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Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America

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Running title: Tuberculosis and airflow obstruction

Abstract

Question of the study: To evaluate the association between history of tuberculosis and airflow obstruction.

Materials/patients: Population-based, multi-centre study including 5600 subjects aged 40 years or older living in five Latin American metropolitan areas – Sao Paulo (Brazil), Montevideo (Uruguay), Mexico City (Mexico), Santiago (Chile), and Caracas (Venezuela). Subjects performed pre and post-bronchodilator spirometry and were asked whether they had ever been diagnosed with tuberculosis by a physician.

Results: The overall prevalence of airflow obstruction (FEV 1 / FVC <0.7 post-bronchodilator) was 30.7% among those with a history of tuberculosis, compared to 13.9% among those without a history. Males with a medical history of tuberculosis were 4.1 times more likely to present airflow obstruction than those without such a diagnosis (P=0.000). This remained unchanged after adjustment for confounding by age, sex, schooling, ethnicity, smoking, exposure to dust and smoke, respiratory morbidity in childhood and current morbidity. Among women, the unadjusted and adjusted odds ratios were 2.3 (P=0.001) and 1.7 (P=0.08), respectively.

Answer to the question: History of tuberculosis is associated with airflow obstruction in Latin American middle-aged and older adults.

Key words: chronic bronchitis, COPD, developing countries, smoking, spirometry, tuberculosis.

Introduction

According to the global burden of disease projections(1), chronic obstructive pulmonary diseases - COPD (6^{th}) and tuberculosis (8^{th}) are among the ten leading causes of death and disability for low and middle income countries in the beginning of the 21^{st} century. This scenario differs from that observed in high income countries, where tuberculosis is not among the top ten causes.(1) Brazil, the largest country in Latin America, is one of the 22 countries in the world that account for 80% of the tuberculosis cases according to the World Heath Organization.(2) Poverty, undernutrition, high rates of HIV infection, smoking and the huge socioeconomic disparities observed in low and middle-income countries contribute to the high prevalence of tuberculosis.(2)

Previous studies have suggested that pulmonary tuberculosis is associated with airflow obstruction. Most were carried out in Africa (3-6) and Asia.(7-9) The Latin American literature on this issue is scarce; we found only two papers – one from Chile and one from Brazil – published in the last 10 years.(10, 11) Most studies had small samples and only one was population-based. Post-bronchodilator spirometry, the gold standard for measuring airway obstruction, was used in few studies, but not in the population-based survey.(4)

The PLATINO study, a multi-centre population-based project conducted in five sites of Latin America, allowed us to investigate the association between airflow obstruction - measured by spirometry - and tuberculosis (evaluated by medical diagnosis). The aim of this paper is to evaluate the association between airflow obstruction and tuberculosis.

Methods

The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO; http://www.platino-alat.org) was launched in 2002. The project focused on COPD and related variables, including five major cities in Latin America: São Paulo (Brazil), Santiago (Chile), Mexico City (Mexico), Montevideo (Uruguay), and Caracas (Venezuela). The detailed methodology of the multi-centre study was published elsewhere.(12) In brief, multistage sampling strategies were used to select subjects aged 40 years or older in the five metropolitan areas, after stratification by administrative regions (main city and suburbs) and by socioeconomic status of census tracts. An average of 15 households in 68 census tracts was visited per site. The sample was self-weighted in each city.

Interviews and examinations took place at the subjects' home. Subjects performed pre and post bronchodilator (BD) spirometry using a portable, battery operated, ultrasound transit-time based spirometer (Easy-One™; NDD Medical Technologies, Chelmsford MA and Zurich, Swizerland). Almost 90% of all tests achieved "grade A" and almost 95% fulfilled the American Thoracic Society (ATS) criteria of quality. Exclusion criteria for spirometry followed the ATS recommendations. Spirometric results were first presented as continuous variables - pre and post BD forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC. Two categorical variables were also created: airflow obstruction (yes or no) using a cut-off point of 0.7 in the post BD FEV1/FVC ratio (13) and the GOLD stages, using predicted values for normal lung function derived from the data from the present study.(14) GOLD categories II-IV were combined due to the small number of subjects in stages III and IV.

Information on medical diagnosis of tuberculosis was based on the question “Has a doctor or other health care provider ever told you that you had tuberculosis”? For those who answered yes, we asked whether or not the subject used medication to treat the disease. Confounding variables included sex, age, ethnicity, schooling, smoking status, pack-years of smoking, hospital admissions due to pulmonary problems in childhood, exposure to domestic biomass and coal pollution, occupational exposure to dust, body mass index, and co-morbidity (medical diagnosis of heart problems, hypertension, diabetes and stroke).

