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Pulmonary functional assessment: longitudinal study after treatment of pulmonary tuberculosis

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ABSTRACT

Even when treated adequately, pulmonary tuberculosis can lead to pulmonary sequelae. Patients treated for PTB between 2012 and 2016 answered a standardized questionnaire and underwent chest radiography and spirometry, measurement of absolute pulmonary volume, Diffusing Capacity for Carbon Monoxide (DLCO) and the 6-min walk test (6MWT) on two occasions: within the first year after the end of treatment (follow-up 1), and one and two years after follow-up 1 (follow-up 2). A total of 55 patients they underwent spirometry, 23 (41.82%) had obstructive ventilatory disorder (OVD) and eight (14.5%) had moderate OVD. In total, 29 patients underwent pulmonary function tests (PFTs) and 24 patients underwent the 6MWT on two occasions. The functional changes after PTB treatment appear not to have varied between one and two years of follow-up. There was a correlation between low FEV_1 and low DLCO ($p<0.001$); low DLCO and low 6MWT ($p<0.001$) and radiographic abnormalities and low FEV_1 ($p=0.033$). The most frequently observed change in spirometry was found in patients with OVD.

KEYWORDS: Spirometry. 6-minute walk test. Lung capacity. Tuberculosis sequelae.

INTRODUCTION

Tuberculosis (TB) is a global public health problem and its control has been a challenge in recent decades. In 2019, the incidence of the disease ranged from 8.9 to 11.1 million new cases of active TB and between 1.1-1.3 million deaths due to TB according to the World Health Organization (WHO), indicating that TB is currently the leading cause of death from infectious causes worldwide and is among the top 10 causes of death in general[1].

Even when treated adequately, pulmonary TB (PTB) can lead to pulmonary sequelae. Reduction in the total lung capacity (TLC) due to scar fibrosis is common[2]. In addition, destructive changes in the pulmonary parenchyma can lead to airflow obstruction[3]. These changes might affect the pulmonary compliance, resulting in peripheral airway collapse and, consequently, air trapping, leading to changes in pulmonary function[2].

Radiological sequelae of PTB might be related to dynamic changes in pulmonary function after the end of treatment[2]. According to a longitudinal study by Chung *et al*.[4], deterioration in the pulmonary function might occur up to 18 months after the end of treatment.

Functional changes resulting from the sequelae might manifest as ventilatory restriction, ventilatory obstruction or a combined disorder (obstructive–restrictive together)[5].

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In a systematic review, after the evaluation of 156 articles, obstruction was mentioned in 52 (33%)[6], and even in countries with low incidences of PTB, respiratory diseases are frequent after treatment of PTB[7]. The proportion of obstruction is variable and was related to the extent of radiological changes[8,9]. On the other hand, the restriction has been the most frequent disorder in recently published studies, observed in 52 to 68%[10-12]. A multicentric study in Brazil, that evaluated the functional changes in patients treated for PTBafter excluding smoking patients and those with respiratory diseases prior to PTB treatment, the restriction has also been the predominant change[9].

The 6-minute walk test (6MWT), used to evaluate an individual's response to exercise, is reliable and has been validated according to the guidelines of the American Thoracic Society[13]. Some studies have reported patients with PTB who walked shorter distances during the 6MWT in comparison with healthy individuals; this was seen even in patients during treatment or who had successfully completed the treatment regimen[14-16]. In recent years, a difference in the 6MWT distance has been noted after the end of treatment in patients with TB and human immunodeficiency virus (HIV) infection[17].

Another test to assess the pulmonary function is the diffusing capacity of carbon monoxide (DLCO)[18]. Patients with PTB might have low DLCO and only a few studies evaluated the specific relationship between DLCO and PTB[2,8]. The mean DLCO varied from 74.1% to 78.8% in patients with TB sequelae, highlighting the importance of evaluating this parameter to assess pulmonary function[2,18].

A recent review found an abundance of studies on the prevalence and proportion of post PTB disorders. On the other hand, there was a lack of studies on the disease progression and patients' management[6]. There was consensus on the need for follow-up after PTB treatment as some evidences have emerged pointing to an increased risk of morbidity and mortality in the post PTB period[19]. Thus, this study aimed to evaluate the magnitude and progression of respiratory changes in spirometry according to the variables: absolute pulmonary volume, DLCO and 6MWT in patients treated for PTB.

MATERIALS AND METHODS

This prospective study included new cases of TB confirmed by smear microscopy or GeneXpert®MTB/RIF (Cepheid, Sunnyvale, CA, USA) and positive culture for *M. tuberculosis* in patients who sought the Tuberculosis Outpatient Clinic of the Clinical Hospital of the Federal University of Minas Gerais, who were successfully treated for PTB from January 1st, 2012 to December 30th, 2016.

All patients signed an informed consent and received multiple treatments for PTB. Patients presenting with extrapulmonary TB, coinfected with the human the immunodeficiency virus (HIV) or presenting with unacceptable or non-reproducible spirometry curves were excluded.

