J Bras Pneumol. 2018;44(2):145-152
http://dx.doi.org/10.1590/S1806-37562017000000443

REVIEW ARTICLE

Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs

Denise Rossato Silva[1,a], Marcela Muñoz-Torrico[2,b], Raquel Duarte[3,4,c], Tatiana Galvão[5,d], Eduardo Henrique Bonini[6,7,e], Flávio Ferlin Arbex[6,f], Marcos Abdo Arbex[6,g], Valéria Maria Augusto[8,h], Marcelo Fouad Rabahi[9,i], Fernanda Carvalho de Queiroz Mello[10,j]

1. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, – UFRGS – Porto Alegre (RS) Brasil.
2. Clínica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias – INER – Ciudad de México, México.
3. Instituto de Saúde Publica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal.
4. Centro Hospitalar de Vila Nova de Gaia/ Espinho, Porto, Portugal.
5. Serviço de Pneumologia, Hospital Especializado Octávio Mangabeira, Secretaria de Saúde do Estado da Bahia, Salvador (BA) Brasil.
6. Faculdade de Medicina, Universidade de Araraquara, Araraquara (SP) Brasil.
7. Hospital Nestor Goulart Reis, Secretaria de Estado da Saúde do Estado de São Paulo, Américo Brasiliense (SP) Brasil.
8. Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
9. Faculdade de Medicina, Universidade Federal de Goiás, – UFG – Goiânia (GO) Brasil.
10. Instituto de Doenças do Tórax, Faculdade de Medicina, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.

a. http://orcid.org/0000-0003-0230-2734
b. http://orcid.org/0000-0002-8453-3634
c. http://orcid.org/0000-0003-2257-3099
d. http://orcid.org/0000-0002-3038-7715
e. http://orcid.org/0000-0002-0334-7718
f. http://orcid.org/0000-0003-4971-5050
g. http://orcid.org/0000-0003-3556-6875
h. http://orcid.org/0000-0003-0401-1260
i. http://orcid.org/0000-0002-4050-5906
j. http://orcid.org/0000-0003-3250-6738

Submitted: 16 December 2017.
Accepted: 9 March 2018.

Study carried out in the Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre (RS) Brasil.

ABSTRACT

Tuberculosis continues to be a major public health problem. Although efforts to control the epidemic have reduced mortality and incidence, there are several predisposing factors that should be modified in order to reduce the burden of the disease. This review article will address some of the risk factors associated with tuberculosis infection and active tuberculosis, including diabetes, smoking, alcohol use, and the use of other drugs, all of which can also contribute to poor tuberculosis treatment results. Tuberculosis can also lead to complications in the course and management of other diseases, such as diabetes. It is therefore important to identify these comorbidities in tuberculosis patients in order to ensure adequate management of both conditions.

Keywords: Tuberculosis/epidemiology; Tuberculosis/prevention & control; Diabetes mellitus/prevention & control; Smoking/adverse effects; Alcohol drinking/adverse effects; Street drugs/adverse effects.

RISK FACTORS FOR TUBERCULOSIS

Diabetes mellitus

Patients with diabetes mellitus (DM) are at a higher risk of transitioning from latent to active tuberculosis. A diagnosis of DM also increases the risk of progressing from the initial infection to active tuberculosis.[1] Case-control studies have demonstrated that the odds ratio of developing tuberculosis is 2.44 to 8.33 times higher in patients with DM than in those without.[2-5] A systematic review of 13 observational studies found that a diagnosis of DM triples the risk of developing tuberculosis (relative risk = 3.11; 95% CI: 2.27-4.26).[6] Some studies have shown that patients with DM are more likely to develop multidrug-resistant tuberculosis (MDR-TB), although there is as yet no explanation for that association.[7-9] In fact, other studies have shown no increased risk of MDR-TB in patients with DM.[10-123]

Approximately 15% of tuberculosis cases worldwide might be linked to DM.[1] The reported prevalence of DM among tuberculosis patients ranges from 1.9% to 45.0% worldwide. The reported prevalence of tuberculosis among DM patients ranges from 0.38% to 14.0%, and the overall median prevalence is reported to be 4.1%, with an interquartile range (IQR) of 1.8%-6.2%.[14] The World Health Organization (WHO) collaborative framework for tuberculosis and DM currently recommends bidirectional screening—screening for DM in all patients with tuberculosis and vice versa.[15]

Active tuberculosis develops most frequently in patients with poor glycemic control. One study of patients with DM showed that the risk of active tuberculosis was three times greater among those who with a hemoglobin A1c (HbA1c) level ≥ 7% than among those with an HbA1c level < 7% (hazard ratio = 3.11; 95%

Correspondence to:
Denise Rossato Silva. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Sala 2050, Santa Cecília, CEP 90035-903, Porto Alegre, RS, Brasil.
Tel.: 55 51 3359-8241 or 55 51 99647-0343. E-mail: denise.rossato@terra.com.br
Fernanda Carvalho de Queiroz Mello. Instituto de Doenças do Tórax, Rua Professor Rodolpho Paulo Rocco, 255, 1° andar, Sala 01 D 58, Cidade Universitária, CEP 21941-913, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 3938-2887. E-mail: fcqmello@idt.ufrj.br
Financial support: None.