The combined sample size (~5,600 individuals) allowed us to detect as significant odds ratios of 1.8 or greater for the association between airflow obstruction (prevalence of approximately 15%) and medical diagnosis of tuberculosis (prevalence of approximately 2.5%) with power of 80% and confidence level of 95%.

All analyses were stratified by study site. The analyses included a description of the sample, calculation of the prevalence of tuberculosis according to categories of the confounding variables, evaluation of mean spirometric results for subjects with and without a medical diagnosis of tuberculosis, and logistic regression using the history of tuberculosis as the main exposure of interest. In the unadjusted analyses, Wald tests for heterogeneity or linear trend were applied, except when continuous variables were analyzed; in this case, one-way ANOVA was used. Three logistic regression models for the association between medical diagnosis of tuberculosis and airflow obstruction were used. In the first, the crude association between the variables was studied. Second, the association

was adjusted for socio-demographic variables, smoking, indoor and occupational exposure to pollution, and history of hospitalization were added. In the last model, co-morbidity indicators were also included. All analyses were repeated for men and women separately. The complex sampling strategy was dealt with using the STATA (STATA 8.0; STATA Corporation, College Station Texas, 2004) "svy" commands.

The study was approved by the Ethical Review Boards of the five institutions from the participating countries. Written informed consent was obtained from all participants, and confidentiality was ensured.

Role of the funding sources

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Results

Detailed data on the sample included in the PLATINO study are available in previous publications.(15) In brief, 1,000 individuals aged 40 years or more were interviewed in Sao Paulo, 1,208 in Santiago, 1,063 in Mexico City, 943 in Montevideo and 1,357 in Caracas. Non-response rates, including the spirometric evaluation, ranged from 31.1% in Mexico City to 16.3% in Sao Paulo. Non-respondents were very similar to

respondents in terms of cigarette smoking and age; the non-response rate was higher in men than in women.(15)

Out of 5,570 subjects, 132 (2.4%) reported a medical diagnosis of tuberculosis. Of these, 105 reported the utilisation of medication to treat the disease. Table 1 describes the sample in terms of socio-demographic, behavioural, indoor and occupational exposure, past and current morbidity. The male/female ratio was 0.65, mean age 56.6 years (SD 11.9), the median duration of schooling 6.0 years and more than half of the subjects (3,012 of 5,553) reported their skin colour as white. Prevalence of current smoking was 29.2% (1,625 of 5,569) and 30.0% (1,660 of 5,536) of all subjects were obese (BMI $\geq$ 30 kg/m^2). History of hospitalization due to respiratory problems in childhood was present for 2.2% (121 of 5,569) of the subjects. Exposure to coal for cooking or heating was reported by 22.8% (1,269 of 5,563) of the subjects, while exposure to biomass was positive for 44.4% (2,467 of 5,559). Half of the subjects (2,840 of 5,564) had never been exposed do dust at the workplace, while 27.8% (1,548 of 5,564) were exposed for 10 years or more. In terms of co-morbidity, 34.9% (1,943 of 5,570) of the subjects reported suffering from hypertension, 13.6% (755 of 5,570) from heart problems, 10.0% (554 of 5,569) from diabetes, and 2.4% (133 of 5,568) had a history of stroke.

Table 1 also presents the prevalence of medical diagnosis of tuberculosis according to the independent variables included in the survey. A positive association was detected between tuberculosis and age. Tuberculosis was reported more often by subjects who were admitted to hospitals in childhood due to respiratory problems, those who were exposed to dust at the workplace, and those who were exposed to coal or biomass for

cooking or heating. In terms of co-morbidity, subjects with medical diagnoses of hypertension or stroke were more likely to report a medical diagnosis of tuberculosis.

In table 2, spirometric results are compared among subjects with and without a medical diagnosis of tuberculosis. For all spirometric indices, those with tuberculosis performed less well, although the relative difference tended to be greater for FEV1 than for FVC. When the spirometric values were converted into categorical outcomes, the association between tuberculosis and airflow obstruction was still significant and strong. In Figure 1, we show the prevalence of medical diagnosis of tuberculosis according to the COPD stages of severity proposed by the GOLD classification. A history of tuberculosis was clearly associated with more severe grades of obstruction.

