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TUBERCULOSIS ASSOCIATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Saqib Jamal[1], Wei Guan[2]

[1,2] Department of Respiratory Medicine, Affiliated Hospital of Qinghai University, Xining, China

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Abstract:

Objectives: Reviewed the epidemiology, clinical characteristics, mechanisms, and treatment of tuberculosis associated chronic obstructive pulmonary disease.

Data source: We searched PubMed, EMBASE, and the CINAHL. We used the following search terms: Tuberculosis, COPD, and Tuberculosis associated COPD, and so forth. All types of study were chosen.

Result and Conclusion:

Chronic obstructive pulmonary diseases (COPD) and tuberculosis (TB) are serious public health issues and are the major causes of morbidity and mortality worldwide significantly in developing countries. Even though, chronic obstructive pulmonary diseases (COPD) and tuberculosis (TB) both have common risk factors such as smoking, low socioeconomic status and dysregulation of host defense functions. Previous history of pulmonary TB as a risk factor of chronic airway tract obstruction has been described in numerous studies, which may progress throughout the development of tuberculosis or after completion of TB treatment and management. To reduce the future burden of chronic airflow obstruction early diagnosis and treatment of tuberculosis should be emphasized.

Keywords: *Chronic obstructive pulmonary disease, smoking, TOPD, tuberculosis*

Corresponding author:

Wei Guan,

Department of Respiratory Medicine,

Affiliated Hospital of Qinghai, University, Xining, China

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1. INTRODUCTION:

The global initiative for chronic obstructive lung disease (GOLD) [1] defined chronic obstructive pulmonary disease (COPD) as "a common preventable and treatable disease, characterized by persistent airflow limitation that is usually advanced and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. COPD is a serious public health issue worldwide due to its high incidence, morbidity, and mortality [2] [3] .It also constitutes an important socioeconomic burden. [4] Prevalence of COPD worldwide in 2010 was 11.7%, with projected that 384 million people suffering from COPD. The recent World Health Organization (WHO) report showed that in the year 2012, more than 3 million people died of COPD, and over 90% of these deaths happened in developing countries [3]. COPD was the fourth leading cause of death in 1990 and currently, it is the third leading cause of death globally moreover its mortality is showing increased tending [5]. Tuberculosis (TB) is one the leading cause of death from a single infectious agent (above HIV/AIDS). According to the World Health Organization's 2018 Global Tuberculosis Report there were an estimated 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017 and caused an estimated 1.3 million deaths in the same year 2017 [6]. Around 58% of world's tuberculosis cases arise in South-East Asia and china contributes to 9% of the global tuberculosis burden [6].Economic development has been related to an obvious epidemiological change, resulting in a lower burden of infectious diseases, but a significantly increased burden of non-communicable diseases (NCDs) [7]. Developing countries are facing the double burden of communicable diseases such as tuberculosis and Human immunodeficiency virus infections and non-communicable diseases like smoking and COPD [8]. The convention of these epidemics could raise the vulnerability to the diseases. The best monitoring of these conditions needs detailed assessment of all the relating epidemics.

Tobacco smoking is a conventional risk factor in the progression of COPD but not the only one .Risk factors of COPD in non-smokers might include genetic factors, persistent respiratory infections in early childhood, long-standing chronic asthma, biomass fuel smoke exposure, outdoor air pollution, exposure to various dust, chemicals and pollutants, diet, pulmonary tuberculosis and so on, mainly in the low socio-economic countries. Previous history of pulmonary tuberculosis has recently risen as a risk factor for future progression of COPD [9]. Allwood et al. named the condition of tuberculosis-associated obstructive pulmonary disease as TOPD [10]. Although; it is still not very clear the association of TOPD and chronic respiratory obstruction and also it is a matter of discussion.

1.1 Pulmonary tuberculosis and chronic airway tract obstruction

Pulmonary tuberculosis affects the lungs and causes an airway tract obstruction over a period of time. The occurrence of airway tract obstruction in TB is variable, depending on the geographical settings, study nature and also on the bases of the definition used. Prior studies have shown that COPD is a common co-morbidity in the patients with TB [11]. Though, the main disadvantage in the early studies was lack of adequate controls; hence; the different consequence of smoking on airway tract obstruction was not adjusted.