Recruited patients answered a standardized questionnaire comprising questions on sociodemographic and clinical data, gender, age (≥ 18 years), history of smoking habit and comorbidities. Some of these patients participated in a previous study by the same authors[9]. The sociodemographic variables were self-declared skin color/ethnicity (white or non-white) and marital status (single or stable union). Regarding respiratory signs and symptoms, the presence of dyspnea, classified according to the modified Medical Research Council (mMRC) scale[20], cough, sputum and wheezing was evaluated. These data were obtained on the day the pulmonary function tests (PFTs) were carried out. Individuals who smoked at least 100 cigarettes or the equivalent during their lifetimes were considered smokers, and individuals who had quit smoking for >12 months prior to study inclusion were considered ex-smokers[21]. Comorbidities were self-reported and valued when described in the medical records. Diagnosis of lung diseases (asthma, chronic obstructive pulmonary disease [COPD], bronchiectasis, interstitial lung disease and silicosis) prior to PTB treatment was reviewed by pulmonologists involved in this study, according to the definitions proposed by international guidelines such as the Global Initiative for Asthma, the Global Initiative for Obstructive Chronic Lung Disease and Pulmonology Practice[22-24].

PFTs were performed in the first follow-up within the first year after the end of treatment (follow-up 1) and repeated between one and two years after the follow-up 1 (follow-up 2). The Collins CPL system (Ferraris Respiratory, Louisville, CO, USA) was used to perform the tests. The acceptance and reproducibility criteria for PFTs were set according to the recommendations of the American Thoracic Society (ATS)[25]. Data were reported as absolute values and percentages in relation to the predicted values for the Brazilian population[26]. The following variables were analyzed: total lung capacity (TLC), residual volume (RV), RV/TLC ratio, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio[27]. DLCO was performed using the single-breath method, and the values suggested by Crapo and Morris[28] were used.

OVD was considered when the FEV_1/FVC ratio was below the lowest limit of normal (LLN) and TLC was ≥ LLN; combined ventilatory disorder (obstructive–restrictive together) was considered when the FEV_1/FVC

ratio was below the LLN and TLC was < LLN; RVD was considered when the FEV_1/FVC ratio was above or equal to the LLN and TLC was < LLN; and the non-specific pattern (IVD) was considered when the FVC value was below the LLN, the FEV1/FVC ratio was equal to or above the LLN, and TLC was ≥ LLN.[27] To classify the severity of obstruction in the PFTs, a percentage of predicted FEV_1 and FEV_1/FVC was used, with ≥ 60% corresponding to mild, 41-59% to moderate, and ≤ 40% to severe obstruction; to predict the percentage of prediction, FVC ≥ 60% corresponded to mild, 51-59% to moderate, and ≤ 50% to severe restriction[29].

The 6MWT was performed in a 30-m corridor using a portable oximeter (Nonin Medical, INC. Plymouth, MN, USA) according to the recommendations of the ATS[30]. All patients underwent two walking tests, with a minimum interval of 30 minutes; encouraging phrases were provided every minute. The following parameters were recorded: heart rate, respiratory rate and dyspnea score (Borg score of dyspnea); saturation was measured by pulse oximetry (SpO2) at the beginning and at the end of the test; and the walking distance at the end of the 6MWT[30]. The test with the greatest distance covered in the 6MWT was selected. The 6MWTD findings were expressed as absolute values and percentages of the predicted values calculated using the reference equation proposed by Soares and Pereira[31] for the Brazilian population.

Chest X-rays were performed on days close to the spirometry, they were evaluated by radiologists and classified by pulmonologists. Chest X-rays that showed no abnormalities were classified as normal. Chest X-rays that showed abnormalities were classified according to the National Tuberculosis Association (NTA), as follows: NTA I or minimum; NTA II or moderately advanced - the injury could be in one lung or in both lungs, its extension should not exceed the volume corresponding to an entire lung if the lesions are not confluent, and in the presence of confluent lesions, they should occupy no more than the equivalent of one-third of the lung; NTA III or very advanced -exceeding the moderately advanced limit[32].

The sample calculation considered a 95% confidence interval and a margin of error < 5%, including the average number of patients diagnosed with PTB evaluated per year at the Tuberculosis Outpatient Clinic of the Clinical Hospital of UFMG and the percentage of patients who developed pulmonary sequelae. The estimated minimum sample size resulted in 32 patients.

Data were collected using an Excel spreadsheet and analyzed using the Statistical Package software for the Social Sciences, version 24.0 (SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normality of continuous numerical variables distribution. C variables are expressed as means and standard deviations or as medians and interquartile intervals, while categorical variables are expressed as absolute and relative frequencies. The chi-square test was used for the comparison of categorical variables. To analyze the variables of lung function tests between follow-ups 1 and 2, the unpaired Student's test or the Mann–Whitney test was performed, as indicated. To verify the direction and the degree of association between pulmonary function variables, either Pearson or Spearman's coefficient was performed; as indicated. We set the significance level at 5% ($p < 0.05$).

This study is part of a project approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE Nº 14606113.7.0000.5149).