CI: 1.63-5.92). In addition, insulin dependence is purported to be a risk factor for tuberculosis. In the Philadelphia Diabetic Survey, the likelihood of developing tuberculosis was found to be twice as high among patients with DM using more than 40 units of insulin per day than among those using lower doses.[16]

Poorly controlled DM can lead to multiple complications, including increased susceptibility to infection. Diabetes causes increased susceptibility to tuberculosis through several mechanisms, including hyperglycemia and cellular insulinopenia, which have indirect effects on macrophage and lymphocyte function.[14] However, tuberculosis can temporarily cause impaired glucose tolerance, which is a risk factor for developing DM.[1] Transient hyperglycemia can occur due to the inflammation induced during tuberculosis.[9] Therefore, to establish a new diagnosis of DM, glucose levels should be measured again after 4 weeks of treatment for tuberculosis, especially after the patient is no longer febrile.[9,17]

Tuberculosis patients with DM have a worse clinical presentation and more symptoms, especially weight loss, fever, dyspnea, and night sweats.[16] Patients with tuberculosis and previously-diagnosed DM are usually female, older, and obese. In contrast, patients with tuberculosis and newly-diagnosed DM are more likely to be male and younger, as well as to have lower levels of HbA1c.[9]

Radiologically, patients with tuberculosis and DM have more extensive lesions, more often have multilobar disease, and more frequently present cavitation.[13] Lower-lung involvement is typically as common in DM patients as it is in controls, except in patients > 40 years, among whom it is more common in the presence of DM.[16]

In comparison with patients without DM, the bacillary burden at presentation is higher in patients with DM, who also take longer to transition to culture negativity. However, the rates of sputum-culture conversion after 2 months of treatment are similar between the two patient populations.[16]

Rifampin is a powerful inducer of the hepatic microsomal enzyme system and can lower the serum levels of sulfonylureas and biguanides,[17] leading to hyperglycemia, either directly, or indirectly via interactions with oral hypoglycemic drugs.[16] Therefore, in patients with DM who take rifampin, the doses of oral antidiabetic drugs should be adjusted upwards according to plasma glucose levels. In patients with severe DM, insulin should be used initially.[17] In addition, if isoniazid is prescribed, pyridoxine should also be given, in order to avoid the peripheral neuropathy associated with the use of the former.[16]

The likelihood that a person with tuberculosis will die or relapse is significantly higher if the person also has DM.[1] Two retrospective cohort studies have shown that, in patients with pulmonary tuberculosis, the risk of death is 6.5–6.7 times higher for those who have DM than for those who do not.[18,19] In a systematic review and meta-analysis, Baker et al. concluded that patients with tuberculosis and DM have a nearly 4-fold higher risk of relapse than do those with tuberculosis alone.[9] In addition, one study showed that patients with DM are at a 3.9 times higher risk of treatment failure.[16] Tuberculosis patients with DM are also more likely to be lost to follow-up than are those without.[15]

Smoking

It is estimated that, worldwide, 1.3 billion people consume tobacco and that most of them live in underdeveloped or developing countries, where the tuberculosis rates are also higher.[20] Therefore, the greatest impact of smoking in terms of public health issues related to infection is probably the increase in the risk of tuberculosis. Some systematic reviews and meta-analyses of observational studies have shown an unfavorable association between the global epidemics of tuberculosis and smoking, exposure to tobacco smoke having been associated with tuberculosis infection, active tuberculosis, and tuberculosis-related mortality.[21,22]

The role that cigarette smoke plays in the pathogenesis of tuberculosis is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count, increasing susceptibility to infection with *Mycobacterium tuberculosis*.[20] The alveolar macrophage binds to the bacillus through complement receptors 1, 3, and 4. Activated lymphocytes release cytokines while recruiting macrophages, fibroblasts, and other lymphocytes. The major cytokine involved in granuloma formation is TNF-α, which is released by macrophages immediately after exposure to *M. tuberculosis* antigens. The TNF-α activates macrophages and dendritic cells. In smokers, nicotine, acting through the α7 nicotinic receptor, reduces the production of TNF-α by macrophages, thereby preventing its protective action and favoring the development of tuberculosis.[23,24]

Secretion of IL-12 by macrophages induces the production of IFN-γ in natural killer cells. This immune response aspect, known as the Th1 response, aims to destroy *M. tuberculosis* by forming a fibrous granuloma. Cigarette smoke selectively promotes low production of interleukin-12 and TNF-α, impeding granuloma formation, which would contain the infection at this stage in immunocompetent individuals, smoking therefore creating conditions that allow the development of active tuberculosis.[23,24]