1.1.1 Epidemiology

Early study of Anno and Tomashefski stated the impairment of respiratory function in pulmonary tuberculosis patients. They found an increased residual volume (RV), residual volume/total lung capacity (TLC) ratio, and a decrease in inspiratory residual volume (IRV) in a certain group of tuberculosis patients [12]. Gaensler et al [13] in 1959 reported the evidence of airway tract obstruction in about 61% of 1533 tuberculosis patients. In a population-based study Lam et al [14] involved Guangzhou Biobank Cohort stated after adjusting for age, sex and smoking exposure, the previous history of TB as an independent association with chronic airway tract obstruction with an odd ratio of 1.37. Although, to define airway tract obstruction in this study, the pre-bronchodilator FEV_1: FVC ratio was used instead of conventional post-bronchodilator FEV_1/FVC ratio. Snider et al [15] in a cross-sectional study assessed 1430 patients admitted in Chicago Municipal tuberculosis Sanatorium with pulmonary tuberculosis from 1964 to 1966 and reported airway tract obstruction [defined by forced expiratory volume in one second and forced vital capacity (FEV1:FVC) ratio <70%] in 23% patients. In spite of a high prevalence of smoking in the study patients, the authors found no remarkable association between smoking and airway tract obstruction. Recently, several studies had further assured the previous outcomes of the association between tuberculosis and progression of chronic airway tract obstruction. PLATINO [16], a population-based, multicenter study was carried out and included 5,571 subjects aged ≥40 yrs.' projected the association between previous history of TB and progression of airway tract obstruction in five Latin American Countries. After the modification for confounders like age, sex, ethnicity, smoking, exposure to dust and smoke, respiratory disease in childhood and current morbidity with the odd ratio of 2.33.The overall prevalence of airway tract obstruction was about

30.7% among with a previous history of tuberculosis, compared with 13.9% among with those without a previous history of tuberculosis. After adjusted the odd ratio of 3.99 and 1.71 the risk was higher in males than females respectively. In non-smokers the association of tuberculosis and chronic airway obstruction was even stronger. BOLD [17] study also reported a previous history of tuberculosis as an independent risk factor for developing chronic airway obstruction in the future with the adjusted odd ration of 2.51. Recently, two systemic reviews also established the association between past history of tuberculosis and chronic airway tract obstruction [18] [19]. Allwood et al [18] a systemic review evaluated the association between tuberculosis and the development of chronic airway tract obstruction. Total 19 studies, including 1 case series, 3 case-control studies, 4 cohort studies, 8 single-center cross-sectional studies, and 3 multicenter cross-sectional studies were analyzed. The authors established a positive relationship with a prior history of TB and the progression of chronic airway tract obstruction. This relationship was independent of smoking and biomass fuel exposure. In another systematic review and meta-analysis Byrne et al [19] reported the strongest association between previous history of TB and the advancement of chronic airway tract obstruction in non-smokers and young people in (age <40). Progression of chronic airway tract obstruction also depends on the geographical settings. Incidences of chronic airway tract obstruction are, the higher in developing countries due to high tuberculosis occurrence.