Table 3 presents the odds ratios for airflow obstruction (FEV1/FCV < 0.70) according to reported tuberculosis. In the unadjusted analysis, the odds ratio for obstruction was 4.06. Adjustment for different combinations of confounding variables did not change the crude results for males, with the adjusted odds ratio being 3.99. For females, the magnitude of the association was lower than for males in the unadjusted analysis (OR 2.34); it was further reduced to 1.71 in the fully adjusted model (P=0.08). For both sexes combined, those with tuberculosis presented an odds ratio of 2.33 compared to those without tuberculosis in the fully adjusted model. Slightly stronger associations are obtained if airflow obstruction is defined as a FEV1/FVC lower than the fifth percentile for age, height and gender (14), that different from the GOLD criteria, takes into account the decrease in FEV1/FVC with aging (data available upon request).

Discussion

In a population-based multi-centre study, covering five large metropolitan areas in Latin America, we showed a strong association between a medical history of tuberculosis and airflow obstruction among subjects aged 40 years or more. To our knowledge, this is the first population-based study exploring this association using post-BD spirometry. Previous studies on the subject included occupational cohorts with high prevalence of lung disease or addressed the natural history of tuberculosis including its effect on airflow obstruction, without an internal comparison group. It is well known that history of tuberculosis may affect lung function, either by pleural changes, bronchial stenosis or parenchymal scarring. Extensive lesions may produce restrictive changes with reduced Tlco, but obstructive alterations were also identified many years ago.(16, 17)

The association of tuberculosis with FEV1 values (mean difference 0.35 ml) was stronger than for FVC (0.25 ml), and as a result the FEV1/FVC ratio showed a marked reduction, characterizing an obstructive pattern. Earlier studies, that did not rely on post bronchodilator spirometry, suggested that tuberculosis can lead to chronic airflow obstruction (18-20), but subjects diagnosed with obstruction may be asthmatic – which is markedly less likely when a bronchodilator is used.(13)

The current definition of COPD according to GOLD (13) takes into account history of smoking; therefore we opted to use the terminology “airflow obstruction” instead of COPD throughout the manuscript. Our findings suggest that the limitation to airflow caused by tuberculosis is independent from smoking, which is in accordance with previous studies. Hnizdo and colleagues (5) expanded this finding by showing that lung

damage is directly associated with the number of episodes of tuberculosis, among patients suffering from silicosis. Possible mechanisms include bronchial stenosis and lung scarring, and in addition, similarly to exposure to smoke, tuberculosis increases the activity of the matrix metalloproteinases (MMPs) enzymes, thus contributing to pulmonary damage.(21) Tobacco smoking and biomass smoke inhalation, in addition to increasing the risk of tuberculosis, may compound the airflow obstruction caused by tuberculosis.(22-25) In fact, a review study has recently suggested that subjets smoking 20 cigarettes per day or more are 2-4 more likely to present tuberculosis than non-smokers.(26)

Our findings are relevant for public health. The projections from the global burden of disease rank COPD as 6th in terms of mortality in low and middle-income countries in 2001. Tuberculosis comes right after, in the 8th position, and HIV infection, which is strongly associated with tuberculosis, ranks 4th. The reduction of tuberculosis is part of the 6th Millennium Development Goals.(27) Our findings suggest that by controlling tuberculosis, the prevalence of airflow obstruction may also be reduced.

Some limitations of our study should be considered. First, medical diagnosis of tuberculosis may not reflect the actual incidence of the disease, because it may be affected by access to diagnostic and therapeutic facilities. Our analyses were repeated after excluding all subjects with less than primary education, and results were unchanged; the overall unadjusted odds ratio, which was 2.75 in the whole sample, was 2.61 among those with at least secondary education. Adjustment for schooling did not substantially affect the association between tuberculosis and airflow obstruction. Recall bias may also affect the results – subjects who suffer from chronic respiratory

conditions may be more likely to recall previous tuberculosis episodes than those who did not have any sequelae. We believe that subjects who received treatment for tuberculosis are unlikely to underreport, given the long duration and complexity of treatment, particularly in the past. We repeated the analyses excluding subjects who were not treated (N=21), and the unadjusted odds ratio was slightly increased (3.14 versus 2.75 in the original analyses). Another limitation is the fact that the medical diagnosis of tuberculosis was not confirmed by records or image exams due to logistic and financial limitations. Although this was a cross-sectional study, reverse causality was unlikely: the peak incidence of tuberculosis occurs in young adults whereas COPD peaks much later, and the survey was restricted to subjects aged 40 years or more. Prospective studies are needed on this topic.

Relative to previous studies on this issue, it is important to highlight that ours relied on probability samples of defined urban areas. Non-response rates were lower than in most population-based studies including a physical examination, like spirometry.(12) The measurements of lung function followed strict rules and standardization(12), and the fieldwork teams in each country were trained by the same supervisors, improving comparability in data collection.