RESULTS

From the 57 selected patients, 55 were included in the analyses and two were excluded because they did not meet all inclusion criteria (Figure 1). Table 1 shows the main characteristics of the participants. The mean age was 50.4 years (22.2–77.1 years), 52.7% (29/55) were female, 43.6% (24/55) were non-white and 52.7% (29/55) patients had a stable union. Some comorbidities were observed in 60% (33/55) of patients, and systemic arterial hypertension

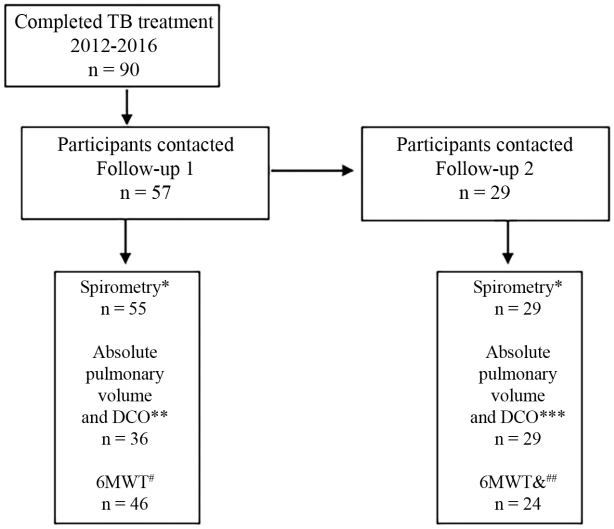

Figure 1 - Flowchart of the participants' eligibility and their inclusion in the study. *2 patients did not meet all inclusion criteria of spirometry; **19 participants did not have pulmonary volume measurements and DLco in follow-up 1 due to technical problems with the equipment; #9 Participants did not have 6MWT in follow-up 1; 2 for disability due rheumatoid arthritis and 7 for absence on the day of the exam; ***7 participants did not have PFTs during follow-up 2 due to technical problems with the equipment; ##22 participants did not have 6MWT during follow-up 2, 15 due to lack of medical request for the exam and 7 for absence on the day of the exam.

was observed in 41.82% (23/55) of patients. Respiratory symptoms were reported by 81.8% (45/55) of patients, and 78.2% (43/55) reported dyspnea (Table 1). In total, 54.5% (30/55) of patients were smokers or ex-smokers. The smoking load was 33.9 packs-year, with a minimum of 2 packs-year and a maximum of 174 packs-year. Furthermore, 61.8% (34/55) of patients had minimal abnormalities on their chest X-ray (Table 1). Considering the 55 patients who underwent at least one examination with acceptable and reproducible spirometry curves, 36 patients underwent tests for absolute pulmonary volume and DLCO and 46 patients underwent the 6MWT (Figure 1). The absolute values and percentages of the predicted values obtained in the PFTs are shown in Table 2. The most prevalent ventilatory disorder was OVD; it was observed in 23/55 (41.82%) patients; 8/55 (14.5%) patients had moderate OVD (Table 3).

From the 55 selected patients, 29 underwent pulmonary volume and DLCO tests, and 24 patients underwent the 6MWT on two occasions (Table 4). The median duration between the end of treatment and follow up 1 was 147 days (range, 75-363), and between follow-up 1 and follow-up 2 was 634 days (range, 458-1127). When the results of PFTs and 6MWTD variables were compared in the two follow-ups, no statistical difference was observed between the

Table 1 - Sociodemographic and clinical characteristics of the sample (n=55).

	Characteristics	n (55)	%
Gender	Male	26	47.3
	Female	29	52.7
Age group (in years)	Up to 29	5	9.1
	30-49	20	36.3
	50-59	13	23.6
	≥ 60	17	30.9
Self-declared skin Color/Ethnicity	White	19	34.5
	Not White	36	65.5
Marital status	Single	26	47.3
	Not single (stable relationship)	29	52.7
Comorbidities	SAH	23	41.8
	DM	6	10.9
	Silicosis	5	9.1
	CKD	5	9.1
	Cancer	3	5.4
	RA or SS	3	5.4
	Granulomatous polyangiitis	1	1.8
	COPD	7	12.7
Signs/Symptoms	Cough	19	34.5
	Wheezing	12	21.8
	Dyspnea mMRC 0-1	32	58.2
	mMRC 2 – 4	23	41.8
Smoking	No	25	45.5
	Former smoker	11	20.0
	Yes	19	34.5
Chest X-ray	Normal	9	16.4
	NTA I	34	61.8
	NTA II	7	12.7
	NTA III	1	1.8
	Not informed	4	7.3

SAH = systemic arterial hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; RA = rheumatoid arthritis; SS = systemic sclerosis; COPD = chronic obstructive pulmonary disease; NTA = National Tuberculosis Association; mMRC = modified Medical Research Council.

Table 2 - Basal variables (follow-up 1) of pulmonary function tests in patients treated for pulmonary tuberculosis.