1.1.2 Clinical features of TOPD

Limited studies associated the clinical presentation of patients with tuberculosis obstructive pulmonary disease (TOPD) to chronic obstructive pulmonary disease (COPD). In a case control study Lee et al [20] calculated the pulmonary function tests of 21 TOPD patients and associated it with the COPD patients carefully matched by age, sex and predicted value of FEV_1 %. There were no major differences were noted for cough, dyspnea, and exacerbation between these two groups: although, hemoptysis was most common and persistent in the patients with TOPD as compared to COPD patients, also TOPD patients had low FVC and post-bronchodilator FEV_1 values. Response to bronchodilators was significantly low in the patients with TOPD indicated the permanent airway tract obstruction. Gunen et al [21] divided the COPD hospitalized patients into two different groups according to the presence or absence of TB scars on radiological studies and found the previous history of tuberculosis scars were significant risk factors for the progression and advancement of COPD. Although, mortality rate between these two groups were similar. Total 598 COPD patients were included in the study and 93 patients had previous TB scars on their chest X-rays (15.5%). COPD patients with TB scars were significantly young ($P = .002$). The diagnosis of COPD was made five years earlier in patients with TB scars as compared to no TB scar patients (58.6 ± 12.3 years versus 63.2 ± 11.2 years; p <0.001). Seo et al [22] assessed the clinical characteristics of admitted patients in the intensive care unit (ICU) with TOPD and COPD and found significant higher rate of reoccurrence of tuberculosis pneumonia and tracheostomies in TOPD patients compared to COPD patients. In a retrospective study of Park et al [23] from South Korea reviewed that data of mechanically ventilated 38 ICU admitted patients with destroyed lung from tuberculosis found majority were males and 52% of them were non-smokers. Pulmonary function tests, reports of 21 patients in the previous 12 months showed severe airway obstruction with the mean FEV_1 of 0.77 L (29.3% predicted), mean FVC of 1.52 L (41% predicted) and a mean FEV_1/FVC ratio of 55.1%, though, due to restriction in the study setting, the major effect of smoking could not be ruled out. Patients with tuberculosis destroyed lungs the airflow limitation is an independent risk factor for acute exacerbation. Kim et al [24] stated significant high incidences of acute exacerbation in patients with limited airflow when compared to non-limited airflow patients (89.1 vs. 67.7%, respectively; $P = .009$). The study found that the patients with limited airflow group, annual decline of FEV_1 were significantly low as compared to non-limited airflow group with 2 mL and 36 mL ($P < .001$) respectively. The FEV_1 decline depends on the baseline of FEV_1 value; Low baseline FEV_1 value of the imitated airflow group can explain this finding. Higher the baseline FEV_1 value, greater is the rate of FEV_1 decline. Lung function decline was more severe in the group without airflow limitation in the tuberculosis destroyed lung. In a retrospective study Rhee et al [25] evaluated 595 patients with tuberculosis damage lungs and analyzed the clinical features and compared it with the 2 groups of limited airflow and non-limited airflow. The Mean FVC, FEV_1, FEV_1/FVC ratio, and bronchodilator response were 2.06 ± .03 l (61.26% ± 0.79), 1.16 ± .02 l (49.05% ± 0.84), 58.03% ± 0.70, and 5.70% ± 0.34, respectively. Study stated a significant association between lung lobes involved with FVC, FEV_1, and exacerbation reoccurrence. Patients with wide parenchymal involvement were at higher risk of exacerbations and must be given a special attention and treatment. Over a period of time the follow up data of pulmonary function tests (PFTs) were observed to analyze FEV_1. Patient with tuberculosis damage lungs the value of FEV_1 showed significant decline similar to COPD with a mean annual decrement of 38.24 ± 7.98 mL. On

multiple regression the change in FEV_1 were analyzed which showed a correlation with the initial FEV_1 %, Age and with exacerbation frequencies. Bronchodilators response showed a major difference in the patients with tuberculosis damage lungs and COPD. The response of bronchodilators in tuberculosis damage lung was low compared to COPD, which signifies the airway obstruction due to bronchial stenosis and damage lung tissues. This study also stated a major improvement in FEV_1 with the use of long-acting muscarinic antagonists (LAMA), long-acting beta-2 agonists plus inhaled corticosteroids (LABA + ICS).

1.1.3 Lung function limitations in patients with pulmonary tuberculosis

Pulmonary tuberculosis (TB) can cause parenchymal destruction by up regulation of several proteases and dysregulation of protease control. [26]. Pulmonary tuberculosis patients commonly progresses to maximum loss of lung function within 6 months of the diagnosis of TB and it stabilizes in 18 months after completion of treatment [27][28]. Rhee[29] Incidence and severity of airway tract obstruction in pulmonary tuberculosis depends on the number of occurrence of tuberculosis Hnizdo et al[30] found decrease in values of FEV_1 of 56.8 mL/month and observed the lowest FEV_1 value of 326mL in the 6 month of post tuberculosis treatment which stabilized later in 7 to 12 months. Vargha et al [31] in patients with tuberculosis discharged in 1958/59, assessed vital capacity (VC), FEV1, and Residual volume (RV). Total 40 patients were obstructive based on the percentage of FEV1/VC. Re-evaluation was carried out in 1974. FEV1's shift was 35.3 mL / year. Nevertheless, during such a long follow-up time, the influence of other negative environmental factors could not be excluded. Hnizdo et al[30] This relationship was studied in 27,660 gold miners in South Africa. Chronic airflow obstruction rate was directly proportional to the number of tuberculosis episodes. The prevalence of persistent airflow obstruction after one tuberculosis episode was 18.4 percent, whereas the prevalence was 27.1 percent and 35.2 percent respectively after two and some 3 episodes. With the growing number of episodes of tuberculosis, structural damage to the lungs rises and continues in a significant number of patients given anti-tubercular chemotherapy. The observed drop in FEV1 was also highest in this sample, probably due to the compounding effects of other factors such as smoking and exposure to dust; this study did not make adjustments for these factors. The increase in the number of tuberculosis episodes further accelerates the loss of FEV1 and the total Loss of 153 mL, 326 mL and 410 mL after one, tw o and three or more episodes of tuberculosis respectively. Plit et al[32] The effect of anti-tubercular chemotherapy on the function of the lung of newly diagnosed patients with pulmonary tuberculosis was prospectively assessed. Anti-tubercular chemotherapy in 54 percent of patients resulted in better lung function. Nevertheless, in 28 percent and 24 percent of patients respectively, residual airflow restriction or restrictive pattern was seen.

