



Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis?

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ABSTRACT

The role of tuberculosis as a public health care priority and the availability of diagnostic tools to evaluate functional status (spirometry, plethysmography, and DLCO determination), arterial blood gases, capacity to perform exercise, lesions (chest X-ray and CT), and quality of life justify the effort to consider what needs to be done when patients have completed their treatment. To our knowledge, no review has ever evaluated this topic in a comprehensive manner. Our objective was to review the available evidence on this topic and draw conclusions regarding the future role of the “post-tuberculosis treatment” phase, which will potentially affect several million cases every year. We carried out a non-systematic literature review based on a PubMed search using specific keywords (various combinations of the terms “tuberculosis”, “rehabilitation”, “multidrug-resistant tuberculosis”, “pulmonary disease”, “obstructive lung disease”, and “lung volume measurements”). The reference lists of the most important studies were retrieved in order to improve the sensitivity of the search. Manuscripts written in English, Spanish, and Russian were selected. The main areas of interest were tuberculosis sequelae following tuberculosis diagnosis and treatment; “destroyed lung”; functional evaluation of sequelae; pulmonary rehabilitation interventions (physiotherapy, long-term oxygen therapy, and ventilation); and multidrug-resistant tuberculosis. The evidence found suggests that tuberculosis is definitively responsible for functional sequelae, primarily causing an obstructive pattern on spirometry (but also restrictive and mixed patterns), and that there is a rationale for pulmonary rehabilitation. We also provide a list of variables that should be discussed in future studies on pulmonary rehabilitation in patients with post-tuberculosis sequelae.

Keywords: Tuberculosis/complications; Tuberculosis/rehabilitation, Tuberculosis/therapy; Quality of life; Diagnostic imaging; Respiratory function tests.

INTRODUCTION

The World Health Organization (WHO) estimated that 3.3% of the new cases of tuberculosis and 20% of the previously treated cases of the disease are due to multidrug-resistant tuberculosis (MDR) strains of *Mycobacterium tuberculosis* worldwide in 2014. The highest prevalences of MDR tuberculosis (MDR-TB) have been reported in Eastern European and Central Asian countries, although relatively high prevalence rates have been described in Latin America. As of today, the “world record” MDR-TB prevalence has been described in Belarus (34% among new cases and 69% among retreatment cases), where 29% of the cases are reported to be extensively drug-resistant tuberculosis (XDR-TB).⁽¹⁾

It is unfortunately well known that outcomes of MDR-TB and XDR-TB cases (particularly those with a resistance pattern beyond XDR-TB) are poor, since the treatment success rate is below 20% and the failure and death rates combined are 49%.^(2,3)

The WHO has recently published two core documents addressing the critical importance of preventing the emergence of drug resistance, both underlining the relevance of managing MDR-TB adequately.^(1,4-8) The WHO action framework “Towards tuberculosis elimination for low-incidence countries” presents eight priority action areas, two of which are focused on, namely, (action #5) optimizing the management of MDR-TB and (action #7) investing in research on new diagnostic tools and drugs.^(1,4,6,9)

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However, the scientific and programmatic focus is presently on diagnosis and treatment of the disease, whereas post-cure follow-up is seen as an approach to evaluate the proportion of relapse, particularly in MDR-TB/XDR-TB cases.

The role that tuberculosis plays as a public health care priority, as well as the importance of diagnostic tools being available in order to evaluate the patients thoroughly, by means of their functional status—via spirometry, plethysmography, and determination of DLCO—arterial blood gas analyses, their capacity to perform exercise—via the six-minute walk test (6MWT)—the description of their lesions—via chest X-rays (CXRs) and CT—and their quality of life (QoL)—via the Saint George's Respiratory Questionnaire (SGRQ)—justifies the effort to consider what needs to be done when patients have completed their treatment successfully. This vision has ethical, clinical, organizational, programmatic, and economic implications.

To our knowledge, the follow-up of tuberculosis patients who completed their treatment has never been reviewed in a comprehensive manner in the literature. Therefore, the objective of the present study was to review the available evidence on this topic and to draw some conclusions regarding the future role of the "post-tuberculosis treatment" phase, which will potentially have an impact on several million cases every year around the globe.

METHODS

We carried out a non-systematic review of the literature based on a PubMed search using specific keywords, including various combinations of the terms "tuberculosis", "rehabilitation", "MDR-TB", "pulmonary disease", "obstructive lung disease", and "lung volume measurements". The reference lists of the most important studies were also retrieved in order to improve the sensitivity of the research. Manuscripts written in English, Spanish, and Russian were selected. The main areas of interest that we identified in order to describe the topic were as follows:

1. Tuberculosis sequelae following diagnosis and treatment of tuberculosis
2. Destroyed lung
3. Functional evaluation of sequelae
4. Pulmonary rehabilitation (PR) interventions, such as physiotherapy, long-term oxygen therapy (LTOT), and ventilation
5. MDR-TB

After describing each of these areas of interest, we will provide a summary of the evidence compiled from the literature search (Table 1) and concluding remarks.

TUBERCULOSIS SEQUELAE FOLLOWING DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

Although the potential role of PR has been clearly underlined in a study discussing the role of the new WHO recommendations on shorter treatment

regimens,⁽¹⁰⁾ the concept that rehabilitation is a component of tuberculosis treatment is as old as that of sanatoria.^(11,12) In 1964, Chapman and Hollander wrote that, based on their experience with 454 patients with active tuberculosis "placed on a program of intensive physical exercise, combined with chemotherapy," "the concept of minimum exercise and prolonged bed rest in the hospital and a prolonged convalescent period after discharge is no longer justified."⁽¹²⁾

In 2006, a group of authors in India⁽¹³⁾ prospectively studied the clinical presentation and predictors of outcome in 116 patients with acute exacerbations of COPD who had to be admitted to the ICU and found that 28.4% of those had had pulmonary tuberculosis previously. Among those patients, some required invasive mechanical ventilation and a few died. The authors concluded that "an intriguing relationship" existed among smoking, pulmonary tuberculosis, and COPD "which merits further study."⁽¹³⁾

In 2010, Jordan et al.⁽¹⁴⁾ wrote that "the global prevalence of bronchiectasis, a recognized sequela of tuberculosis, is unknown, but is by no means insignificant. The pathophysiology of chronic airflow obstruction in both of these diseases is poorly understood, but it is associated with an accelerated rate of loss in pulmonary function."