	Variable	Mean (SD)
Spirometry (n=55)	FVC, L	3.25 (0.94)
	FVC, %	87.79 (18.02)
	$FEV_{1,}$ L	2.37 (0.69)
	$FEV_{1,}$, %	78.39 (17.46)
	$FEF_{25-75,}$ L/S	2.11(1.01)
	$FEF_{25-75,}$ %	72.65 (35.28)
	FEV_{1}/ FVC, %	73.73 (19.07
Absolute Pulmonary Volume (n =36)	TLC, L	5.27 (1.37)
	TLC, %	101.21 (18.78)
	VR,L	1.81 (0.80)
	VR, %	100.96 (34.12)
	RV/TLC, %	33.97 (9.87)
DCO (n=36)	DCO, mL min^{-1} $mmHg^{-1}$	25.46 (8.36)
	DCO, %	86.48 (23.59)
6MWTD (n=46)	6MWTD, m	526.07 (95.07)
	6MWTD, %	90.31 (14.58)

SD = standard deviation; L = liters; % = predicted percentage; m = meters; VC = vital capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FEF_{25-75} = forced expiratory flow between 25 and 75% of the forced vital capacity; TLC = total lung capacity; VR = residual volume; DCO = diffusing capacity for carbon monoxide; 6MWTD = 6-min walk test distance; 6MWTD% = 6-min walk test distance.

evaluated parameters (Tables 4 and 5, and Supplementary Figure S1).

Analyses of chest X-ray abnormalities and FEV1 values revealed that patients with X-ray changes had lower FEV1 values (p=0.033), (Supplementary Figure S2). A significant correlation was observed between FEV1 and DLCO (R=0.564; p<0.001), (Supplementary Figure S3), and between FEV1 and 6MWTD (R=0.506, p<0.001), (Supplementary Figure S4); between DLCO and 6MWTD (R=0.592, p<0,001), (Supplementary Figure S5). Thus, patients with lower FEV1 and lower DLCO had a worse performance in the 6MWT, i.e. walked shorter distances.

There was no significant correlation between chest X-ray abnormalities and DLCO (p=0.246), presence of symptoms and DLCO (p=0.163), FEV1 and DLCO (p=0.384) and 6MWTD and DLCO (p=0.357).

DISCUSSION

The main study results showed that the functional changes after PTB treatment seem not to vary between one and two years follow-up.

We did not find significant differences in pulmonary function of patients 12 and 24 months after PTB treatment. Allwood *et al.*[2] showed that during treatment, lung volumes improved and computed tomography fibrosis scores decreased, but features of airflow obstruction and gas trapping emerged, while reduced DLCO seen in a majority of patients persisted. Furthermore, one year after the end of treatment, 18.6% of patients had residual restriction disorders, 16.3% had airflow obstruction, and 78.6% had reduced DLCO. Chung *et al.*[4] found lower spirometry values 18 months after treatment; however, their study included patients in treatment for non-tuberculosis mycobacteria (NTM). Hnizdo *et al.*[33] reported decreased values approximately 6 months after treatment, with stabilization of the changes between 7-12 months; despite the fact that their sample was composed of coal miners and included patients with more than one episode of PTB. A strength of our study, in comparison with authors who

Table 3 - Functional classification of ventilator disorders detected during the follow-up of patients treated for pulmonary tuberculosis (n=55).

Ventilatory disorder	n	%	Graduation	n	%
No	19	34.54			
OVD	23	41.82	Mild	11	20
			Moderate	8	14.55
			Severe	4	7.27
RVD	8	14.54	Mild	8	14.54
MVD	4	7.27	Mild	1	1.81
			Moderate	2	3.65
			Severe	1	1.81
NVD	1	1.83	-	1	1.81
Total	55	100.0	-	-	-

OVD = Obstructive Ventilatory Disorder; RVD = Restrictive Ventilatory Disorder; DVC = Mixed Ventilatory Disorder; NVD = Nonspecific Ventilatory Disorder.

Table 4 - A comparison of pulmonary function tests results between follow-ups 1 and 2 (n=29).

	Variable	Follow-up 1 Mean (SD)	Follow-up 2 Mean (SD)	p-value
Spirometry	VC, L	3.3 (1.0)	3.1 (0.9)	0.983
	VC, %	84.3 (19.6)	83.4 (20.1)	0.396
	FVC, L	3.1 (1.0)	3.1 (0.9)	0.767
	FVC, %	75.2 (27.8)	81.1 (17.4)	0.258
	FEV_1	2.1 (0.9)	2.2 (0.9)	0.666
	FEV_1, %	58.7 (29.8)	69.0 (23.4)	0.330
	$FEF_{25-75\%,}$ L	1.6 (1.2)	1.9 (1.4)	0.360
	$FEF_{25-75\%,}$ %	64.02 (36.06)	62.78 (42.95)	0.556
	FEV_1/ FVC	70.64 (14.53)	68.53 (19.83)	0.458
Absolute Pulmonary Volume	TLC	5.7 (1.4)	4.9 (1.1)	0.878
	TLC, %	102.3 (21.7)	93.1(16.2)	0.878
	VR,L	2.1 (1.1)	1.8 (1.8)	0.919
	VR, %	112.1(40.3)	101.8 (24.5)	0.646
	FRC, L	3.2 (1.1)	2.8 (0.8)	0.444
	FRC,%	100.7 (26.9)	91.1 (19.4)	0.799
	RV/TLC	38.6 (12)	37.6 (10.1)	0.889
DLCO	DLCO, mL min^{-1} $mmHg^{-1}$	25.1 (9.2)	22.8 (9.78)	0.310
	DLCO, %	82.1 (26.1)	75.4(21.7)	0.398

