects in the study

	N	%
Gender		
Female	22	21.4
Male	81	78.6
Education		
Primary	82	79.5
High school	17	16.5
College	4	3.9
Marital Status		
Married	84	81.6
Bachelor	19	18.4
Residency		
In Istanbul	66	54.4
Out of Istanbul	47	45.6
MDR-TB in family		
Present	10	9.7
Absent	93	90.3
Multidrug-resistance		
Primary	41	39.8
Acquired	62	60.2
Concomitant disease		
Diabetes Mellitus	17	16.5
COPD	6	5.8
Anaemia	2	1.9
Chronic Renal Failure	1	0.9
Chronic Active Hepatitis	1	0.9
Epilepsy	1	0.9
Rheumatoid Fever	1	0.9

N: number of cases, %: percent

Eighty-nine cases (86.4%) were evaluated in the group with a successful outcome. The group with poor outcome totalled 14 cases (2 defaulters, 4 treatment failures, and 8 deaths). Extensive radiologic involvement was noted in 21.4% of all cases and was more common in the group with poor outcome ($p=0.005$) (Table 2). Among all cases, 40.8% were never smokers, 33% were current smokers, and 26.2% were ex-smokers. There was no statistically significant difference in the distribution of smokers among the groups with successful or poor outcomes, but there was a correlation with the level of cigarette consumption between the two groups. The mean cigarette consumption in the group with a successful outcome was 14.7±19.9 pack-years, whereas in the group with poor outcome it was 40.5±44.4 ($p=0.0001$).

DISCUSSION

Although there is considerable evidence that smoking (both current and former, passive and active) is associated with the risk of being infected with M. tuberculosis, as well as the risk of developing TB, the severity of disease and of death, the specific link between smoking and MDR-TB has been largely ignored [5-12]. Barroso and colleagues examined this in a case-control study investigating risk factors for acquired MDR-TB, and through univariate analysis they identified an association of smoking with acquired MDR-TB [20]. In multivariate analysis ('smoking alone' was excluded), the combination of 'alcoholism and smoking' was associated with acquired MDR-TB. Ruddy et al. [21] conducted a cross-sectional study to investigate both prevalence and risk factors of drug resistance, and smoking was found to be associated with isoniazid resistance. The authors concluded that more evidence was needed to explain this association.

Previous studies of patients with TB have reported a significantly higher likelihood of default and failure in association with smoking through univariate analyses [22,23]. Investigators in Hong Kong conducted a case-control study to assess risk factors for defaulting from anti-TB treatment under a 'directly observed' treatment programme and found that current smokers were significantly more likely to default than never smokers [24]. In studies based on univariate analysis or multivariate analysis controlling for age, gender, family screening, new vs. relapse, smear status, and presence of cough, haemoptysis, or cavity, non-smokers were significantly more likely to adhere to treatment [25-29]. In the cohort study of Qazi et al., [30] current smoking was found as one of the strong predictors of delayed time to culture conversion. Controlling for initial drug resistance, alcoholism, and treatment irregularity, smokers (habitual and current) were significantly more likely to relapse than non-smokers [29].

Tobacco smoke has been reported to have various effects on the lung in both animal and human studies. More specifi-

Table 2. Univariate analysis of the factors and treatment outcome

	Successful Outcome	Poor Outcome	p value
Gender (n)			
Male	69	12	0.48
Female	20	2	
Education (n)			
Primary	69	11	0.54
High school	16	3	
University	4	-	
Residency (n)			
In Istanbul	47	9	0.42
Out of Istanbul	42	5	
Radiologic involvement (n)			
Limited	74	7	0.005
Extensive	15	7	
Smoking status (n)			
Never smoker	39	3	0.19
Former smoker	21	6	
Current smoker	29	5	
Cigarette consumption			
(Mean of pack-years)	14.7±19.9	40.5±44.4	0.0001

n: number of cases

cally, smoking has been associated with changes in pulmonary macrophages and lymphocytes that play a major role in cellular immunity [31]. Ever-smokers were more likely to have evidence of upper zone involvement, cavity and 'miliary' appearance on chest radiographs than non-smokers [32,33]. A cross-sectional study by Altet-Gomez et al., [34] revealed that after controlling for confounders including age, sex, alcohol consumption and intravenous drug use, smokers were significantly more likely to have cavitary lesions, positive bacilloscopy and pulmonary TB than non-smokers.