Hassan and Al-Jahdali⁽¹⁵⁾ reported that "in addition to its acute clinical consequences, patients with pulmonary tuberculosis may be left with significant long-term sequelae," "associated with considerable morbidity, mortality, and health expenditure," and commented that both obstructive and restrictive functional abnormalities were present.

Shah and Reed⁽¹⁶⁾ described, among the commonest complications of tuberculosis, "mycetomas developing within residual tuberculosis cavities, impaired pulmonary function, or focal neurologic deficits from tuberculomas," and, therefore, "public health tuberculosis programs and health systems require additional resources to provide comprehensive tuberculosis and post-tuberculosis care."

Bansal and Prasad⁽¹⁷⁾ commented that "COPD, interstitial lung disease, tuberculosis, and lung cancer together are the leading causes of morbidity and mortality," which are "increasing all over the world"; they also stated that "early fatigue and breathlessness" make patients "socially isolated and depressed". Functional disability and repeated hospitalizations reduce the efficiency of the patients at home and at work place, being associated with increased expenditures and utilization of health care systems, which results in a socioeconomic burden. PR, an evidence-based, multidisciplinary, and comprehensive non-pharmacological intervention, has emerged as a recommended standard of health care for patients suffering from respiratory diseases. PR is advised for patients with chronic lung conditions who have dyspnea or other respiratory symptoms, reduced exercise tolerance, restriction in activities, or impaired health status despite optimal pharmacological treatment. Early leaders observed two centuries ago

Table 1. Summary of the major studies that performed functional evaluation of patients with pulmonary tuberculosis.

Authors, year	Study location (name) ^a	Participants ^b (n)	Cases investigated	Investigations performed	Major functional findings	Conclusions
Rhee et al., 2013 ⁽²⁴⁾	South Korea	595	History of PTB	Spirometry; CXR, CT	Mean number of lobes involved: 2.59 ± 0.05 . Pleural thickening in 54.1% of the patients. Significant correlation between the number of lobes involved and FVC% ($r = -0.24$; $p < 0.001$) and FEV ₁ % ($r = -0.21$; $p < 0.001$)	Decreased lung function, exacerbations, and progressive decline of FEV ₁ were found in the patients with PTB "destroyed lung"
Lee et al., 2003 ⁽²⁴⁾	South Korea	21 CAO patients vs. 11 COPD patients	History of PTB	Spirometry	Patients with CAO due to PTB vs. COPD patients: FVC (2.14 ± 0.73 L vs. 2.60 ± 0.69 L; $p < 0.05$); FVC% ($57.97\% \pm 14.8\%$ vs. $70.07\% \pm 14.8\%$; $p < 0.01$); and response rate/% of change in post-bronchodilator FEV ₁ significantly lower in CAO patients	Bronchodilator therapy useful to treat CAO
Bález-Saldaña et al., 2013 ⁽²⁵⁾	Mexico	127	Cured PTB	CXR and spirometry	123 patients (96.85%) with CXR abnormalities; degree of CXR abnormalities independently associated with decreases in FVC (0.07 L; 95% CI: -0.01 to -0.04); FEV ₁ (0.07 L; 95% CI: -0.10 to -0.05); FVC% (2.48; 95% CI: -3.45 to -1.50); and FEV ₁ % (2.92; 95% CI: -3.87 to -1.97)	Spirometric results associated with degree of abnormalities on CXR assessed by a simple scoring method
Willcox et al., 1989 ⁽²⁶⁾	USA	71	History of PTB	Spirometry	48 (68%) with evidence of airway obstruction	Treated PTB is a cause of significant CAO.
Hnizdo et al., 2000 ⁽²⁶⁾	South Africa	2,137 (1 TB episode); 366 (2 TB episodes); and 96 (with 3 or + TB episodes)	History of PTB	Spirometry	Chronic airflow impairment (FEV ₁ < 80% of predicted) detected in 18.4% (1 TB episode); 27.1% (2 TB episodes); and 35.2% (3 or + TB episodes)	PTB can cause chronic impairment of lung function, which increases incrementally with the number of TB episodes
Amaral et al., 2015 ⁽²⁷⁾	Multinational (BOLD study) ^c	14,050	Self-reported history of TB	Spirometry	Airflow obstruction: aOR = 2.51 (95% CI: 1.83-3.42); and airflow restriction: aOR = 2.13 (95% CI: 1.42-3.19)	History of TB associated with both airflow obstruction and spirometric restriction
Jung et al., 2015 ⁽²⁸⁾	South Korea (KMHANES study 2008-2012) ^c	14,967	History of PTB and no sequelae on CXR	CXR and spirometry	822 (5.5%) with a history of PTB vs. 14,145 (94.5%) without TB history: FVC% (84.9 vs. 92.6), FEV ₁ % (83.4 vs. 92.4), and FEV ₁ /FVC% (73.4 vs. 77.9); among the subjects with normal CXR, those with a history of PTB (296; 2.3%) had significantly lower FEV ₁ % and FEV ₁ /FVC than did those without a TB history (90.9 vs. 93.4 and 76.6 vs. 78.4, respectively)	Subjects with prior PTB, inactive lesions on CXR, or no TB sequelae can show impaired pulmonary function and increased respiratory symptoms
Saitaja et al., 2015 ⁽²⁹⁾	India	56	Cured PTB	Spirometry	Obstructive, restrictive, and mixed patterns in 35 (62.50%), 9 (16.07%), and 12 (21.42%), respectively	PTB causes significant impairment of lung function, predominantly airway obstruction due to lung destruction and inflammation.
Pefura-Yone et al., 2014 ⁽³⁰⁾	Cameroon	177	Cured PTB	Spirometry	Distal airflow obstruction (FEF _{75-75%} < 65%) in 67 (62.9%); and at least one chronic respiratory sign in 110 (62.1%)	FEF _{75-75%} < 65% is a useful instrument to evaluate post-TB distal airflow obstruction
Ralph et al., 2013 ⁽³¹⁾	Papua New Guinea	200 PTB patients vs. 40 healthy subjects	Smear-positive TB (direct sputum examination)	Spirometry, 6MWT, and SGRQ	Mean pre-treatment FEV ₁ % predicted (controls vs. PTB patients) = 92 vs. 63 ($p < 0.0001$); 6MWD = 497 m vs. 408 m ($p < 0.0001$); SGRQ = 0 vs. 36.9 ($p < 0.0001$)	Early TB detection and treatment are key in minimizing residual impairment.
Vecino et al., 2011 ⁽³²⁾	USA	123	Culture-positive PTB	Spirometry	In PTB patients, post-treatment FEV ₁ % = 71 ($p < 0.0001$ vs. controls); 6MWD = 470 m ($p = 0.02$); and SGRQ = 4.3 ($p < 0.0001$)	
					Spirometry at 20 weeks of treatment and at the end of it; mean changes: FVC = -0.02 L (95% CI: -0.09 to 0.06 L); FVC% predicted = -0.02% (95% CI: -2.17% to 2.12%); FEV ₁ = 0 L (95% CI: -0.05 to 0.06 L); FEV ₁ % predicted = -0.11% (95% CI: -1.82% to 1.60%)	Pulmonary impairment after PTB treatment was not associated with duration of delay in TB diagnosis and treatment and did not significantly change during follow-up

Table 1. Continued...