SD = Standard Deviation; L = liters; % = predicted pergentage. ; RV = Residual Volume; FRC = Functional Residual Capacity; TLC = Total Lung Capacity; VC = Vital Capacity; FVC = Forced Vital Capacity; FEV_1 = Forced Expiratory Volume in 1s; FEF_{25-75} = Forced Expiratory Flow Between 25 and 75% of the CVF; DLCO = Diffusing Capacity for Carbon Monoxide.

Table 5 - Comparison of the 6-min walk tests results between follow-ups 1 and 2 (n=24).

Variable	Follow-up 1 Mean (SD)	Follow-up 2 Mean (SD)	p-value
SpO_2 initial (%)	96.21(1.46)	95.81 (1.60)	0.652
SpO_2 final (%)	93.03 (4.35)	90.44 (5.96)	0.681
HR initial (bpm)	80.53 (16.73)	80.38 (14.07)	0.103
HR final (bpm)	115.95 (16.62)	122.88 (14.96)	0.948
RR initial (brpm)	18.0 (3.04)	17.25 (3.49)	0.222
RR final (brpm)	26.49 (4.86)	24.73 (3.31)	0.254
6MWTD, m	498.3 m (114.4)	494.0 (94.4)	0.999
6MWTD, %	85.7 (21.2)	86.7 (18.2)	0.470

SD = standard deviation; SpO2 = saturation by pulse oximetry; HR = heart rate; RR = respiratory rate; brpm = breaths per minute; 6MWTD = 6-min walk test distance; bpm = beats per minute; 6MWTD **% =** 6-min walk test distance in predicted percentage.

have also evaluated lung function longitudinally, was to include patients who performed lung function after the end of treatment, thus reducing the interference of changes in lung function during the acute phase of PTB infection. In addition, as shown by Allwood *et al.*[2], between 6 and 18 months after the diagnosis of PTB, tomography changes are more stable. Ravimohan *et al.*[3] described the complexity of possible immunological and inflammatory pathways that can result in destruction of the lung tissue, consequently leading to changes in long term changes in lung function.

The most prevalent ventilatory disorder found in our study was of mild OVD, which is consistent with findings reported in most studies[7,34,35]. The pathophysiological mechanism that leads to obstructive functional changes after PTB is not well established. One possibility would be the occurrence of bronchiectasis and bronchial stenosis. Another explanation is that they are caused by dysregulation of macrophage activity, leading to an initial destruction of

pathogenic microorganisms, favoring tissue healing and playing a central role in tissue remodeling[3]. Restrictive disorders could be due to destruction of pulmonary parenchyma by the deregulation of the mechanism of protease control, i.e., pulmonary damage caused by matrix metalloproteinases leading to fibrotic changes[3]. Around 50% of restrictions take place one year after the PTB treatment[10,11].

Among patients who reported respiratory symptoms, dyspnea was the most frequent symptom, although it was not correlated with pulmonary function changes, since most patients had mild dyspnea (mMRC scale score: 0-1), similar to a previous study[36]. Another study described self-reported symptoms, airflow obstruction and functional impairment 1-5 years after TB treatment with poor correlation between physiology, functional capacity and symptoms, although it was also a cross-sectional study[34].

Most patients did not show radiological abnormalities or had minimal lesions. However, patients with radiological changes had lower FEV_1. Allwood *et al*.[2] showed that these changes may be secondary to the trapping of physiological gases, suggesting the development of airflow limitation at the level of the small airways.

A good correlation between FEV1 and DLCO with 6MWTD is an interesting and new finding in our study; when FEV1and DLCO was lower in patients who walked shorter distances as shown by the 6MWT, suggesting worsening of gas exchange and greater severity of the disease in these patients[18]. However, the equipment that measures DLCO is not widely available in most underdeveloped or developing countries, exactly in places in which the prevalence of post-PTB treatment changes is more significant[6].

In our study, patients walked distances close to the predicted value in two different times and without significant difference, which might demonstrate the stability of functional capacity. A South Africa cohort demonstrated similar 6MWTD results with respect to ours despite including patients that underwent up to six treatments for TB[34]. In a previous study with only nine participants, five of the nine showed values below LLN after PTB treatment[37]. Our results can be justified by the Latin American population included in this study, which are used to walk longer distances than Nordic populations, probably due to lifestyle habits[38].This study has some limitations. Firstly, this was a single-center trial; hence, the results cannot be generalized, however, to our knowledge, there are few studies that evaluated lung function at different periods after the end of TB treatment in the same patients. Secondly, this study included patients with COPD and smokers, which might have interfered with the results. Nevertheless, the high prevalence of smoking among these patients reflects the real-life clinical practice. People who are at higher risk to contract TB are often the same ones exposed to other risk factors for chronic respiratory diseases, including exposure to household smoke, ambient air pollution and occupational exposure to dust[6].