We found an important contribution of tuberculosis to airflow obstruction, linking two of the most common ailments in the world. Our results suggest that the prevention and adequate treatment of tuberculosis would reduce the burden of airflow obstruction in developing countries.

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Table 1. Prevalence of medical diagnosis of tuberculosis according to socio-demographic and behavioural variables, occupational and indoor exposures, past and current morbidity.

Variable	Description of the sample	Medical diagnosis of tuberculosis	
	N	%	P*
Sex			0.11
Men	2192	2.0	
Women	3379	2.6	
Age (years)			0.000
40-49	1988	1.5	
50-59	1625	2.3	
≥ 60	1894	3.4	
Schooling (highest degree)			0.68
0-2	733	2.2	
3-4	858	2.9	
5-8	1882	2.2	
≥ 9	2090	2.4	
Ethnic origin			0.23
White	3012	2.4	
Mixed	1889	2.1	
Black	323	2.8	
Indigenous	277	4.3	
Asian	52	1.9	
Smoking status			0.56
Never smoker	2400	2.2	
Former smoker	1544	2.7	
Current smoker	1625	2.3	
Smoking exposure (pack-years)			0.87
0-9.9	3801	2.3	
10-19.9	712	2.5	
≥ 20	1030	2.5	
Body mass index (kg/m^2)			0.15
< 25	1597	2.9	
25-29.9	2279	2.0	
≥ 30	1660	2.4	
Hospital admission due to pulmonary problems in childhood			0.000
No	5448	2.1	
Yes	121	13.2	
Indoor exposure to coal for cooking or heating			0.000
No	4294	1.8	
Yes	1269	4.3	
Indoor exposure to biomass for cooking or heating			0.000
No	3092	1.7	
Yes	2467	3.3	
Exposure to dust at the workplace			0.03

Never	2840	1.9	
<10	1176	2.6	
≥ 10	1548	3.0	
Medical diagnosis of hypertension			0.001
No	3627	1.9	
Yes	1943	3.3	
Medical diagnosis of diabetes			0.97
No	5015	2.4	
Yes	554	2.4	
Medical diagnosis of heart problems			0.57
No	4815	2.3	
Yes	755	2.7	
Medical diagnosis of stroke			0.000
No	5435	2.2	
Yes	133	7.5	

* Wald test for heterogeneity (dichotomous exposures and ethnicity) or linear trend (ordinal exposures)