Authors, year	Study location (name) ^a	Participants ^b (n)	Cases investigated	Investigations performed	Major functional findings	Conclusions
Lee et al., 2011 ⁽³³⁾	South Korea (KNHANES II study 2001) ^c	3,687	Evidence of PTB on CXR	CXR and spirometry	Evidence of PTB on CXR is associated with airflow obstruction (aOR = 2.56; 95% CI: 1.84- 3.56)	PTB is an independent risk factor for obstructive lung disease in never-smokers.
Chung et al., 2011 ⁽³⁴⁾	Taiwan	115	Culture-positive PTB	Spirometry	Nadir of pulmonary function occurs approximately 18 months after treatment completion; risk factors for pulmonary function deterioration were positive sputum smear microscopy, extensive pulmonary involvement, prolonged anti-TB treatment, and reduced improvement on CXR after treatment	In patients with significant respiratory symptoms and multiple risk factors, pulmonary function tests should be used to monitor progression of functional impairment
Lam et al., 2010 ⁽³⁵⁾	China (Guangzhou Biobank Cohort Study)	8,066 (73.6% women and 26.4% men)	Evidence suggestive of inactive PTB on CXR	CXR and spirometry	Prevalence of prior TB was 24.2%; prior PTB is associated with airflow obstruction (aOR = 1.37; 95% CI: 1.13-1.67); smoking did not modify this relationship	Prior TB is an independent risk factor for airflow obstruction, regardless of smoking status
Bajig et al., 2010 ⁽³⁶⁾	Pakistan	92	History of PTB with chronic exertional dyspnea with or without cough. Evidence of inactive PTB on CXR	Spirometry	26 (65.3%) with obstructive pattern [severe/ stage III in 18 (69.2%); moderate/ stage II in 6 (23.0%); mild/ stage I in 2 (5.9%)]; 14 (29.7%) with restrictive pattern; and 7 (14.8%) with mixed pattern	COPD can occur as one of the chronic complications of PTB
Paspandya et al., 2007 ⁽³⁷⁾	USA	107 PTB patients and 20 LTBI patients	Culture-positive PTB or PTB and extrapulmonary TB patients who had completed at least 20 weeks of therapy	Spirometry	PTB survivors are more likely to have abnormal spirometric results than patients with LTBI (aOR = 5.4; 95% CI: 2.98- 9.68)	Pulmonary impairment after TB is associated with disability worldwide and demands more aggressive/prevention strategies and post-treatment evaluation
Menezes et al., 2007 ⁽³⁸⁾	Mexico, Venezuela, Brazil, Uruguay, Chile (PLATINO study) ^c	5,571	Self-reported history of PTB	Spirometry	Airflow obstruction in 30.7% of the sample; history of PTB is associated with airflow obstruction (aOR = 2.33; 95% CI: 1.50-3.62)	History of PTB is associated with airflow obstruction
de la Mora et al., 2015 ⁽³⁹⁾	Mexico	70	Cured PTB	Spirometry and CAT	Nonreversible chronic obstruction in 24 (34.3%); mean post-bronchodilation FEV ₁ = 1.32 ± 0.6 L and 57.30% ± 9.95% of predicted; CAT score = 15.1 ± 10.4	Functional abnormalities are frequent in PTB patients
Di Naso et al., 2011 ⁽⁵³⁾	Brazil	37 (25 DS-PTB vs. 12 MDR-PTB)	Cured PTB	CXR, spirometry, 6MWT, and pressure manometry	Severe combined respiratory disorder was the more prevalent in MDR-PTB patients (9/12); MDR-PTB group (vs. DS-PTB) showed significantly lower values in FVC% of predicted (43.58 ± 16.03 vs. 72.06 ± 14.95); FEV ₁ of predicted (33.08 ± 15.64 vs. 66.13 ± 19.87); MIP (49.58 ± 12.55 cmH ₂ O vs. 68.40 ± 22.78 cmH ₂ O); MEP (59.08 ± 12.23 cmH ₂ O vs. 87.20 ± 27.30 cmH ₂ O); and 6MWD (334.75 ± 104.07 m vs. 484.21 ± 74.01 m)	Patients with MDR-PTB who have undergone multiple treatments have more severe respiratory and functional impairment than do patients who have had just a single treatment
de Vallèrièrè et al., 2004 ⁽⁵⁴⁾	South Africa	33 MDR-PTB	Cured PTB	CXR and spirometry	Cavitation was present in more than half of the patients. 31 (94%) with abnormal lung function tests: restrictive pattern in 14 (42%); combined pattern in 13 (39%); obstructive pattern in 4 (12%); and normal spirometric results in 2 (6%)	Residual lung damage in MDR-PTB patients who completed treatment is common and extensive

PTB: pulmonary tuberculosis; CXR: chest X-ray; CAO: chronic airway obstruction; TB: tuberculosis; aOR: adjusted odds ratio; 6MWT: six-minute walk test; SGRO: Saint George's Respiratory Questionnaire; 6MWD: six-minute walk distance; LTBI: latent TB infection; CAT: COPD assessment test; DS-PTB: drug-susceptible PTB; and MDR-PTB: multidrug-resistant PTB. ^aBOLD: Burden of Obstructive Lung Disease; KNHANES: Korean National Health and Nutrition Examination Surveys; and PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar*. ^bAll studies included both men and women. ^cPopulation-based studies.

that exercise is an important element in the care of patients with lung and heart diseases, especially in tuberculosis.⁽¹⁷⁾