CONCLUSION

In the present study, 55 treated TB patients were evaluated. They underwent spirometry, 23 (41.82%) had obstructive respiratory disorders (OVD) and eight (14.5%) s had moderate OVD. Twenty-nine patients underwent pulmonary function tests (PFTs) and 24 the 6MWT on two occasions. Functional changes after PTB treatment appear not to have varied between one and two years of follow-up. There was correlation between low FEV_1 and low DLCO ($p<0.001$); low DLCO and low 6MWT distance ($p<0.001$) and X-ray abnormalities and low FEV_1 ($p=0.033$). The most frequently observed change in spirometry was found in patients with OVD.

Functional changes appear not to vary between one and two years after PTB treatment. The end of PTB treatment may represent the starting point of another disease with permanent changes in lung function. The importance of performing PFTs should be emphasized, especially in patients who have radiological sequelae.

Further studies should be conducted to identify and evaluate pulmonary changes that are clinically relevant and measures that can help patients with respiratory symptoms after PTB treatment, such as the use of inhaled drugs and pulmonary rehabilitation. Moreover, we emphasize the importance of PTB prevention since sequelae are irreversible despite adequate treatment, leading to clinical and economic losses that the patients would have to bear throughout their lives.

AUTHORS' CONTRIBUTIONS

MPN: data collection, building the database, monitoring analysis and article writing; EVC: co-coordination of study conception and design, data analyses and article writing; NS: monitoring analysis, adjustment of the database, article writing; INA: verification of database, article writing; ALAC: verification of database, article writing; SSM: study conception and design, modeling the questionnaire, data analyses and article writing.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interests.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Federal University of Minas Gerais under protocol Nº CAAE 14606113.7.0000.5149 and all participants agreed to participate and signed a Free Informed Consent.

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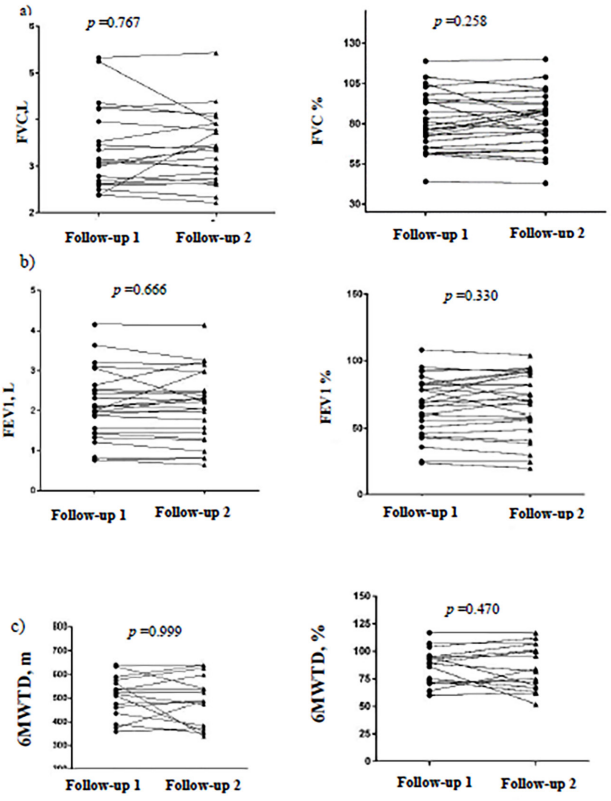
REFERENCES