Tuberculosis-related mortality rates are significantly higher in smokers than in never-smokers.[25] Among individuals without a history of tuberculosis, the risk of death due to tuberculosis is nine times higher for smokers than for never-smokers.[25] One recent study showed that smoking and HIV infection were significant risk factors for mortality in patients with MDR-TB.[26] When smokers quit smoking, the risk of

death due to tuberculosis drops significantly (by 65% compared with that observed for those who continue smoking), which indicates that smoking cessation is an important factor in reducing tuberculosis-related mortality.[25]

A prospective study, conducted in rural China in 2017, underscored the supposition that smoking is an independent risk factor for tuberculosis infection, especially in elderly smokers, as well as demonstrating a direct correlation between smoking history (pack-years) and the risk of latent tuberculosis.[27] Recent investigations suggest that, in the detection of latent tuberculosis with IFN-γ methods, the proportion of false-negative results is higher among smokers than among nonsmokers, and that smoking has a negative impact on the results of tuberculosis treatment, delaying conversion of the sputum culture during the treatment and extending the time of treatment.[28] Likewise, nicotine withdrawal has been shown to be strongly associated with successful completion of the treatment for latent tuberculosis.[29]

A study conducted in Brazil showed that men with a history of tuberculosis are 4.1 times more likely to present airway obstruction than are those with no such history, and those results remained unchanged after having been adjusted for age, gender, level of education, ethnicity, smoking, exposure to dust or smoke, respiratory morbidity in childhood, and current morbidity. In conclusion, a history of tuberculosis is associated with airway obstruction in middle-aged and older adults.[30]

Passive and active exposure to cigarette smoke are both associated with an increased risk of infection with *M. tuberculosis* and of the development of active tuberculosis. A qualitative systematic review, published in 2007, highlighted the strong correlation between smoking and active tuberculosis, as well as showing that passive smoking correlated moderately with active tuberculosis and with the need for retreatment.[31] A history of parental smoking is already part of the investigation of episodes of respiratory infection in children. A recent study also showed that the risk of infection with *M. tuberculosis* was increased in children living in a region endemic for tuberculosis, and that parental smoking was significantly associated with the risk of active tuberculosis, even after having been adjusted for associated factors.[32] Therefore, the effects of passive smoking are also a concern regarding active tuberculosis, and every smoker with tuberculosis should be educated about the harm that their addiction can cause to other individuals, especially their contacts, who are at greater risk of contracting active tuberculosis. A study of children who were household contacts of tuberculosis patients showed that exposure to passive smoking, as confirmed by the measurement of urinary nicotine levels, is a major risk factor for active tuberculosis (OR = 5.39; 95% CI: 2.44-11.91).[33]

Another crucial point in the control of tuberculosis is the abandonment of treatment. Smoking has been associated with the abandonment of tuberculosis treatment, and that association has been found to be independent of alcohol or illicit drug use.[34] Therefore, abandonment of tuberculosis treatment might be related to the psychosocial aspects of smoking, the predominance of males, and the lower socioeconomic status of the affected populations, all of which are factors associated with lower rates of adherence to treatment.[34] The recognition of that association is of paramount importance in combating exposure to tobacco smoke in order to reduce the risk of tuberculosis, as is simultaneous treatment for smoking and tuberculosis, both of which mainly affect the respiratory system. Because the smoking epidemic is increasing in some parts of the world and tuberculosis control is still far from being achieved, the prospects are quite worrisome. In one study, a mathematical model was applied in order to evaluate the impact of smoking on the incidence of tuberculosis, that impact being calculated on the basis of the trend in smoking, as well as on the projections for tuberculosis incidence, prevalence, and mortality from 2010 to 2050.[35] The authors estimated that smoking will produce in excess of 18 million tuberculosis cases and 40 million deaths if the number of smokers around the world continues to increase at the current rate. They also estimated that, between 2010 and 2050, smoking will be responsible for a 7% increase in the number of new cases of tuberculosis (from 256 million to 274 million) and a 66% increase in the number of tuberculosis-related deaths (from 61 million to 101 million), making it even more problematic to reach the tuberculosis control targets set by the WHO.[35] For a tuberculosis control program to be effective in daily clinical practice, patients with tuberculosis should be encouraged to undergo smoking cessation treatment, which can also improve the quality of life of such patients.

Alcohol use

Although the consumption of alcohol is considered socially acceptable worldwide, it can lead to dependence. Alcohol consumption problems vary widely. The harmful use of alcohol ranks among the top five risk factors for disease, disability, and death, as well as being a causal factor in more than 200 disease and injury conditions, including tuberculosis, worldwide.[36] It has been estimated that approximately 10% of all tuberculosis cases are attributable to alcohol use.[37]