In a recent American Thoracic Society (ATS)/European Respiratory Society (ERS) statement, as well as in a guideline from South Africa for the management of COPD, tuberculosis is clearly among the diseases that require the use of PR.^(18,19)

“DESTROYED LUNG”

Late diagnosis is often responsible for extensive bilateral lesions, usually due to bronchiectasis, scarring, parenchymal deformation, lung volume loss, and pleural thickening, which might develop to the so-called “destroyed lung” (Figure 1).⁽²⁰⁾

Two studies described the effect of “destroyed lung” on the pulmonary function of patients treated for pulmonary tuberculosis, both carried out in South Korea.^(21,22) Rhee et al.⁽²¹⁾ studied 595 tuberculosis patients from 21 hospitals between 2005 and 2011. The mean extension of the lesions was 2.59 ± 0.05 lobes, and pleural thickening was observed in 54.1% of the patients. Various lung function parameters were reduced (mean values): FVC = 2.06 ± 0.03 L (61.26% \pm 0.79% of predicted); FEV₁ = 1.16 ± 0.02 L (49.05% \pm 0.84% of predicted); FEV₁/FVC ratio = 58.0% \pm 0.70%; bronchodilator response = 5.70% \pm 0.34%; and number of exacerbations/year = 0.40 ± 0.04 . The number of lobes involved significantly correlated with FVC, FEV₁, and the number of exacerbations/year. The use of long-acting muscarinic antagonists or long-acting β_2 agonists plus inhaled corticosteroids achieved bronchodilator effects. Initial FEV₁% and the number of exacerbations during follow-up were independent factors affecting FEV₁ deterioration in the multivariate analysis.

Lee et al.⁽²²⁾ investigated lung function and post-bronchodilator response in 21 patients with



Figure 1. Chest X-ray of a 39-year-old male patient with a history of pan-susceptible tuberculosis treated for six months in 2007. The patient was considered cured. Later in time, he reported a six-month history of cough, mild dyspnea, but no fever. Tuberculosis relapse was ruled out; sputum smear microscopy and culture were negative. The image shows a giant cavity in the right upper lobe and some fibrotic changes.

“destroyed lung”-related chronic airflow obstruction against a cohort of COPD patients matched by sex, age, and pulmonary function parameters. The mean FVC values (both in L and in % of predicted) of the patients with “destroyed lung” were significantly lower than those of the COPD patients (2.14 ± 0.73 L vs. 2.60 ± 0.69 L and $57.9\% \pm 14.8\%$ vs. $70.0 \pm 14.8\%$, respectively). The tuberculosis patients presented with significantly lower FVC and post-bronchodilator FEV₁ than did the COPD patients. In addition, among the tuberculosis patients, those with wheezing symptoms showed significantly lower FEF_{25-75%} and higher airway resistance than did those without wheezing. Tuberculosis patients with wheezing responded better to the bronchodilator than did those without it. The authors concluded that bronchodilator therapy could be useful in those patients.

In Mexico, 127 cured tuberculosis patients underwent spirometry and CXR; 123 (96.85%) exhibited some degree of radiographic abnormalities.⁽²³⁾ The extent of lung damage was measured by dividing the lung parenchyma into four quadrants and scoring it from 0 to 5; the mean number of radiographic abnormalities was 6.45 ± 4.14 . In that sample, 30 patients (24%) showed an obstructive spirometric pattern, and 22 (17%), a restrictive pattern; only 15 (12%) had a positive bronchodilator test, and 21 (17%) had an SpO₂ < 90%. The adjusted multilinear regression model showed that the degree of radiographic abnormalities was independently associated with a decrease in the absolute values of FVC (0.07 L; 95% CI: -0.01 to -0.04) and FEV₁ (0.07 L; 95% CI: -0.10 to -0.05 ; $p < 0.001$); as well as in their % of predicted values (FVC = 2.48%; 95% CI: -3.45 to -1.50 ; and FEV₁ = 2.92%; 95% CI: -3.87 to -1.97). That study showed that spirometric values were associated with the degree of radiographic abnormalities assessed by a simple scoring method.

FUNCTIONAL EVALUATION OF SEQUELAE

Several studies investigated the mechanical lung function in tuberculosis patients (Figure 2).

Already in 1961, Hallet and Martin⁽²⁴⁾ described the diffuse obstructive pulmonary syndrome (measured via the maximal expiratory flow rate) in 34% of 710 tuberculosis patients admitted to a sanatorium during a one-year period. The factors significantly associated with the incidence of that syndrome were age, severity of tuberculosis, and some comorbidities (bronchial asthma, pulmonary malignancy, frequent and protracted chest colds, and silicosis). The authors concluded that the measurement of maximal expiratory flow rate is a useful tool in determining diffuse obstructive pulmonary disease.

Willcox and Ferguson⁽²⁵⁾ investigated 71 patients previously treated for tuberculosis up to 16 years prior. Evidence of airway obstruction was found in 48 (68%) of the patients. An inverse relationship between the extent of the disease on the original CXRs and FEV₁

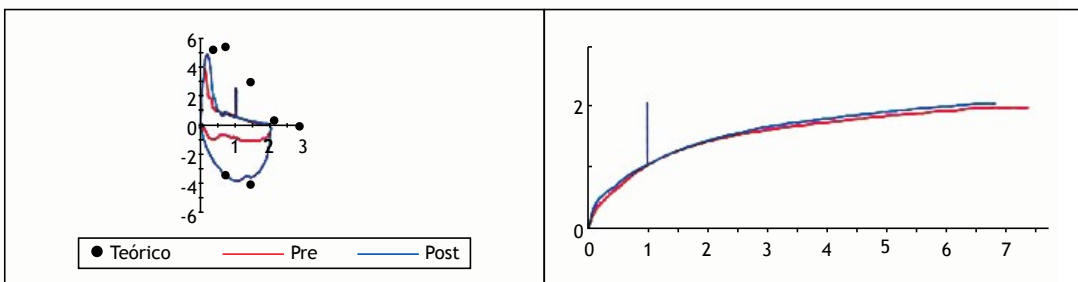
was identified. The authors identified a similar inverse relationship of the amount of sputum produced with FEV₁ and with the extent of the disease on the CXRs. The authors concluded that treated tuberculosis is a cause of COPD.