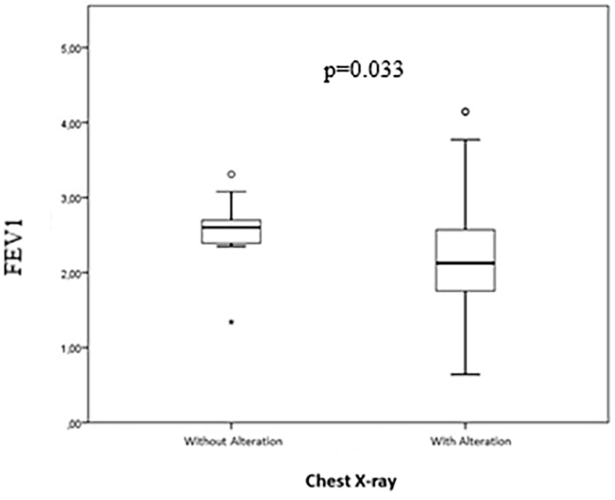
1. World Health Organization. Global tuberculosis report 2020. Geneva: WHO; 2020. [cited 2021 Jul 19]. Available from: https://www.who.int/publications/i/item/9789240013131
2. Allwood BW, Maasdorp E, Kim GJ, Cooper CB, Goldin J, Van Zyl-Smit RN, et al. Transition from restrictive to obstructive lung function impairment during treatment and follow-up of active tuberculosis. Int J Chron Obstruct Pulmon Dis. 2020;15:1039-47.
3. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. Eur Respir Rev. 2018;27:170077.
4. Chung KP, Chen JY, Lee CH, Wu HD, Wang JY, Lee LN, et al. Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis. Clinics (Sao Paulo). 2011;66:549-56.
5. Manji M, Shayo G, Mamuya S, Mpembeni R, Jusabani A, Mugusi F. Lung functions among patients with pulmonary tuberculosis in Dar es Salaam: a cross-sectional study. BMC Pulm Med. 2016;16:58.
6. van Kampen SC, Wanner A, Edwards M, Harries AD, Kirenga BJ, Chakaya J, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. BMJ Glob Health. 2018;3:e000745.
7. Basham CA, Karim ME, Cook VJ, Patrick DM, Johnston JC. Post-tuberculosis airway disease: a population-based cohort study of people immigrating to British Columbia, Canada, 1985-2015. EClinicalMedicine. 2021;33:100752.
8. Sarkar M, Srinivasa, Madabhavi I, Kumar K. Tuberculosis associated chronic obstructive pulmonary disease. Clin Respir J. 2017;11:285-95.
9. Mancuzo EV, Martins Netto E, Sulmonett N, Viana VS, Croda J, Kritski AL, et al. Spirometry results after treatment for pulmonary tuberculosis: comparison between patients with and without previous lung disease: a multicenter study. J Bras Pneumol. 2020;46:e20180198.
10. Gupte AN, Paradkar M, Selvaraju S, Thiruvengadam K, Shivakumar SV, Sekar K, et al. Assessment of lung function in successfully treated tuberculosis reveals high burden of ventilatory defects and COPD. PLoS One. 2019;14:e0217289.
11. Khosa C, Bhatt N, Massango I, Azam K, Saathoff E, Bakuli A, et al. Development of chronic lung impairment in Mozambican TB patients and associated risks. BMC Pulm Med. 2020;20:127.
12. Mathew D, Kirthana G, Krishnapriya R, Srinivasan R. To assess the pulmonary impairment in treated pulmonary tuberculosis patients using spirometry.Int Arch Integr Med. 2016;3:94-9.
13. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1447-78.
14. Godoy MD, Mello FC, Lopes AJ, Costa W, Guimarães FS, Pacheco AG, et al. The functional assessment of patients with pulmonary multidrug-resistant tuberculosis. Respir Care. 2012;57:1949-54.
15. Guessogo WR, Mandengue SH, Assomo Ndemba PB, Medjo UO, Minye EE, Ahmaidi S, et al. Physical and functional follow-up of tuberculosis patients in initial intensive phase of treatment in Cameroon using the 6-min walk test. J Exerc Rehabil. 2016;12:333-9.
16. Sivaranjini S, Vanamail P, Eason J. Six minute walk test in people with tuberculosis sequelae. Cardiopulm Phys Ther J. 2010;21:5-10.
17. van Aswegen H, Roos R, McCree M, Quinn S, Mer M. Investigation of physical and functional impairments experienced by people with active tuberculosis infection: a feasibility pilot study. Afr J Disabil. 2019;8:515.
18. Lopes AJ, Camilo GB, Menezes SL, Guimarães FS. Impact of different etiologies of bronchiectasis on the pulmonary function tests. Clin Med Res. 2015;13:12-9.
19. Allwood BW, van Der Zalm MM, Amaral AF, Byrne A, Datta S, Egere U, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. Int J Tuberc Lung Dis. 2020;24:820-8.
20. Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, et al. Chronic obstructive pulmonary disease and health-related quality of life. Ann Intern Med. 1997;127:1072-9.
21. Centers for Disease Control and Prevention. Cigarette smoking among adults and trends is smoking cessation: United States, 2008. MMWR Morb Mortal WKY Rep. 2009;58:1227-32.
22. Global Initiative for Asthma. Pocket guide for asthma management and prevention: for adults and children older than 5 years. [cited 2021 Jul 19]. Available from: http://ginasthma.org/2018-pocket-guide-for-asthma-management-and-

prevention/%0Ahttps://ginasthma.org/download/836/
23. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2018 report. [cited 2021 Jul 19]. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf
24. Maciel R, Aidé MA, organizadores. Prática pneumológica. 2ª ed. Rio de Janeiro: Guanabara Koogan; 2017.
25. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.
26. Pereira CA, Sato TR, Rodrigues SC. Novos valores de referência para espirometria forçada em brasileiros adultos de raça branca. J Bras Pneumol. 2007;33:397-406.
27. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68.
28. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis. 1981;123:185-9.
29. Pereira CA. Espirometria. J Bras Pneumol. 2002;28 Suppl 3:S1-82.
30. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428-46.
31. Soares MR, Pereira CA. Six-minute walk test: reference values for healthy adults in Brazil. J Bras Pneumol. 2011;37:576-83.
32. Ribeiro SN, Gehardt FG, Silva JR, Fonseca L, Gontijo P, Sant'Anna CC, et al. Tuberculose. In: Bethlem N, editor. Pneumologia. 4ª ed. São Paulo: Atheneu; 1995. p.379-448.
33. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55:32–8.
34. Allwood BW, Stolbrink M, Baines N, Louw E, Wademan DT, Lupton-Smith A, et al. Persistent chronic respiratory symptoms despite TB cure is poorly correlated with lung function. Int J Tuberc Lung Dis. 2021;25:262-70.
35. Chushkin MI, Ots ON. Impaired pulmonary function after treatment for tuberculosis: the end of the disease? J Bras Pneumol. 2017;43:38-43.
36. Santra A, Dutta P, Manjhi R, Pothal S. Clinico-radiologic and spirometric profile of an Indian population with post-tuberculous obstructive airway disease. J Clin Diagn Res. 2017;11:OC35-8.
37. Silva TS, Borges GF. Tolerância ao exercício em indivíduos pós-tratamento de tuberculose pulmonar: um estudo observacional. Lect Educ Fis Deportes. 2021;25:96-107.
38. Casanova C, Celli BR, Barria P, Casas A, Cote C, Torres JP, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Respir J. 2011;37:150-6.