One major obstacle to making a diagnosis of alcohol abuse is the difficulty in quantifying alcohol intake. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association, alcohol use disorder (AUD) is a chronic, relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. The presentation of AUD can range from mild to severe, and recovery is possible

regardless of the level of severity.[38] The prevalence of AUD among tuberculosis patients varies depending on the population studied. Russia and countries of the former Soviet Union are among the regions most critically impacted by alcohol use. In a cohort of individuals starting tuberculosis treatment in Tomsk, Siberia, 60.2% had a lifetime history of AUD and, most importantly, approximately 28% were female.[39] In a prospective study conducted in New York City, a cohort of individuals with AUD were followed for 8 years and the incidence of tuberculosis was found to be 464 cases/100,000 person-years, which was 9 times the incidence found for the age-matched general population.[40]

The association between alcohol use and tuberculosis has long been known, although there have been inconclusive findings related to various confounding factors, because it is still not known whether the increased risk of tuberculosis is due to the use of alcohol per se or because of the sequelae of AUD, such as liver damage and nutritional deficiency, or social factors, such as crowding, malnutrition, homelessness, and imprisonment, independently of the alcohol consumption. However, in vivo and in vitro studies have demonstrated that alcohol use significantly disrupts the immune response, increasing susceptibility to respiratory diseases such as tuberculosis.[41]

Various population-based studies have shown that there is a strong association between AUD and tuberculosis.[42,43] In a meta-analysis that included 3 cohort studies and 18 case-control studies,[44] heavy alcohol use (defined as ≥ 40 g alcohol per day) or a clinical diagnosis of AUD was found to have a pooled relative risk for the development of active tuberculosis of 3.50 (95% CI: 2.01-5.93). Neither exclusion of the smaller studies (because of suspected publication bias) nor adjustment for various sets of confounders altered the results significantly. In a prospective study conducted in China, a cohort of adults were followed for a mean of 16.8 ± 5.2 years.[45] The authors found that alcohol consumption (≥ 2 drinks per day) were associated with an increased risk of tuberculosis when accompanied by smoking (hazard ratio = 1.51; 95% CI: 1.11-2.05), which is another risk factor for the development of active tuberculosis.[46]

Alcohol abuse influences not only the incidence of tuberculosis but also its clinical evolution and outcome. Individuals with AUD are considered more infectious because AUD has been associated with the finding of cavitary disease on chest X-rays and therefore with smear positivity.[46,47] In addition, AUD has been associated with higher rates of treatment default (OR = 1.99; 95% CI: 1.04-3.81) and relapse (OR = 3.9; 95% CI: 2.5-6.1).[48,49] There are several reasons for that, including precarious living conditions and the increased risk of hepatotoxicity due to tuberculosis treatment in this group of patients.[50]

Whether alcohol abuse increases the risk of MDR-TB is not well established. In a case-control study conducted in Botswana, the prevalence of alcohol use was found to be higher among the individuals with MDR-TB than among those in three different control groups, even after adjustment for several confounders.[51]

Ensuring healthy lives and promoting well-being for individuals of all ages are among the United Nations Sustainable Development Goals for 2030, calling for the prevention and treatment of substance abuse, including the harmful use of alcohol.[52] It is clear that AUD has an negative impact on tuberculosis risk and treatment outcomes. Therefore, in populations at high risk for AUD, it is important to evaluate this condition, integrating the management of AUD and the treatment for tuberculosis, as well as to monitor treatment adherence in order to avoid default and to follow patients closely to identify adverse events.

Illicit drug use

It is estimated that 1 in 20 adults, or a quarter of a billion people between 15 and 64 years of age, used at least one illicit drug in 2015. That is the equivalent of the combined populations of France, Germany, Italy, and the United Kingdom. Over 29 million people who use drugs are estimated to suffer from drug use disorders, 12 million of those are injection drug users, and 14% of injection drug users are living with HIV. Therefore, the impact of drug use, in terms of its consequences on health, continues to be devastating, with an estimated 207,400 drug-related deaths in 2014. Among all forms of illicit drug use, the most common is the use of the cocaine. In 2015, cocaine (either in powder form or as crack cocaine) was used by 18.3 million people, corresponding to 0.3-0.4% of the global population. The magnitude of the harm caused by illicit drug use is evidenced by the estimated 7.4 million illicit drug users seeking treatment via health care systems and the 1 million disability-adjusted life years lost in 2014 because of drug-related premature death and disability.[53,54] According to the WHO, approximately 10% of people living in large urban centers consume psychoactive substances, regardless of gender, age, level of education, or social status. That has been confirmed in a study of large urban centers in Brazil.[55]

Cocaine can be administered by inhalation (smoking or snorting) or by intravenous injection. Currently, the most widely used route of administration is inhalation, especially in the form of crack, or freebase, cocaine smoking. The shift in preference from intravenous injection to inhalation in recent decades is mainly due to the increase in HIV transmission via injection drug use, to the intense euphoric effect (occurring within the first few minutes) of crack, and to the lower cost of the latter.[56]