In a large study in South Africa,⁽²⁶⁾ a cohort was followed in order to study the chronic effect of initial and recurrent pulmonary tuberculosis: 27,660 black South African gold miners who had reliable pulmonary function test results between January of 1995 and August of 1996 were retrospectively followed for the incidence of tuberculosis to 1970. In that cohort of miners, 2,137; 366; and 96 had had, respectively, one, two, and three or more episodes of tuberculosis. The mean time between the diagnosis of the last episode of tuberculosis and lung function testing was 4.6 years (range: 1-372 months). The loss of lung function was the highest within the first 6 months after tuberculosis being diagnosed and stabilized after 12 months, when the loss was considered chronic. The estimated mean deficits in FEV₁ after one, two, and three or more episodes of tuberculosis were 153 mL, 326 mL, and 410 mL, respectively, whereas the corresponding deficits in FVC were 96 mL, 286 mL, and 345 mL. The loss of lung function was similar in HIV-positive and HIV-negative individuals. The proportion of individuals with chronic airflow impairment (FEV₁ < 80% of predicted) was 18.4%, 27.1%, and 35.2%, respectively, in those with one, two, and three or more episodes of tuberculosis. The authors concluded that tuberculosis can cause chronic impairment of lung function, which increases with the number of episodes of the disease, and that early diagnosis and treatment of tuberculosis coupled with the prevention of HIV, silica dust exposure, silicosis, and poverty are important interventions.

In a recent multicenter, cross-sectional, general population-based study,⁽²⁷⁾ the association of having a history of tuberculosis with airflow obstruction and spirometric abnormalities was studied in adults. A self-reported history of tuberculosis was associated

with airflow obstruction (adjusted OR = 2.51; 95% CI: 1.83-3.42) and spirometric restriction (adjusted OR = 2.13; 95% CI: 1.42-3.19). The authors concluded that a history of tuberculosis was associated with both airflow obstruction and spirometric restriction, and should be considered as an important cause of obstructive disease and impaired lung function, particularly where tuberculosis is common.

In a study performed in South Korea between 2008 and 2012,⁽²⁸⁾ lung function impairment and persistency of respiratory symptoms were studied in 14,967 adults with and without a history of pulmonary tuberculosis. The adults were also divided into two groups: those showing residual sequelae on CXR and those without showing it in order to determine the risk factors for airflow obstruction. Among the population studied, 822 participants (5.5%) had been treated for pulmonary tuberculosis (mean) 29.0 years prior to study initiation. The individuals with a history of tuberculosis, when compared with those without that, presented with significantly lower FVC% (84.9 vs. 92.6), FEV₁% (83.4 vs. 92.4), and FEV₁/FVC% (73.4 vs. 77.9). Among the 12,885 subjects with no sequelae on CXR, those with a history of pulmonary tuberculosis (n = 296; 2.3%) had significantly lower FEV₁% (90.9 vs. 93.4) and FEV₁/FVC% (76.6 vs. 78.4). Subjects with a history of pulmonary tuberculosis but no sequelae on CXR reported a significantly higher frequency of cough and physical activity limitations due to pulmonary symptoms than those without that history (p < 0.001 for both). A history of pulmonary tuberculosis (OR = 2.314), along with older age, male gender, asthma, and smoking were independent risk factors for airflow obstruction. Finally, the study suggested that inactive tuberculosis lesions on CXR (OR = 2.3) were risk factors for airflow obstruction in subjects with a history of pulmonary tuberculosis. The authors concluded that the patients treated for tuberculosis should undergo regular lung function testing and stop smoking in order to prevent chronic airway disease.



	Pre-Bronch			Post-Bronch		
	Real	Teórico	%Teórico	Real	%Teórico	%Cambio
--ESPIROMETRÍA--						
FVC (L)	1.99	2.85	69	2.04	71	+2
FEV1 (L)	1.05	1.63	64	1.06	65	+1
FEV1/FVC (%)	53	71	74	52	73	-1

Figure 2. Spirometry of the same patient shown in Figure 1. FEV₁/FVC ratio was below 70%. FEV₁ was decreased and unresponsive to bronchodilator. FVC was also diminished. Fixed airway obstruction was detected, and mild restriction was considered. The final diagnosis was pulmonary sequelae of tuberculosis. Espirometría: spirometry; teórico: predicted; pre/post bronch: pre-/post-bronchodilator; real: observed; and cambio: change.

In a recent study,⁽²⁹⁾ 56 treated tuberculosis patients who were considered cured underwent simple spirometry, and pre- and post-bronchodilator FEV₁, FVC, FEV₁/FVC ratio were recorded. Obstructive, restrictive, and mixed patterns were identified in 62.50%, 16.07%, and 21.42% of the patients, respectively.

In a cross-sectional study⁽³⁰⁾ involving 177 individuals who had been previously treated for tuberculosis in Cameroon between 2012 and 2013, spirometry was performed in order to evaluate the clinical impact of low FEF_{25-75%}. Distal airflow obstruction (DAO) was defined by an FEF_{25-75%} < 65% and a FEV₁/FVC ratio ≥ 0.70. At least one chronic respiratory sign was present in 110 (62.1%) of the participants, and DAO was identified in 67 (62.9%). Duration of symptoms prior to the diagnosis of tuberculosis > 3 months (adjusted OR = 2.91) and presence of DAO (OR = 2.22) were independent determinants that were significantly associated with persisting respiratory signs. The authors concluded that FEF_{25-75%} < 65% is a useful instrument to evaluate post-tuberculosis DAO.

In Papua New Guinea, presently a hot spot for MDR-TB, a study⁽³¹⁾ evaluated morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis cases undergoing spirometry, 6MWT, and evaluation of QoL (SGRQ). The authors evaluated 200 pulmonary tuberculosis patients (at baseline and after 6 months of treatment) and 40 healthy volunteers. The distance walked in the 6MWT (6MWD) was 497 m in controls vs. 408 m in tuberculosis patients at baseline ($p < 0.0001$) and 470 m after 6 months ($p = 0.02$), whereas the SGRQ score was zero in controls vs. 36.9 in tuberculosis patients at baseline ($p < 0.0001$) and 4.3 after 6 months ($p < 0.0001$). The mean predicted FEV₁ was 92% in controls vs. 63% among tuberculosis patients at baseline ($p < 0.0001$) and 71% after 6 months ($p < 0.0001$). After six months of treatment, 27% of the tuberculosis patients still showed at least moderate-to-severe pulmonary function impairment, and 57% had respiratory symptoms, although most of them achieved "successful" treatment outcomes and self-reported good QoL. More advanced disease at baseline (longer illness duration and worse results on CXR at baseline) and HIV-positive status predicted residual disability. The authors concluded that early detection and treatment of tuberculosis are key in minimizing residual impairment.