The impairment of residual lung functions depends on the radiological extent of the disease both before and after treatment. This study suggested that impa irment of lung functions may occur even after succ essful tuberculosis treatment.

Various predictors of impaired pulmonary functions have been reported in patients with pulmonary tuberculosis, including smear-positive disease, extensive pulmonary involvement prior to anti-tuberculosis treatment, reduced post-treatment radiographic improvement, and prolonged treatment duration. [34] The additional risk factor for COPD is also delay in starting anti-tuberculosis treatment. Lee et al. evaluated the impact of pulmonary tuberculosis, delayed initiation, and non-adherence to anti-tuberculosis treatment on the future risk of COPD in a population-based cohort study conducted in Taiwan. Previous history of pulmonary tuberculosis has been identified as an independent risk factor for COPD development (hazard ratio 2.054[1.768–2.387]). The risk persisted after being diagnosed with tuberculosis for at least six years. An additional risk factor was the delayed initiation of anti-tubercular therapy as it extended the duration and increased the severity of inflammation of the airway. It contributes to accelerated lung damage rate and eventual lung function loss. In order to control both tuberculosis and COPD epidemics, early diagnosis, and prompt initiation of anti-tuberculosis treatment are therefore essential.

Patients with tuberculosis incurred radiological changes in the chest should be a candidate for COPD screening. Hwang et al [35] in a population-based analysis, the relationship between tuberculosis and airflow obstruction radiological shifts was evaluated. GOLD standards specified airflow obstruction between subjects with radiological changes, the incidence of airflow obstruction was 26.3%. Without any radiological changes, it was significantly higher than patients. The unadjusted airflow obstruction odds ratio based on radiological shift was 3,788 (95 percent CI: 2,544–5,642) and was over 3.12 when adjusted for smoking. Radiological altered patients were at higher GOLD levels. It can be explained by decreased loss of lung function in patients with radiological changes in tuberculosis. Ross et al [36] studies had shown South African Gold miners rapid loss of lung function after pulmonary tuberculosis.

After adjusting age, height, baseline lung function, silicosis, years of employment, smoking, and other respiratory diagnoses, the mean annual loss of FEV1 was 40.3 mL / year. Interestingly; obstruction of airflow occurred mostly in patients with limited radiological changes, suggesting that the airflow obstruction mechanism was chronic airway inflammation rather than airway fibrosis seen in advanced radiological involvement.

Pulmonary tuberculosis is also a higher risk factor for persistent obstruction of airflow compared to smoking. COPD prevalence study in Colombia (PREPOCOL) examined COPD incidence and risk factors in five different-altitude Colombian cities. There was a strong association (odds ratio of 2.94) between a history of tuberculosis and the occurrence of airflow obstruction, and it was stronger than that with smoking. [37] Similarly, Ehrlich et al [38] a nationwide survey of 13,826 adults in South Africa found a history of pulmonary tuberculosis to be a greater indicator of COPD than cigarette smoking or exposure to biomass fuel smoke. Pefura-Yone et al [39] reported 62.9% of successfully treated patients with pulmonary tuberculosis distal obstruction of airflow. Distal obstruction of airflow has been linked with recurrent chronic pulmonary symptoms independently. Ngahane et al [40] in a tuberculosis reference clinic in Cameroon, the prevalence and predictors of lung function impairment were studied. They reported loss of lung function in 45.4% of patients. Symptom duration and fibrotic radiological pattern were independent risk factors on multivariate analysis of lung function impairment Patients treated with pulmonary tuberculosis can develop distal airflow obstruction identified by forced expiratory flow at 25–75% of forced vital capacity (FEF25–75%) < 65% and an FEV1/FVC ratio of 0.70.