A limitation of the present study was that the cohort size was insufficient to permit analysis of all risk factors, and this precluded determining the effect of cigarette consumption on treatment outcome of MDR-TB through multivariate analysis. Another limitation was that the history of smoking status was self-reported and did not depend on the full definitions in the guidelines. The knowledge about smoking history was limited to the answer of the question "if they were currently smoking or not". However, if there was a responder bias in revealing smoking status, it would in theory make it more likely that smokers be misclassified as non-smokers and this would lead to an underestimation of the effects of smoking on TB.

In conclusion, understanding the impact of smoking on the outcome of MDR-TB is critically important for successful management of the disease. Patients with MDR-TB need, and should receive, counselling and assistance in quitting smoking. Prospective clinical studies are necessary to evaluate if aggressive smoking cessation intervention combined with chemotherapy will improve the survival of patients with MDR-TB.

Conflict of Interest
No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Süreyyapaşa Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions
Conception - T.K.; Design - P.P.; Supervision - T.K.; Fundings - P.P.; D.Y.D.; Ö.Y.M.; Materials - P.P.; D.Y.D.; Ö.Y.M.; Data Collection and/or Processing - D.Y.M.; Ö.Y.M.; P.P.; Analysis and/or Interpretation - P.P.; Literature Review - P.P.; Writer - P.P.; Critical Review - T.K.

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REFERENCES

1. World Health Organization. Anti-tuberculosis drug resistance in the world, Report from the WHO/IUALTD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 1997: 118-9.
2. Goble M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993;328:527-32. [CrossRef]
3. Mahmoud AMD, Michael D, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. JAMA 1993;270:65-8. [CrossRef]
4. Webb GB. The effect of the inhalation of cigarette smoke on the lungs. A clinical study. Am Rev Tuberc 1918;1:25-7.
5. Slama K, Chiang CY, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systemic review and meta-analysis. Int J Tuberc Lung Dis 2007;11:1049-61.
6. Chiang CY, Slama K, Enarson DA. Associations between tobacco and tuberculosis. Tuberc Lung Dis 2007;11:258-62.
7. Leung CC, Lam TH, Ho KS, et al. Passive Smoking and Tuberculosis. Arch Intern Med. 2010;170:278-92. [CrossRef]
8. Preez KD, Mandalakas AM, Kirchner HL, et al. Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children. Int J Tuberc Lung Dis 2011;15:1490-6. [CrossRef]
9. Feng Y, Kong Y, Barnes PF, et al. Exposure to cigarette smoke inhibits the pulmonary T-cell response to Influenza virus and Mycobacterium Tuberculosis. Infect Immun 2011;70:229-37. [CrossRef]