Post-pulmonary tuberculosis impairment was studied after 20 weeks of tuberculosis treatment and again on, or after, treatment completion.⁽³²⁾ The median duration between the first and the second spirometry was 15 weeks. The mean change in FVC was -0.02 L (95% CI: -0.09 to 0.06 L), and that in FVC% of predicted was -0.02% (95% CI: -2.17% to 2.12%), whereas that in FEV₁ was 0 L (95% CI: -0.05 to 0.06), and that in FEV₁% of predicted was -0.11% (95% CI: -1.82 to 1.60). Pulmonary impairment was not related to the delay in tuberculosis diagnosis or treatment, older age, or smoking habits.

The relationship between previous tuberculosis and the risk of COPD was studied in South Korea in a population-based investigation⁽³³⁾ involving 3,687 individuals performing spirometry and CXR. Among those, 294 subjects had radiological evidence of previous tuberculosis with no evidence of active disease. Radiological evidence of previous tuberculosis was independently associated with airflow obstruction (adjusted OR = 2.56) after adjustments for sex, age, and smoking history. Previous tuberculosis was still a risk factor (adjusted OR = 3.13) with the exclusion of ever-smokers or subjects with advanced radiological lesions. Among the never-smokers, the proportion of subjects with previous tuberculosis on CXR increased as obstructive lung disease became more severe. The authors concluded that previous tuberculosis is an independent risk factor for COPD, even in never-smokers.

The trends toward deterioration of pulmonary function and its risk factors were studied in 115 patients with pulmonary tuberculosis after treatment completion.⁽³⁴⁾ A model with a locally weighted scatterplot smoothing technique was used in order to evaluate the trends toward changes in pulmonary function. The median interval between the end of antituberculosis treatment and pulmonary function testing was 16 months. The nadir of pulmonary function occurred approximately 18 months after completion of the treatment. The risk factors associated with pulmonary function deterioration included positive sputum smear microscopy, extensive pulmonary involvement prior to antituberculosis treatment, prolonged antituberculosis treatment, and poor radiographic improvement after treatment. The authors concluded that pulmonary function testing should be used as a follow-up tool in order to monitor the progression of functional impairment, especially within the first 18 months after the completion of antituberculosis treatment.

A study in China⁽³⁵⁾ investigated the relationship between history of tuberculosis, smoking, and airflow obstruction in a population sample of 8,066 participants in the Guangzhou Biobank Cohort Study. The participants underwent spirometry, CXR, and a structured interview on lifestyle and exposures. Prior tuberculosis was defined as the presence of radiological evidence suggestive of inactive tuberculosis. In that sample, 24.2% of the individuals had a history of tuberculosis. After controlling for sex, age, and smoking exposure, prior tuberculosis remained independently associated with an increased risk of airflow obstruction (OR = 1.37; 95% CI: 1.13-1.67). Further adjustments for exposure to passive smoking, biomass fuel, or dust did not alter that association. Smoking did not modify the association between prior tuberculosis and airflow obstruction. The authors concluded that prior tuberculosis is an independent risk factor for airflow obstruction, which might partly explain the high prevalence of COPD in China.

In a study in Pakistan,⁽³⁶⁾ the prevalence of COPD was studied in 47 patients previously treated for pulmonary

tuberculosis and reporting chronic exertional dyspnea with no other apparent cause. Of the 47 patients, 26 (55.3%) showed an obstructive pattern on spirometry (severe in 18, moderate in 6, and mild in 2), whereas 14 (29.7%) were found to have a restrictive pattern, and 7 (14.8%) revealed a mixed obstructive and restrictive pattern.

In a case-control study,⁽³⁷⁾ the lung function of 107 prospectively identified patients with pulmonary tuberculosis who had completed at least 20 weeks of therapy was compared with that of 210 patients with latent tuberculosis infection (LTBI). Impairment was present in 59% of the tuberculosis patients and in 20% of the LTBI control subjects. In comparison with the controls, the pulmonary tuberculosis patients showed significantly lower FVC, FEV₁, FEV₁/FVC ratio, and mid-expiratory phase of FEF. A VC < 50% of predicted was found in 10 (9.40%) and 1 (0.53%) of the patients, respectively, in the pulmonary tuberculosis and LTBI groups. In addition, a VC between 20% and 50% of the predicted was found in 42 (39%) and in 36 (17%) of the patients in the same groups, respectively. After adjusting for risk, tuberculosis survivors were 5.4 times more likely to have abnormal lung function test results than were LTBI patients ($p > 0.001$; 95% CI: 2.98-9.68). Lung damage was more common in cigarette smokers; however, after adjusting for demographic and other risk factors, that difference was not significant. The authors concluded that "microbiological cure is the beginning, not the end of their illness".

In a population-based multicenter study conducted in five Latin American cities including 5,571 subjects, a self-reported history of pulmonary tuberculosis was clearly associated with varying degrees of airflow obstruction, defined by a post-bronchodilator FEV₁/FVC ratio < 0.7. In that study, 30.7% of subjects with a history of tuberculosis presented with airflow obstruction vs. 13.6% of those without that history. The association between a self-reported history of tuberculosis and the presence of airflow obstruction remained unchanged even after adjustments for confounding variables (adjusted OR = 2.33; 95% CI: 1.50-3.62).⁽³⁸⁾

In Tijuana, Mexico,⁽³⁹⁾ 70 cured pulmonary tuberculosis patients were evaluated in order to determine the prevalence and the severity of COPD and its impact on QoL. Among those patients, 24 (34.3%) had nonreversible chronic airway obstruction (mean post-bronchodilation FEV₁ = 1.3 ± 0.6 L). In addition, patients with chronic airway obstruction had a COPD assessment test score of 15.1 ± 10.4—a score ≥ 10 points indicates a significant impact on QoL. The authors concluded that functional abnormalities are frequent in tuberculosis patients, and those with chronic airway obstruction are often symptomatic and experience a significant impact on their QoL.

PR INTERVENTIONS

The mechanisms behind lung damage following tuberculosis and its treatment have been described by

Zhuk,⁽⁴⁰⁾ who underlined the advantages of PR and who identified that about 50% of those patients undergo PR programs during hospital admissions in Russia.