Epidemiological data suggest that the relationship between tuberculosis and illicit drug use is increasing, leading to a public health problem because it involves political, human, social, and economic aspects.[57,58] The presence of illicit drug users infected with tuberculosis in families and communities is a crucial

factor in maintaining the chain of tuberculosis transmission. Among illicit drug users, infection with *M. tuberculosis* and the progression to active disease are both promoted by a number of factors[55]: the risky lifestyle of such users; the crowded housing conditions; the accumulation and isolation of people indoors for the consumption of illicit drugs; the sharing of materials such as pipes; the malnutrition and severe cough presented by many users; the spread of HIV infection among illicit drug users; and the high number of imprisonments. The proportion of individuals who present risk factors for infection with *M. tuberculosis* and progression to active tuberculosis is 8.0% among injection drug users, compared with only 0.2% in the general population.[54]

Marked and repeated exposure to smoked cocaine has been associated with a broad spectrum of pulmonary complications, including pulmonary edema, diffuse alveolar hemorrhage, acute asthma exacerbations, barotrauma, pulmonary eosinophilic infiltrates, nonspecific interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia, as well as acute pulmonary infiltration, together with a variety of clinical and pathological findings, collectively referred to as "crack lung".[59] Hard drugs such as cocaine can be injected intravenously or ingested through other routes such as inhalation. However, the respiratory damage caused by habitual cocaine smoking makes the users more vulnerable to pulmonary tuberculosis. That might be attributable to the fact that cocaine consumption has been shown to impede the production of alveolar macrophages and immunoregulatory cytokines, both of which are of vital importance in conferring resistance against active tuberculosis. Cocaine use causes a significant reduction in inducible nitric oxide synthase activity, which in turn reduces the antibacterial activity of alveolar macrophages. In addition, cocaine decreases proinflammatory responses, including those involving IFN-γ, chemokine CCL2, TNF-α, and GM-CSF, which are required in the immune response to tuberculosis. Overall, cocaine use attenuates the capacity of monocyte and alveolar macrophage protective mechanisms, resulting in failure to respond to a mycobacterial challenge, the ultimate consequence of which is a failure to prevent active tuberculosis.[60]

In two separate studies,[61,62] the use of powder or crack cocaine was found to correlate directly with the prevalence of active and latent tuberculosis; delays in the diagnosis of the disease; noncompliance with and abandonment of treatment; higher rates of retreatment; and the emergence of multidrug-resistant strains. A study conducted in the United States showed that the use of crack cocaine correlated with a positive PPD skin test result in 147 individuals with schizophrenia. The relative risk of a positive PPD result was 3.53 for the crack cocaine users when compared with the non-drug-using patients.[63] A study conducted in the Brazilian city of Porto Alegre evaluated diagnostic delays in 153 patients with tuberculosis. The authors reported that the median total time of the delay was 60 days (IQR: 30.0-90.5 days), the median patient delay and health care system delay being 30 days (IQR: 7.0-60.0 days) and 18 days (IQR: 9.0-39.5 days), respectively. The factors that were found to be independently associated with a patient delay > 30 days were crack cocaine use (OR = 4.88; p = 0.043) and powder cocaine use (OR = 6.68; p = 0.011).[64]

In a case-control study of patients with pulmonary tuberculosis, conducted in London, England, 19 (86%) of 22 crack cocaine users were smear positive at diagnosis, compared with 302 (36%) of 833 non-drug-using patients.[65] The authors found that smear positivity at the time of diagnosis of pulmonary tuberculosis was 2.4 times and 1.6 times more likely in patients who were crack cocaine users and in patients who were hard drug users not known to use crack cocaine, respectively, than in their non-drug-using counterparts. There was also a significant difference between the crack cocaine users and the users of other drugs, in terms of smear positivity at diagnosis.

A study carried out at a university hospital in the city of São Paulo, Brazil, studied the causes of abandonment of treatment in 100 patients with pulmonary tuberculosis followed as outpatients.[66] The authors showed that alcoholics, smokers, and illicit drug users abandoned tuberculosis treatment with greater frequency than did the patients who did not present any of those risk factors. Among the illicit drug users, marijuana use was reported in 33%, inhaled cocaine use was reported in 29%, intravenous cocaine use was reported in 17%, and crack cocaine use was reported in 11%; half of the illicit drug users reported using combinations of those drugs. The authors of a study conducted in Portugal used data from the Portuguese National Surveillance Center to evaluate the causes of failure to treat tuberculosis (bankruptcy, abandonment of treatment, and death) between 2000 and 2012.[67] The overall rate of such failure was found to be 11.9%, the rate being higher in patients with tuberculosis/HIV coinfection (OR = 4.93), patients over 64 years of age (OR = 4.37), patients who used illicit drugs (OR = 2.29), patients with other diseases, excluding DM/HIV (OR = 2.09), and patients undergoing retreatment (OR = 1.44).

Casal et al.[68] evaluated risk factors for multidrug resistance among patients with pulmonary tuberculosis in four European Union countries (France, Germany, Italy, and Spain) between 1997 and 2000.[68] The authors evaluated a total of 138 cases and 276 controls. In the four countries as a whole, the most statistically significant risk factors were as follows: intravenous drug use (OR = 4.68); asylum-seeker support as income (OR = 2.55); living in a nursing home (OR = 2.05); a history of pulmonary tuberculosis (OR = 2.03); imprisonment (OR = 2.02); known contact with an active tuberculosis case (OR = 2.01); immunosuppression other than that related to HIV infection (OR = 1.96); AIDS (OR = 1.96); current

pulmonary tuberculosis (OR = 1.77); and being a health care worker (OR = 1.69).