10. Wang J, Shen H. Review of cigarette smoking and tuberculosis in China: intervention is needed for smoking cessation among tuberculosis patients. BMC Public Health 2009;9:292-300. [CrossRef]
11. Wen CP, Chan TC, Chan HT, et al. The reduction of tuberculosis risks by smoking cessation. BMC Infectious Diseases 2010;10:156-64. [CrossRef]
12. Basu S, Stuckler D, Bitton A, Glants SA. Projected effect of tobacco smoking on worldwide tuberculosis control: mathematical modelling analysis. BMJ 2011;343:d5506. [CrossRef]
13. Karagoz T, Duman YD, Pazarli P, Moçin OY. Treatment result of multidrug resistant tuberculosis patients whose treatments were managed by a single center and with an indirect observation during whole treatment. Solunum 2009;11:1-6.
14. Maher D, Chaulet P, Spinaci S, Harries A. Treatment of Tuberculosis: Guidelines for National Programmes. World Health Organisation, Geneva, 1997.
15. Crofton J, Chaulet P, Maher P. Guidelines for the Management of Drug Resistant Tuberculosis. World Health Organization, Geneva, 1997.
16. Initial Therapy for Tuberculosis in the era of Multidrug Resistance: Recommendations of the Advisory Counsil for the Elimination of Tuberculosis. MMWR Morb Mortal Wkly Rep 1993;42:RR-7.
17. World Health Organization. Anti-tuberculosis drug resistance in the world: The WHO/IUATLD Global Project on Anti-Tuberculosis Dug Resistance Surveillance. Report 3: Prevalence and trends. Geneva, 2004 (WHO/HTM/TB/2004.343).
18. Goble M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tubeculois resistant to isoniasid and rifampin. N Engl J Med 1993;328:527-32. [CrossRef]
19. Farmer P, Kim JY, Mitnick CD, Becerra M. Protocol for the implementation of individualized treatment regimens for multidrug resistant tuberculosis in resource poor settings. In: Espinal MA (ed). Multidrug resistant tuberculosis (MDR TB): Basis for development of an evidence-based case-management strategy for MDR TB within the WHO's DOTS strategy. World Health Organization, Geneva.1999: Part 5 (Report no. WHO/TB/99.260).
20. Barroso EC, Mota RMS, Santos RO, et al. Risk factors for acquired multidrugresistant tuberculosis. J Pneumol 2003; 29: 89-97. [CrossRef]
21. Ruddy M, Balabanova Y, Graham C, et al. Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia. Thorax 2005;60:130-5. [CrossRef]
22. Santha T, Garg R, Frieden TR, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur district, South India, 2000. Int J Tuberc Lung Dis 2002;6:780-8.
23. Santha T, Renu G, Frieden TR, et al. Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India. Int J Tuberc Lung Dis 2002;7:258-65.
24. Chang KC, Leung CC, Tam CM. Risk factors for defaulting from antituberculosis treatment under directly observed treatment in Hong Kong. Int J Tuberc Lung Dis 2004;8:1492-8.
25. Al-Hajjaj MS, Al-Khatim IM. High rate of non-compliance with antituberculosis treatment despite a retrieval system: a call for implementation of directly observed therapy in Saudi Arabia. Int J Tuberc Lung Dis 2000;4:345-9.
26. Davidson H, Schluger NW, Feldman PH, et al. The effects of increasing incentives on adherence to tuberculosis directly observed therapy. Int J Tuberc Lung Dis 2000;4:860-5.
27. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis short-course chemotherapy trial: effectiveness, toxicity, and acceptability. Ann Intern Med 1990;112:397-406. [CrossRef]
28. Balbay O, Annakkaya AN, Arbak P, et al. Which patients are able to adhere to tuberculosis treatment? A study in a rural area in the northwest part of Turkey. Jpn J Infect Dis 2005;58:152-8.
29. Thomas A, Gopi PG, Santha T, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis 2005;9:556-61.
30. Qazi F, Khan U, Khowaja S, et al. Predictors of delayed culture conversion in patients treated for multidrug-resistant tuberculosis in Pakistan. Int J Tuberc Lung Dis 2011 15:1556-9. [CrossRef]
31. Carnevali S, Petruzzelli S, Longoni B, et al Cigarette smoke extract induces oxidative stress and apoptosis in human lung fibroblasts. Am J Physiol Lung Cell Mol Physiol 2003;284:955-63.
32. Leung CC, Yew WW, Chan CK, et al. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003;7:980-6.
33. Gullón Blanco JA, Suárez Toste I, Lecuona Fernández M, et al. Tobacco smoking and sputum smear conversion in pulmonary tuberculosis. Med Clin (Barc) 2007;128:565-8. [CrossRef]
34. Altet-Gomez MN, Alcaide J, Godoy P, et al. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13 038 cases. Int J Tuberc Lung Dis 2005;9:430-6.