In an experience in Japan,⁽⁴¹⁾ the effectiveness of PR was evaluated for a mean period of 3.9 weeks in 37 inpatients with pulmonary tuberculosis sequelae. The PR program included relaxation, breathing retraining, exercise training, respiratory muscle training, and educational support. Mean VC improved significantly ($n = 37$), from 1.48 L to 1.59 L, whereas FEV₁ ($n = 37$) improved from 0.93 L to 1.02 L, as well as did PaO₂ ($n = 35$), from 67.1 Torr to 72.4 Torr. The gain in the 6MWD ($n = 29$) increased from 303 m to 339 m, and MIP ($n = 17$) increased from 38.5 cmH₂O to 47.5 cmH₂O. There were also improvements in activities of daily living, dyspnea symptoms, and QoL. The effects of PR were independent from previous thoracic surgery for tuberculosis, pattern of ventilatory impairment, findings on CXR, or degree of respiratory insufficiency. The study results suggested that PR is effective in improving pulmonary function, exercise tolerance, symptoms, and QoL in patients with pulmonary tuberculosis sequelae.

A group of authors in Colombia^(42,43) investigated the effects of PR on aerobic capacity and health-related QoL in patients with sequelae of pulmonary tuberculosis who participated in an eight-week PR program within a public hospital. The studies included a pre- and post-test design without a control group, and it involved 8 participants intentionally selected from a public program. The program included physical training (upper and lower limb strengthening and aerobic component), education on tuberculosis, and training on activities of daily living. A treadmill-based training protocol for the lower limbs was established, starting with an initial intensity load of 60%, and then increasing up to a load of 85%; the peak oxygen consumption (VO_{2peak}) was set at 90%. The training sessions were carried out three times a week for eight weeks, and each lasted one hour, which included initial examination, warm-up, exercise protocol, and stretching exercises. Outcome measures (VO_{2peak}, 6MWD, and two QoL questionnaires—the Medical Outcomes Study 36-item Short-Form Health Survey [SF-36] and SGRQ)—were performed prior to the first training session and at eight weeks. Comparing baseline and final results, the VO_{2peak} increased by 1.7 mL/kg/min ($p = 0.039$), and the 6MWD increased by 63.6 m ($p = 0.014$). The QoL questionnaire scores increased as well: SF-36 physical domain score increased by 6.98 points ($p = 0.039$), whereas the SGRQ score increased by 13 points ($p = 0.039$). The authors concluded that the PR program in that sample of patients with pulmonary tuberculosis sequelae resulted in significant improvements in both aerobic capacity and QoL.

A single-blinded randomized controlled study was performed at a clinic in Khayelitsha, Western Cape, South Africa, in order to assess the effects of a six-week home-based PR program in patients receiving treatment for pulmonary tuberculosis.⁽⁴⁴⁾ The program included

baseline and post-rehabilitation measurements of lung function (spirometry), of exercise tolerance (6MWT and Borg exercise exertion scale), and of health-related QoL (EuroQoL—EQ-5 D—questionnaire) in 34 patients receiving outpatient treatment for tuberculosis and in 33 controls. When compared with the controls, there were improvements in the lung function (FEV₁ and FVC), exercise tolerance, and QoL in the tuberculosis patients, although statistical significance was not reached at the end of the six-week PR program. The authors concluded that the rationale for using a PR program for patients with pulmonary tuberculosis is valid and that further evidence is needed.

In a prospective nonrandomized open trial over a nine-week period conducted in Japan,⁽⁴⁵⁾ the effect of PR on patients with post-tuberculosis lung disorders was compared with that on patients with COPD. The post-tuberculosis group comprised 32 patients (25 of whom had undergone thoracoplasty; mean age = 71 ± 5 years; and mean FEV₁ = 0.84 ± 0.29 L) who were compared with 32 age-matched and FEV₁-matched COPD patients (controls). First, the two groups were compared regarding their exercise tolerance (6MWT). Then, the patients were trained to undergo a nine-week outpatient PR program. Improvements were assessed by using clinical dyspnea ratings, a daily activity score, and the results of the 6MWT. When age and FEV₁ were matched, the 6MWD did not differ between the study and control groups. After the PR program, significant improvements were observed in the two groups regarding the Medical Research Council dyspnea scale, transition dyspnea index, and daily activity scores, as well as in the 6MWD—study group = 42 m (*p* < 0.01) vs. control group = 47 m (*p* < 0.01). The gain in the various parameters was comparable between the groups. The authors concluded that the PR program is as beneficial in post-tuberculosis patients with lung disorders as in COPD patients if the severity of the disability is similar.

LTOT AND VENTILATION

The importance of LTOT was investigated in Japan, together with the relevance of tuberculosis as a disease that demands post-treatment rehabilitation.⁽⁴⁶⁾ The importance of ventilation to improve the performance of tuberculosis patients with sequelae was also studied.

In a study involving 7 patients with pulmonary tuberculosis sequelae and severe restrictive ventilatory defect,⁽⁴⁷⁾ nasal intermittent positive pressure ventilation (NIPPV) was applied during exercise in order to determine whether arterial blood gas measurements, breathlessness, and exercise endurance could be improved. The authors reported that NIPPV significantly prolonged exercise endurance time and decreased breathlessness in all of the patients, as well as it significantly improved arterial blood gas measurements.

Yang et al.⁽⁴⁸⁾ described the positive effects of respiratory support with a poncho (wraparound) ventilator and mouthpiece intermittent positive pressure

ventilation on a 44-year-old patient affected by severe restrictive lung disease secondary to right phrenic nerve crush/pneumoperitoneum and left pneumonectomy/decortication for bilateral lower lobe tuberculosis. The patient developed dyspnea, coryza, and somnolence. With the assistance of the two respiratory devices, the patient was able to complete her education, get married, and lead a fulfilling life in the community.

PHYSIOTHERAPY

In 2004, Strelis et al.⁽⁴⁹⁾ proposed a vibration massage-based method to prevent early postresection complications after surgical interventions due to tuberculosis. The method included the use of a light vibromassage apparatus that allowed systemic physiotherapy involving electric vibroacupressure of the whole circumference of the chest. In that case-control study,⁽⁴⁹⁾ early postresection complications were significantly less frequently observed in the study group than in the control group (60 vs. 50 patients). The procedure reduced the likelihood of development of a number of pleuropulmonary events (atelectasis, nonspecific pneumonia, residual postresection pleural cavity, and bronchial fistulas) and enhanced the functional status of the patients.