FINAL CONSIDERATIONS

In addition to having a direct effect on the health of individuals, tuberculosis is a public health problem. Given the complexity of the combination of illicit drug use and tuberculosis, together with the profile of the population affected and the scarcity of studies dealing with this issue, there is a need for authorities and health professionals to create new, better strategies for evaluating user behavior and to establish intervention policies to control this disease combination, the prevalence of which is increasing in Brazil.

ACKNOWLEDGMENTS

The paper is part of the European Respiratory Society/Latin-American Thoracic Association and European Respiratory Society/Brazilian Thoracic Association collaborative projects.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2016 [cited 2016 Dec 1]. Tuberculosis and diabetes. [Adobe Acrobat document, 2p.]. Available from: http://www.who.int/tb/publications/diabetes_tb.pdf
2. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis. 2006;10(1):80-6.
3. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ. 2006;332(7533):85-7. https://doi.org/10.1136/bmj.38684.687940.80
4. Mboussa J, Monabeka H, Kombo M, Yokolo D, Yoka-Mbio A, Yala F. Course of pulmonary tuberculosis in diabetics [Article in French]. Rev Pneumol Clin. 2003;59(1):39-44.
5. Jabbar A, Hussain SF, Khan AA. Clinical characteristics of pulmonary tuberculosis in adult Pakistani patients with co-existing diabetes mellitus. East Mediterr Health J. 2006;12(5):522-7.
6. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5:1091–1101.
7. Bashar M, Alcabes P, Rom WN, Condos R. Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service, 1987 to 1997. Chest. 2001;120(5):1514-9. https://doi.org/10.1378/chest.120.5.1514
8. Fisher-Hoch SP, Whitney E, McCormick JB, Crespo G, Smith B, Rahbar MH, et al. Type 2 diabetes and multidrug-resistant tuberculosis. Scand J Infect Dis. 2008;40(11-12):888-93. https://doi.org/10.1080/00365540802342372
9. Restrepo BI. Diabetes and tuberculosis. Microbiol Spectr. 2016;4(6):1-19.
10. Singla R, Khan N. Does diabetes predispose to the development of multidrug-resistant tuberculosis? Chest. 2003;123(1):308-9; author reply 309. https://doi.org/10.1016/S0012-3692(16)34416-6
11. Subhash HS, Ashwin I, Mukundan U, Danda D, John G, Cherian AM, et al. Drug resistant tuberculosis in diabetes mellitus: a retrospective study from south India. Trop Doct. 2003;33(3):154-6. https://doi.org/10.1177/004947550303300311
12. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is Associated with Severe Adverse Events in Multidrug-Resistant Tuberculosis. Arch Bronconeumol. 2017;53(5):245-250. https://doi.org/10.1016/j.arbr.2016.10.003
13. Muñoz-Torrico M, Caminero Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data. Rev Port Pneumol (2006). 2017;23(1):27-30.
14. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PLoS One 2017;12(4):e0175925. https://doi.org/10.1371/journal.pone.0175925
15. Pizzol D, Di Gennaro F, Chhaganlal KD, Fabrizio C, Monno L, Putoto G, et al. Tuberculosis and diabetes: current state and future perspectives. Trop Med Int Health. 2016;21(6):694-702. https://doi.org/10.1111/tmi.12704
16. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46. https://doi.org/10.1016/S1473-3099(09)70282-8
17. Deng C, Wang X, Liao Y. Current recommendations on managing tuberculosis patients with diabetes & its epidemiology. Microb Pathog. 2016;92:43-45. https://doi.org/10.1016/j.micpath.2015.12.005
18. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80(4):634-9.
19. Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS, Chaisson RE. Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. Clin Infect Dis. 2002;34(6):752-9. https://doi.org/10.1086/338784
20. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. 2010;35(1):27-33. https://doi.org/10.1183/09031936.00072909
21. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. The risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch Intern Med. 2007;167(4):335-42. https://doi.org/10.1001/archinte.167.4.335
22. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med. 2007;4(1):e20. https://doi.org/10.1371/journal.pmed.0040020
23. North RJ, Jung YJ. Immunity to tuberculosis. Ann Rev Immunol. 2004;22:599-623. https://doi.org/10.1146/annurev.immunol.22.012703.104635
24. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med. 2009;360(23):2445-54. https://doi.org/10.1056/NEJMra0804752
25. Wen CP, Chan TC, Chan HT, Tsai MK, Cheng TY, Tsai SP. The reduction of tuberculosis risks by smoking cessation. BMC Infect Dis. 2010;10:156. https://doi.org/10.1186/1471-2334-10-156
26. Mollel EW, Chilongola JO. Predictors for Mortality among Multidrug-Resistant Tuberculosis Patients in Tanzania. J Trop Med. 2017;2017:9241238.
27. Zhang H, Xin H, Li X, Li H, Li M, Lu W, et al. A dose-response relationship of smoking with tuberculosis infection: A cross-sectional study among 21008 rural residents in China. PLoS One. 2017;12(4):e0175183. https://doi.org/10.1371/journal.pone.0175183
28. Altet N, Latorre I, Jiménez-Fuentes MÁ, Maldonado J, Molina I, González-Díaz Y, et al. Assessment of the influence of direct tobacco smoke on infection and active TB management. PLoS One. 2017;12(8):e0182998. https://doi.org/10.1371/journal.pone.0182998
29. Eastment MC, McClintock AH, McKinney CM, Narita M, Molnar A. Factors That Influence Treatment Completion for Latent Tuberculosis Infection. J Am Board Fam Med. 2017;30(4):520-527. https://doi.org/10.3122/jabfm.2017.04.170070
30. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Mui-o A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the