The possibility of subsequent development of COPD is not unique to tuberculosis of Mycobacteria. Also species of non-tuberculosis mycobacterium (NTM) have been reported. Yeh et al [41] In the Taiwanese cohort of 3005 NTM patients, NTM patients showed a 3.08-fold increased risk of developing COPD relative to non-NTM patients. After macrolide treatment, NTM patients with impaired pulmonary function initially showed improvement. [42] An important goal to prevent future development of COPD should be early diagnosis and treatment of NTM disease.

2. Risk Factors:

There are some common risk factors for both the conditions such as smoking, low socioeconomic status (SES), biomass fuel exposure, and vitamin D deficiency.[43][44] Smoking is a common and well-established risk factor for COPD. [45]In addition there is now considerable evidence that smoking is also a risk factor for tuberculosis. Three systematic reviews and meta-analysis have involved active smoking as a risk factor for tuberculosis infection, active tuberculosis disease, and mortality from tuberculosis. [46-48] the effect of active smoking is more on illness with tuberculosis than on infection with tuberculosis. Certain consequences of heavy smoking include the risk of tuberculosis recurrence and death from tuberculosis. After successful completion of treatment for a previous episode of tuberculosis, active smoking can cause recurrent tuberculosis. Yen et al [49] has been shown that smoking more than 10 cigarettes a day increases the risk of recurrence of tuberculosis by2-fold compared to smoking in the past. Active smoking also increases the risk of failure of follow-up, increased infection incidence, drug-resistant tuberculosis, faster processing of smear, and death. [50] Because of the dual epidemic of tuberculosis and smoking present in many developing countries, the impact of smoking on tuberculosis would be enormous. China currently has the world's largest smoker population, over 300 million. Lin et al [51] had been shown that the full cessation of tobacco and solid fuel use by 2033 would reduce the incidence of tuberculosis by 14–52 % if 80 % of DOTS coverage is retained. The mechanistic connection between tuberculosis and smoking is not obvious, but may include the immunological and oxidative pathway .Many smoking-related immunological defects were reversible within six weeks of smoking cessation. [52]

2.1 Biomass Fuel Exposure

Biomass fuel exposure is the most important non-smoking associated cause of COPD in developing countries. [53] The number of people exposed to smoke from biomass fuel is much higher than those exposed to smoking worldwide [52]. India, Nepal, and Brazil have reported exposure to biomass fuel smoke as an independent risk factor for tuberculosis in several studies [54-57]. Mishra et al [58] found that the odds ratio of active tuberculosis in people living in households who primarily use biomass fuel for cooking was 3.56. This risk is important as a large number of people in developing countries use biomass fuel for heating or cooking.

2.2 Low Socio-Economic Status

Low SES is a both COPD and tuberculosis risk factor. SES is a composite measure of several indices such as income, education, jobs, house conditions, residence place, and crowding index. [59]. Low SES is also responsible in COPD patients for poor health-related quality of life. [60]. Kanervisto et al [61] demonstrated in a population-based study a basic education as an independent

risk factor for COPD (odd ratio of 1.8). In a case-control study involving 250 patients with consecutive tuberculosis. Gupta et al [62] fond low SES as a tuberculosis risk factor following variables were found to be significantly and independently correlated with a higher risk of tuberculosis in multivariate logistic regression analysis; age, educational level, crowding, form of housing, water supply, and household number of consumer items. [63]

2.3 Diabetes Mellitus

The interaction of diabetes with tuberculosis is bi-directional. Jeon et al [64] analyzed the association between diabetes and tuberculosis in a systematic review and meta-analysis of 13 observational studies. Among diabetics, there is a 3-fold greater risk of developing active tuberculosis compared to non-diabetic individuals. The risk for insulin-dependent diabetes mellitus (IDDM) is higher than for diabetes mellitus (NIDDM) dependent on non-insulin. Olmos et al [65] in a longitudinal-retrospective study reported the 10-year actuarial probability of developing tuberculosis of 24% in IDDM and 4·8% in NIDDM. The risk of progression to active disease is also increased in patients with diabetes. Baker et al [66] in a systemic review showed that tuberculosis patients with diabetes have a greater risk of failure, relapse, and death while being treated with anti-tuberculosis. There is also bi-directional interaction between diabetes and COPD. Comorbid diabetes aggravates COPD's development and prognosis. It does so by multiple mechanisms: direct effects of hyperglycemia on the physiology of the lung, inflammation, and/or bacterial infection susceptibility. [67]