MDR-TB

The majority of the studies included in the present review article reported drug-susceptible cases. Only three studies discussed PR interventions in MDR-TB patients.

In a cross-sectional cohort study in Brazil,⁽⁵⁰⁾ respiratory function, functional capacity, and QoL were investigated in 18 patients who had been treated for pulmonary MDR-TB for 18 months or more. The subjects underwent the following assessments: forced spirometry, CXR, 6MWT, bioelectrical impedance analysis, MIP, and MEP. They also completed a health-related QoL questionnaire. Spirometric evaluation showed that 78% of the subjects had abnormal ventilatory patterns. All of the subjects presented with significantly decreased MIP and MEP, despite the fact that their nutritional status was within the normal range. In 72% of the subjects, the 6MWD was lower than expected, and residual lesions were present in 100%, whereas 78% reported a worsening in their QoL. The authors concluded that patients achieving MDR-TB cure present impaired respiratory function, as well as mildly reduced functional capacity and QoL, suggesting that a portion of these patients might require PR.

In a cross-sectional study in India,⁽⁵¹⁾ 130 MDR-TB patients who had initiated treatment were evaluated between 2002 and 2006. During the study period, 24 patients died, and 63 (59%) could be traced, of whom 51 were alive. Those patients had completed a mean post-treatment period of 24.0 ± 14.7 months (range, 6–63 months), 40 (78%) had persistent respiratory symptoms, and 50 (98%) had residual sequelae on CXR (40% of which being severe). Abnormal pulmonary

function test results were observed in 45 (96%) of the patients, predominantly with a mixed type ventilatory impairment in 31 (66%), a pure restrictive pattern in 9 (19%), and a pure obstructive pattern in 5 (11%). The authors concluded that functional impairment and radiological lesions are common in patients after completing MDR-TB treatment.

In a case report in Colombia,⁽⁵²⁾ a patient with MDR-TB underwent a PR program. After the completion of the program, there was improvement in the 6MWD (from 240 m to 350 m), in the Medical Research Council dyspnea scale score (from 4 to 1), and in the Borg scale (from 7 to 0). Furthermore, his upper and lower limb muscle strength increased from 3 to 4. The authors concluded that a period of PR lasting 8-10 weeks was sufficient to improve his functionality.

A cross-sectional study carried out in Brazil⁽⁵³⁾ compared functional and respiratory changes between patients with a single episode of tuberculosis and MDR-TB patients who had had multiple episodes before receiving an effective treatment. The MDR-TB group showed significantly lower values in FVC (72.06% ± 14.95% vs. 43.58% ± 16.03% of predicted), FEV₁ (66.13% ± 19.87% vs. 33.08% ± 15.64% of predicted), and 6MWD (484.21 m ± 74.01 m vs. 334.75 m ± 104.07 m). The study⁽⁵³⁾ demonstrated the existence of significant functional limitations in MDR-TB patients who had undergone multiple tuberculosis treatments and strengthened the importance to prevent treatment noncompliance and subsequent rescue regimens.

In a study in Limpopo Province, South Africa,⁽⁵⁴⁾ 33 MDR-TB patients performed spirometry: 14 (42%) had a restrictive pattern, 4 (12%) had obstructive disease, and 13 (39%) showed a combined pattern, although no further studies were performed to corroborate the presence of restriction. In the linear regression analysis, FEV₁ and FVC (both in % of predicted) were negatively associated with the time between the first diagnosis of tuberculosis and the completion of treatment (mean time, 51.8 months). The authors concluded that residual lung damage in MDR-TB patients is common and that extensive efforts should be made in order to ensure rapid diagnosis and treatment.⁽⁵⁴⁾

FINAL CONSIDERATIONS

The present review of the evidence available in the literature suggests that tuberculosis is definitively responsible for lung function sequelae, most of which causing an obstructive pattern, although restrictive and mixed patterns are also present.

Unfortunately, few studies are available in the literature investigating the physiopathology of obstruction, the potential need for PR, and the effects of a PR program. The majority of the studies investigated the functional status by spirometry, a few of them by plethysmography, whereas evidence based on determination of DLCO, arterial blood gas analyses, walk tests, and QoL is anecdotal.

The vast majority of the available studies included patients with drug-susceptible tuberculosis. Details on the characteristics of tuberculosis are rarely complete; in particular, information on the microbiological confirmation of the cases (culture or, at least, sputum smear microscopy) is rarely reported, since most studies tend to focus on the physiopathological aspects of the patients studied. We have found no studies in which a diagnosis of tuberculosis was based on rapid molecular assays, such as Xpert™ MTB/RIF as of today.⁽⁵⁵⁾

Very few studies reported MDR-TB cases, and we have found no studies that investigated whether there is any difference in sequelae between drug-susceptible tuberculosis and MDR-TB cases. The latter patients need a much longer period of treatment (18-24 months in comparison with the tentative 6 months for drug-susceptible cases) and have usually completed more than one previous course of treatment with first or second-line antituberculosis drugs. The impact of the shorter tuberculosis regimen (known as the Bangladesh regimen), which has a duration comparable to that for drug-susceptible tuberculosis (9 months), could not be evaluated since it was recommended by WHO only in May of 2016.^(10,56,57)

Interestingly, although all studies identified that tuberculosis plays a significant role in deteriorating pulmonary function, the additional role of smoking as a factor that creates additional lung function impairment needs to be studied further.

It is recommended that any future evaluation of tuberculosis and MDR-TB sequelae include complete information on

- The characteristics of the patients (age, sex, ethnicity, etc.)
- A complete description of the disease, including history of previous treatments, bacteriological status, pattern of drug resistance, and history of current treatment (drugs and regimen) with an emphasis on adverse events and their management
- A complete description of the physiopathological status of the patients, including spirometry (and bronchodilator response), assessment of lung volumes (plethysmography or others), determination of DLCO, arterial blood gas analysis, 6MWT, radiological evaluation (ideally including CXR), and QoL evaluated with a general instrument and a specific respiratory instrument (SGRQ or others)
- Rationale and consistence of the proposed PR plan, with clear pre- and post-test comparisons and evaluation of costs
- Ideally, further studies should include the number of patients who need PR, since this will help to estimate the need for PR planning

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