PLATINO study in Latin America. Eur Respir J. 2007;30(6):1180-5. https://doi.org/10.1183/09031936.00083507

31. Slama K, Chiang CY, Enarson DA, Hassmiller K, Fanning A, Gupta P, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. Int J Tuberc Lung Dis. 2007;11(10):1049-61.
32. Du Preez K, Mandalakas AM, Kirchner HL, Grewal HM, Schaaf HS, van Wyk SS, Hesseling AC. Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children. Int J Tuberc Lung Dis. 2011;15(11):1490-6, i. https://doi.org/10.5588/ijtld.10.0759
33. Altet MN, Alcaide J, Plans P, Taberner JL, Saltó E, Folguera LI, et al. Passive smoking and risk of pulmonary tuberculosis in children immediately following infection. A case control study. Tuber Lung Dis. 1996;77(6):537-44. https://doi.org/10.1016/S0962-8479(96)90052-0
34. Cherkaoui I, Sabouni R, Ghali I, Kizub D, Billioux AC, Bennani K, et al. Treatment default amongst patients with tuberculosis in urban Morocco: predicting and explaining default and post-default sputum smear and drug susceptibility results. PLoS One. 2014;9(4):93574. https://doi.org/10.1371/journal.pone.0093574
35. Basu S, Stuckler D, Bitton A, Glantz SA. Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modeling analysis. BMJ. 2011;343:d5506. https://doi.org/10.1136/bmj.d5506
36. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2016 Dec 1]. Global Health Risks: Mortality and burden of disease attributable to selected major risks. [Adobe Acrobat document, 70p.]. Available from: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf
37. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, Patra J, Poznyak V, Popova S. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009;9:450. https://doi.org/10.1186/1471-2458-9-450
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Update. Washington (DC): American Psychiatric Association; 2016.
39. Shin SS, Mathew TA, Yanova GV, Fitzmaurice GM, Livchits V, Yanov SA, et al. Alcohol consumption among men and women with tuberculosis in Tomsk, Russia. Cent Eur J Public Health. 2010;18(3):132-8.
40. Friedman LN, Williams MT, Singh TP, Frieden TR. Tuberculosis, AIDS, and death among substance abusers on welfare in New York City. N Engl J Med. 1996;334(13):828-33. https://doi.org/10.1056/NEJM199603283341304
41. Molina PE, Happel KI, Zhang P, Kolls JK, Nelson S. Focus on: Alcohol and the immune system. Alcohol Res Health. 2010;33(1-2):97-108.
42. Francisco J, Oliveira O, Felgueiras Ó, Gaio AR, Duarte R. How much is too much alcohol in tuberculosis? Eur Respir J. 2017;49(1). pii:1601468. https://doi.org/10.1183/13993003.01468-2016
43. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J 2017;50(1). pii: 1700216. https://doi.org/10.1183/13993003.00216-2017
44. Lönnroth K, Williams B, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008;8:289. https://doi.org/10.1186/1471-2458-8-289
45. Soh AZ, Chee CBE, Wang YT, Yuan JM, Koh WP. Alcohol drinking and cigarette smoking in relation to risk of active tuberculosis: prospective cohort study. BMJ Open Respir Res. 2017;4(1):e000247. https://doi.org/10.1136/bmjresp-2017-000247
46. Hermosilla S, You P, Aifah A, Abildayev T, Akilzhanova A, Kozhamkulov U, et al. Identifying risk factors associated with smear positivity of pulmonary tuberculosis in Kazakhstan. PLoS One. 2017;12(3):e0172942. https://doi.org/10.1371/journal.pone.0172942
47. Fiske CT, Hamilton CD, Stout JE. Alcohol use and clinical manifestations of tuberculosis. J Infect. 2009;58(5):395-401. https://doi.org/10.1016/j.jinf.2009.02.015
48. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Kourbatova EV. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. Int J Tuberc Lung Dis. 2007;11(1):46-53.
49. Selassie AW, Pozsik C, Wilson D, Ferguson PL. Why pulmonary tuberculosis recurs: a population-based epidemiological study. Ann Epidemiol. 2005;15(7):519-25. https://doi.org/10.1016/j.annepidem.2005.03.002
50. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax. 1996;51(2):132-6. https://doi.org/10.1136/thx.51.2.132
