



THE ROLE OF CIGARETTE SMOKING AND ALCOHOL CONSUMPTION IN PULMONARY TUBERCULOSIS DEVELOPMENT AND RECURRENCE

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SUMMARY – During a two-year period (2001-2003), 464 patients were treated for tuberculosis at Jordanovac Department for Lung Diseases in Croatia. Besides pulmonary tuberculosis in 97.7% of patients, patients were also treated for tuberculous pleurisy (0.9%), tuberculous laryngitis (0.6%), tuberculous meningitis (0.2%), tuberculous pericarditis (0.2%) and urogenital tuberculosis (0.4%). Out of the total number of patients, 57.3% declared themselves to be active smokers (men were predominant and made up to 80.8%) and 20.9% to be active alcohol consumers. Both risk factors, i.e. smoking and alcohol consumption, were present in 15.1% of all patients. The most common comorbidities were diabetes mellitus (30.4%), cardiac diseases (11.2%) and chronic obstructive pulmonary disease (8.0%). Lung carcinoma was the most common malignant disease (n=51), with *Mycobacterium tuberculosis* isolated in 33% of them. Seventy-two of 464 (15.5%) patients had recurrences of tuberculosis. Of these, 30.5% had one of the risk factors (20.8% were smokers and 9.7% consumed alcohol), while 32.5% of patients had both risk factors. In conclusion, cigarette smoking was proved to be the most significant risk factor for development of pulmonary tuberculosis and its recurrence.

Key words: *Tuberculosis; Cigarette smoking; Alcoholism; Mycobacterium tuberculosis; Croatia*

Introduction

Tuberculosis is an infectious disease caused by the *Mycobacterium (M.) tuberculosis* bacillus. It may involve any organ in the human body, but most commonly affects the lungs (80%-90% of cases)¹. Tuberculosis is a major public health problem worldwide, and one of the top 10 causes of death worldwide, being the leading cause of death among infectious diseases. According to the latest World Health Organization data, in 2016, 10.4 million people were infected with tubercu-

losis and 1.3 million people died during the same year². One-quarter of the entire world population are infected with tuberculosis bacillus³. In 2016, the highest number of patients diagnosed with tuberculosis was recorded in Asia, followed by African countries. Nearly three million people infected with tuberculosis have no clear diagnosis and as such remain untreated^{3,4}.

In 2016, a tuberculosis incidence of 12/100,000 inhabitants was recorded in Croatia, which makes a medium high rate⁵. Many socioeconomic factors such as malnutrition, alcohol abuse and cigarette smoking have been recognized as risk factors for the development and emergence of active tuberculosis recurrence⁶.

The aim of our study was to determine the correlation of cigarette smoking and alcohol consumption with the incidence and severity of tuberculosis recur-

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rence, and to identify which comorbidity is most commonly present in tuberculosis patients.

Patients and Methods

This study was conducted among patients treated for tuberculosis at Jordanovac Department for Lung Diseases during the 2001-2003 period. Analyzing patient history, we collected data on age, sex, habits, comorbidity and clinical manifestations of tuberculosis (pulmonary/extrapulmonary), followed by the number of tuberculosis recurrences. In the microbiological laboratory registry, we found data on the number of directly positive and negative microbiological samples, type of microbiological samples, as well as on drug susceptibility testing. The study included 464 patients treated over two years, with the highest number of patients in 2003, when 230 patients were treated for tuberculosis; all clinical and microbiological indicators were analyzed in separate. The study was approved by the Ethics Committee of the Jordanovac Department for Lung Diseases.