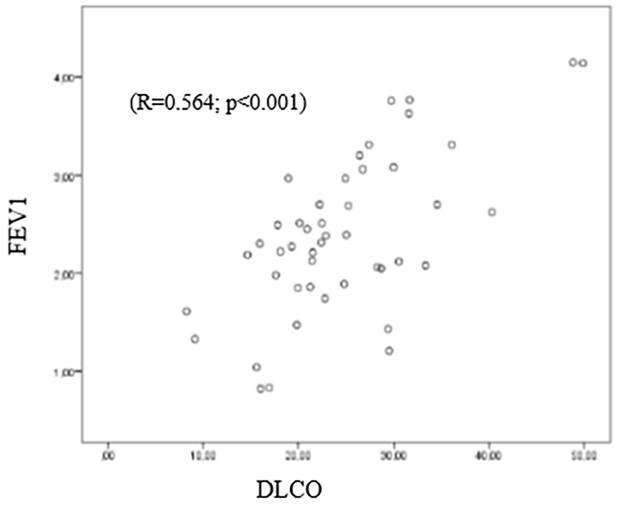
SUPPLEMENTARY MATERIAL



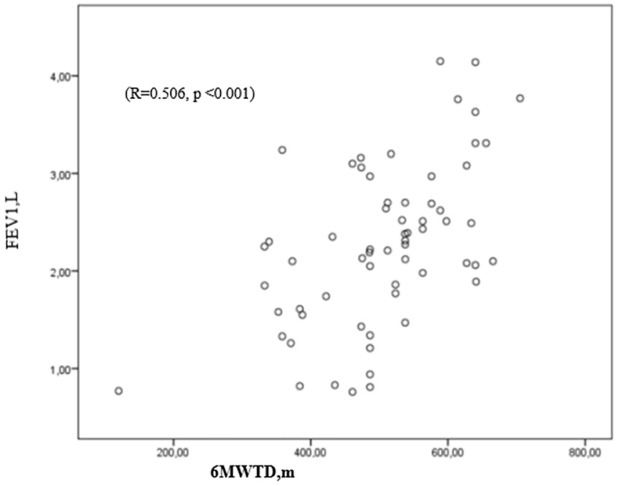
Supplementary Figure S1 – Change of lung function variables between the follow-up 1 and 2. a) FVC in liters and %; b) FEV1 in liters and % c) 6MWTD in meters and %; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; 6MWTD = 6-min walk test distance; L = liters, % = predicted percentual.



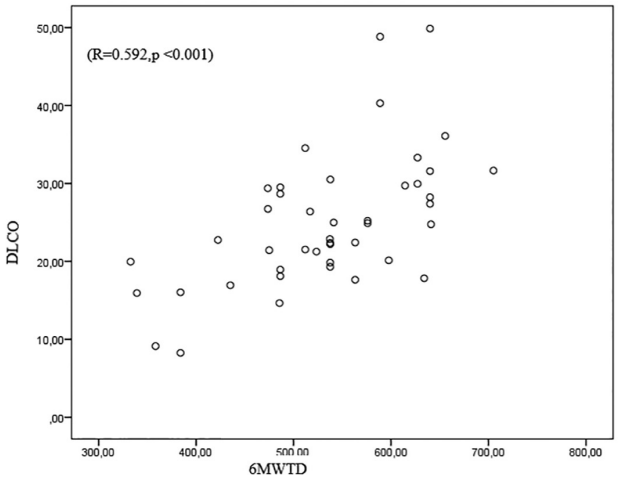
Supplementary Figure S2 - Analysis between FEV1 (liters) and Chest X-ray, during follow-up 1.



Supplementary Figure S3 - Correlation between FEV_1 (liters) and DLCO (mL min^{-1} $mmHg^{-1}$) during follow-up 1. DLCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second.



Supplementary Figure S4 - Correlation between FEV1 (liters) and 6MWTD (meters) during follow-up 1.



Supplementary Figure S5 - Correlation between DLCO (mL min^{-1} $mmHg^{-1}$) and 6MWTD (meters) during follow-up 1.