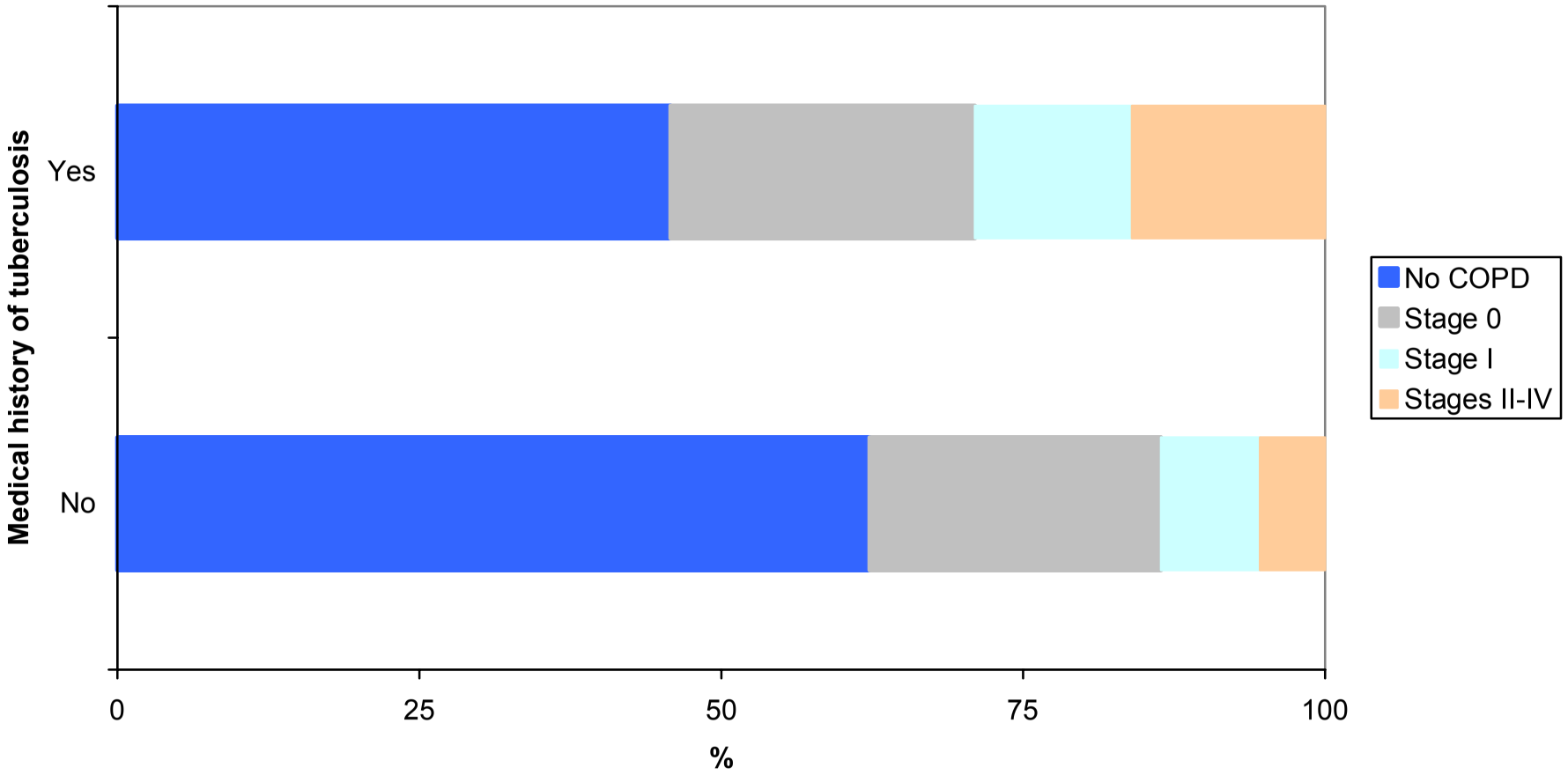

Figure 1. Prevalence of different stages of chronic obstructive pulmonary disease severity according to medical history of tuberculosis.

Table 2. Spirometry results according to medical diagnosis of tuberculosis.

Spirometric values (mean ± SD)	Medical diagnosis of tuberculosis		
	No	Yes	P #
FEV1 pre BD *	2.54 ± 0.77	2.17 ± 0.71	0.000
FEV1 % of predicted pre BD †	95.69 ± 18.32	88.14 ± 22.27	0.000
FEV 1 post BD	2.63 ± 0.77	2.26 ± 0.70	0.000
FEV 1 % of predicted post BD	95.82 ± 17.14	91.43 ± 18.80	0.007
FVC pre BD	3.37 ± 0.97	3.15 ± 0.93	0.009
FVC % of predicted pre BD	98.69 ± 16.96	98.15 ± 20.18	0.72
FVC post BD	3.38 ± 0.94	3.12 ± 0.88	0.003
FVC % of predicted post BD	98.12 ± 15.52	96.13 ± 16.34	0.16
FEV1 / FVC pre BD	0.75 ± 0.09	0.69 ± 0.11	0.000
FEV1 / FVC % of predicted pre BD	97.72 ± 10.76	90.21 ± 13.11	0.000
FEV 1 / FVC post BD	0.78 ± 0.08	0.73 ± 0.11	0.000
FEV 1 / FVC % of predicted post BD	97.85 ± 10.00	91.79 ± 13.27	0.000

* BD = bronchodilator
† Predicted values were based on the PLATINO reference curves (REF)
# One way ANOVA

Table 3. Unadjusted and adjusted odds ratios for airflow obstruction according to medical diagnosis of tuberculosis (reference category = no medical history of tuberculosis).

Analysis	Males		Females		Overall	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Unadjusted	4.06 (2.13; 7.71)	0.000	2.34 (1.39; 3.92)	0.001	2.75 (1.88; 4.03)	0.000
Adjusted for level 1	4.49 (2.27; 8.87)	0.000	1.87 (1.04; 3.35)	0.04	2.57 (1.69; 3.93)	0.000
Adjusted for levels 1 and 2	3.99 (1.92; 8.30)	0.000	1.71 (0.95; 3.09)	0.08	2.33 (1.50; 3.62)	0.000

Level 1: study site, sex, age, schooling, ethnicity, smoking status (never, former, current) and intensity (pack-years), exposure to dust at the workplace, exposure to coal and biomass for cooking or heating, history of hospitalization due to respiratory problems in childhood.
Level 2: co-morbidity (body mass index and history of hypertension, heart problems, diabetes, and stroke)