Results

Demographic characteristics of 464 tuberculosis patients during the two-year follow-up are presented in Table 1. In that period, pulmonary tuberculosis was detected in 97.7% and extrapulmonary tuberculosis in 2.3% of the patients. Additionally, 72 (15.5%) patients experienced recurrence of the disease. Out of all patients with recurrence, 32.5% were tobacco and alcohol consumers, 20.8% were tobacco consumers only, 9.7% exclusively consumed alcohol, while 37.0% did not consume alcohol or tobacco (Table 2). Out of the total number of tuberculosis patients, 20.9% consumed alcohol, 57.3% were active tobacco smokers and 11.0% had ceased smoking just before or during the disease. In the active tobacco smokers, the smoking severity index expressed in pack-years was 41.5 for men and 25.2 for women.

When tuberculosis patients were analyzed in a one-year period, 230 patients treated for tuberculosis in 2003 showed a similar sex distribution, with 143 (62.1%) men and 87 (37.9%) women. The largest number of patients in this period was in the 40-60 age group. Pulmonary tuberculosis was diagnosed in 95.2% of patients, while 16.9% of patients had extrapulmo-

Table 1. Demographic characteristics of tuberculosis patients (sex, age and smoking severity index)

Patient characteristic	N=464	%
Sex:		
male, n	291	62.7
female, n	173	37.3
Age median (yrs):		
male	52.6	
female	58.3	
Smoking severity index:		
male	41.5	
female	25.2	

Table 2. Risk factors among patients with tuberculosis recurrence

Risk factor	N =72* n	%
Cigarette smoking	15	20.8
Alcohol consumption	7	9.7
Cigarette smoking and alcohol consumption	23	32.5
None	27	37.0

*Total number of patients with tuberculosis recurrence: N=72 (15.5% of 464 patients)

nary form of tuberculosis, in combination with the pulmonary form. The most common extrapulmonary form was specific pleuritis in 11.7% (n=27), followed by specific lymphadenitis in 3% (n=7), miliary form of tuberculosis in 1.3% (n=3) and kidney tuberculosis in 0.86% (n=2) of patients. Only one (0.43%) patient had laryngeal tuberculosis. Out of the total number of patients, 26.3% had recurrence and 73.5% were directly positive. Comorbidities were present in 63.8% of patients, most commonly diabetes and chronic obstructive pulmonary disease, which accounted for 12.2% of patients, followed by malignancies with 6.5%. Lung cancer was the most common malignant disease. *M. tuberculosis* was isolated in 33% of the total number of lung cancer patients (n=51). Cigarette smoking was present in 51.3% and alcoholism in 36.5% of patients. In 73.5% of patients, tuberculosis was diagnosed directly by microscopy in sputum, catheter aspirate, tumor tissue, lymph node and wound smear. Resistance to one or more antituberculous drugs was demonstrated by resistance test in ten (4.3%) patients, while

multi-drug resistant tuberculosis was found in four (1.7%) patients.

Discussion

Despite the progress in modern medicine, tuberculosis is still a major clinical problem worldwide. One of the most relevant risk factors, as demonstrated in our study, was cigarette smoking, with 57.3% of tuberculosis patients reported as active smokers, while 11% of patients had ceased smoking just before or during the disease. Alcoholism as a risk factor for tuberculosis recurrence was verified in 20.9% of tuberculosis patients. The results are shown for a two-year period during which tuberculosis patients were monitored. If tuberculosis patients could have been analyzed over a one-year period, 51.3% of those respondents would be cigarette smokers and even 36.5% of them alcohol consumers. Given the results obtained in our study, it is considered that smokers, compared to non-smokers (one-third of cases), have an almost twofold risk of *M. tuberculosis* infection and development of the active form of the disease.