51. Zetola NM, Modongo C, Kip EC, Gross R, Bisson GP, Collman RG. Alcohol use and abuse among patients with multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2012;16(11):1529-34. https://doi.org/10.5588/ijtld.12.0026
52. United Nations. [homepage on the Internet]. New York City: United Nations, c2017 [cited 2017 Dec 1].Transforming our world: the 2030 Agenda for Sustainable Development. [Adobe Acrobat document, 35p.]. Available from: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E
53. United Nations Office on Drugs and Crime [homepage on the Internet]. Vienna: United Nations Office on Drugs and Crime; c2017 [cited 2017 Dec 1]. World Drug Report 2016 [about 2 screens]. Available from: http://www.unodc.org/wdr2016/
54. United Nations Office on Drugs and Crime [homepage on the Internet]. Vienna: United Nations Office on Drugs and Crime; c2017 [cited 2017 Dec 1]. World Drug Report 2017 [about 2 screens]. Available from: https://www.unodc.org/wdr2017/index.html
55. Cruz VD, Harter J, Oliveira MM, Gonzales RI, Alves PF. Crack consumption and tuberculosis: an integrative review. Rev Eletronica Saude Mental Alcool Drog. 2013;9(1):48-55.
56. Almeida RR, Zanetti G, Souza AR Jr, Souza LS, Silva JL, Escuissato DL et al. Cocaine-induced pulmonary changes: HRCT findings. J Bras Pneumol. 2015;41(4):323-30. https://doi.org/10.1590/S1806-37132015000000025
57. Marques AC, Cruz MS. O adolescente e o uso de drogas. Rev Bras Psiquiatr. 2000;22(2):32-6. https://doi.org/10.1590/S1516-44462000000600009
58. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009;48(1):72-82. https://doi.org/10.1086/594126
59. Mançano A, Marchiori E, Zanetti G, Escuissato DL, Duarte BC, Apolinario Lde A. Pulmonary complications of crack cocaine use: high-resolution computed tomography of the chest. J Bras Pneumol. 2008;34(5):323-7. https://doi.org/10.1590/S1806-37132008000500012
60. Kiboi NG, Nebere SN, Karanja JK. Immunological Interactions of Tuberculosis with Drugs and Substance Use: A Systematic Review and Update. J Pulm Respir Med. 2016;6:2. https://doi.org/10.4172/2161-105X.1000326
61. Paixão LM, Gontijo ED. Profile of notified tuberculosis cases and factors associated with treatment dropout [Article in Portuguese]. Rev Saude Publica. 2007;41(2):205-13. https://doi.org/10.1590/S0034-89102007000200006
62. Rodrigues IL, Monteiro LL, Pacheco RH, da Silva SE. Abandonment of tuberculosis treatment among patients co-infected with TB/HIV [Article in Portuguese]. Rev Esc Enferm USP. 2010;44(2):383-7. https://doi.org/10.1590/S0080-62342010000200020
63. Taubes T, Galanter M, Dermatis H, Westreich L. Crack cocaine and schizophrenia as risk factors for PPD reactivity in the dually diagnosed. J Addict Dis. 1998;17(3):63-74. https://doi.org/10.1300/J069v17n03_06
64. Deponti GN, Silva DR, Coelho AC, Muller AM, Dalcin Pde T. Delayed diagnosis and associated factors among new pulmonary tuberculosis patients diagnosed at the emergency department of a tertiary care hospital in Porto Alegre, South Brazil: a prospective patient recruitment study. BMC Infect Dis. 2013;13:538. https://doi.org/10.1186/1471-2334-13-538
65. Story A, Bothamley G, Hayward A. Crack cocaine and infectious tuberculosis. Emerg Infect Dis. 2008;14(9):1466-9. https://doi.org/10.3201/eid1409.070654
66. Ribeiro SA, Amado VM, Camalier AA, Fernandes MA, Schenkman

S. Estudo caso-controle de indicadores de abandono em doentes com tuberculose. J Pneumol. 2000;26(6):291-6. https://doi.org/10.1590/S0102-35862000000600004

67. Costa-Veiga A, Briz T, Nunes C. Unsuccessful treatment in pulmonary tuberculosis: factors and a consequent predictive model. Eur J Public Health. 2017 Oct 3. [Epub ahead of print] https://doi.org/10.1093/eurpub/ckx136

68. Casal M, Vaquero M, Rinder H, Tortoli E, Grosset J, Rüsch-Gerdes S, et al. A case-control study for multidrug-resistant tuberculosis: risk factors in four European countries. Microb Drug Resist. 2005;11(1):62-7. https://doi.org/10.1089/mdr.2005.11.62