More than 20% of tuberculosis prevalence globally is associated with smoking, and cigarette smoking increases the risk of developing tuberculosis by almost two and a half times⁷. It has been shown that affected patients, at the same time smokers, have more frequent disorders such as cough and dyspnea, radiologic bronchodynamic dissemination and caverns, and miliary tuberculosis as the hematogenic form of the disease. Given the great importance of tuberculosis and cigarette smoking association, there are numerous studies that have studied this topic. The available data are also contradictory as some studies suggest that smoking cessation has a positive effect on the control of the disease itself, whereas others indicate that former smokers have weak immune response at the alveolar macrophage level⁸. Some studies indicate that cigarette smoke prevents specific growth and activation of CD4+ T cells and lowers CD4+ and CD8+ T cell levels. Other smoking induced mechanisms include oxidative stress due to infection and disturbances in the function of tracheobronchial cilia⁹. More data on this topic were obtained by research on mice exposed to cigarette smoke and then infected with *M. tuberculosis*. Cigarette smoke exposure amplified the effect of bacteria in the infected mice and directly inhibited the

response of lung T cells to the presence of *M. tuberculosis* in the relevant animal model¹⁰.

Our hypothesis was also confirmed by a major study on 5567 Taiwan tuberculosis patients, which demonstrated the impact of cigarette smoking on tuberculosis development. Active smokers were twice as likely to develop recurrent tuberculosis compared to former smokers and individuals who had never consumed tobacco products¹¹. Another analytical study from Iran showed that 72% of patients infected with *M. tuberculosis* were active smokers. Smoking cessation as a form of intervention resulted in 11% reduction of the mentioned rate at the time of the next visit. This figure was reduced to only 2% several months after treatment¹². Nearly 1.1 million respondents in India participated in the study conducted in 2008, which established that tuberculosis mortality rate was 1.7 times higher in smokers compared to non-smokers¹³. In 2009, a group of scientists reported an increased risk of mortality by 60% in more than a million South Korean smokers suffering from tuberculosis¹⁴. Another major study in Cambodia revealed that the tuberculosis diagnosis was more common in men who consumed tobacco products¹⁵. The data from many meta-studies from other countries and the latest global assessment support the fact that the global reduction in tuberculosis infection is highly dependent on successful smoking control¹⁵.

On the other hand, the study of Gandhi *et al.* among Wistar rats showed that some nicotine analogs had anti-mycobacterial effect after oral and parenteral administration, believing that nicotine was responsible for *M. tuberculosis* destruction¹⁶. The question is why there is a high correlation between smoking and prevalence of tuberculosis, as stated above. The most likely theory is the possibility that nicotine inhibits the production of TNF α necrosis factor in pulmonary macrophages, and thus the patient becomes more susceptible to development of progressive latent infection¹⁷. The effect of cigarette smoking in patients of different age groups was analyzed and compared with the incidence of latent tuberculosis¹⁸. Older patients were more susceptible to the negative effect of smoking and development of latent disease form. The likelihood ratio was significantly higher in older patients than in younger ones, and the greatest risk was observed in patients aged 56-74, declining slowly after the age of 75¹⁸.

Some studies showed that nicotine decreased macrophage ability to destroy *M. tuberculosis* bacteria. An-

alyzing the macrophage response to the presence of tuberculosis infection, O'Leary *et al.* compared functional impairment seen in human alveolar macrophages from nonsmokers, smokers, and ex-smokers¹⁹. They observed an inadequate cytokine response to infection in smokers and skewing the inflammatory mediator profile of macrophages in the lung, which may have affected host susceptibility to the disease¹⁹. Bai *et al.* showed that exposure to nicotine impaired the macrophage anti-*Mtb* defense by inhibition of autophagy *via* binding to nicotinic acetylcholine receptor and activation of immunosuppressive Treg cells²⁰. Their next study showed that passive smokers also had an increased risk of developing latent and active tuberculosis. This susceptibility may be due to the increased exposure to the tubercle bacilli from the increased cough seen in smokers, along with suppressed anti-tuberculosis immunity, enhanced activity of immunosuppressive N2 neutrophils or Tregs, or a combination of these factors²¹. Gleeson *et al.* report on human alveolar macrophages in smokers to be attenuated significantly, with consequent impairment of the glycolytic response to *M. tuberculosis* infection, which is crucial in the early host immune response to the pathogen²².

The combination of tuberculosis and alcoholism, which many consider as the most widespread disease of mankind, represents a medical, social and epidemiological problem. The reduced host resistance to the infection is due to the specific lifestyle of alcoholics. Mortality among alcohol consuming tuberculosis patients is significantly higher compared with mortality of other infected individuals. Affected alcoholics are a significant social and epidemiological problem because they often move among large groups of people such as waiting rooms and restaurants^{23,24}. A recently published study on a mouse model to determine the effects of chronic alcohol consumption on immune responses during *M. tuberculosis* infection demonstrated that alcohol enhanced IFN- α production by CD11b+Ly6G+ cells in the lungs of young *Mtb*-infected mice, which led to macrophage necroptosis and increased mortality. Their findings also suggest that young alcoholic individuals with latent tuberculosis have a higher risk of developing active tuberculosis infection²⁵. The prevalence of alcoholism among patients with tuberculosis is 8%–10%, and there is a significantly higher incidence of tuberculosis recurrence among alcoholics. The results of our study revealed even 20.9% of tuberculosis

patients to be active alcohol consumers and even 15.1% of patients with a combination of cigarette smoking and alcohol.

In conclusion, cigarette smoking proved to be the most important risk factor for pulmonary tuberculosis disease found in 57.3% of patients, and 11.0% of patients had ceased smoking just before or during the disease. Alcoholism as a risk factor for tuberculosis was demonstrated in 20.9% of patients. In addition, the largest number of patients with tuberculosis recurrence was from the smoker group (21%), followed by alcohol consumers (10%). Both risk factors, smoking and alcohol consumption, accounted for 32.5% of patients with recurrent disease. The most common comorbidities in patients with tuberculosis were chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease and malignancies.

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Sažetak

ULOGA PUŠENJA I UZIMANJA ALKOHOLNIH PIĆA U RAZVOJU I PONAVLJANJU PLUĆNE TUBERKULOZE

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Tijekom dvije godine (2001.-2003.) u Klinici za plućne bolesti "Jordanovac", Zagreb, Hrvatska, od tuberkuloze je liječeno 464 bolesnika. Osim najčešće plućne tuberkuloze u 97,7% bolesnika, oboljeli su liječeni i od eksudativnog tuberkuloznog pleuritisa (0,9%), laringealne tuberkuloze (0,6%), tuberkuloznog meningitisa (0,2%), perikardijalne tuberkuloze (0,2%) te tuberkuloze koja je zahvatila urogenitalni sustav (0,4%). Od ukupnog broja bolesnika 57,3% ih se izjasnilo kao aktivni pušači (muškarci 80,8%), dok je 20,9% deklarirano kao aktivni konzumenti alkohola. Ukupno je 15,1% bolesnika imalo oba rizična čimbenika u anamnezi, tj. i aktivno pušenje cigareta i konzumaciju alkohola. Od komorbiditeta najčešća je bila šećerna bolest u 30,4% bolesnika, od srčanih bolesti bolovalo je 11,2% bolesnika, dok je kronična opstruktivna plućna bolest bila prisutna u 8% bolesnika. Karcinom pluća bio je najčešće zastupljen među malignim bolestima. Od ukupnog broja oboljelih od karcinoma pluća (51 bolesnik), *Mycobacterium tuberculosis* izolirali smo u 33% bolesnika. Recidivi tuberkuloze su zabilježeni u 72 (15,5%) bolesnika. Jedan rizični čimbenik imalo je 30,5% bolesnika: pušača je bilo 20,8%, dok je alkohol konzumiralo 9,7% bolesnika, a 32,5% bolesnika imali su oba rizična čimbenika. Zaključno, pušenje cigareta pokazalo se kao najznačajniji rizični čimbenik za razvoj plućne tuberkuloze, kao i za pojavu recidiva tuberkuloze.

Ključne riječi: *Tuberkuloza; Cigarette, pušenje; Alkoholizam; Mycobacterium tuberculosis; Hrvatska*