2.4 Vitamin D Deficiency

Vitamin D deficiency is a potential risk factor for both tuberculosis and COPD. Nnoaham et al [68] in a systematic review and meta-analysis evaluated the association between low serum levels of vitamin D and the risk of active tuberculosis. Seven longitudinal studies were included for review conducted between 1980 and July 2006. Among patients with low serum vitamin D level, there was a higher risk of active tuberculosis. Zeng et al [69] in a meta-analysis identified serum Vitamin D increases the risk of tuberculosis. They reported a statistically significant association with the risk of tuberculosis between serum vitamin D level of at least 25 nmol / L. Nursyam et al [70] in a randomized clinical trial studied the Impact of tuberculosis supplementation with vitamin D. Compared to placebo, treatment of vitamin D resulted in higher sputum conversion rate and increase in radiological improvement. In host immune defense, vitamin D plays an important role against Mycobacterium tuberculosis through an innate and adaptive immune system. [71], [72] In COPD induction, COPD pathogenesis, COPD exacerbations and development of COPD musculoskeletal comorbidities, vitamin D also has a role to play. [73] Early life event has been recognized as a risk factor for COPD, and any event that affects early life lung growth may result in increased risk of COPD. [74] For lung growth, vitamin D is needed and its deficiency has the potential to cause early chronic lung diseases. [75].

3. Mechanisms of airflow obstruction due to Tuberculosis:

The exact mechanism of CAO is not evident in patients with post-tuberculosis. Mechanisms for the production of tuberculosis-associated CAOs are suggested following. These include obliterans of bronchiectasis, bronchiolar narrowing, and bronchiolitis, and sudden increase in emphysematism [18].Figure 1 is showing the mechanisms of airflow obstruction due to tuberculosis.

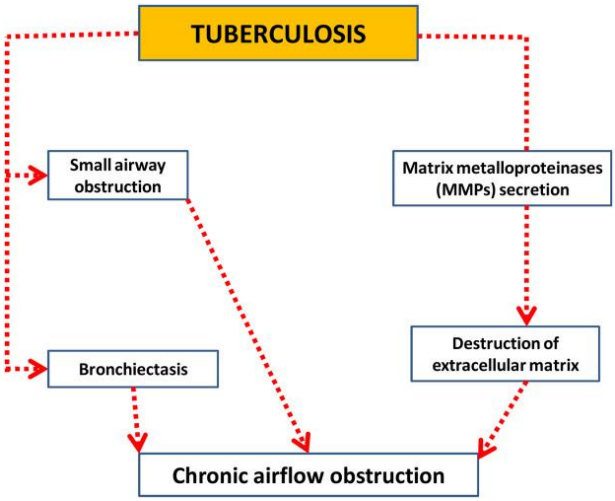

Figure 1 is showing the mechanisms of airflow obstruction due to tuberculosis

3.1 Narrow airway involvement

Small airways are non-cartilaginous airways with an internal diameter of <2 mm. [76] Tuberculosis lesions may involve the small airways that results in airflow obstruction. Im et al [77] reported in 95 %of people with pulmonary tuberculosis, centri-lobular nodules, "tree-in-bud" appearance and poorly defined nodules upon initiation of chemotherapy, these lesions vanish by 5 months. Tuberculosis is an important cause of obliterative bronchiolitis in endemic countries with tuberculosis. In the Gothi et al [78] series 92% Post-infectious cases of obliterative bronchiolitis and 78% Post-tubercular.radiological features of bronchiolitis are gas trapping characterized as areas of decreased attenuation on expiratory CT scans on computed tomography (CT) scan. This radiological

feature can continue after treatment with tuberculosis, despite the resolution of the endo-bronchial and parenchymal changes. [79] Jeong et al [80] Small involvement of airways in patients with NTM infection was also reported. Patients with cured pulmonary tuberculosis and airflow obstruction were evaluated by Allwood et al. through complex quantitative CT lung imaging and spirometry, plethysmography and diffusion ability. Patients with chronic airflow obstruction had higher gas trapping, fibrosis, and emphysema score than those without previous tuberculosis. Also in patients with definite prior TB, the diffusion efficiency was significantly lower. [10]

3.2 Accelerated parenchymal degradation

Lung parenchymal inflammation in tuberculosis can result in the destruction of the extracellular pulmonary matrix (ECM), similar to COPD. [81] Matrix metallo-proteinases (MMPs) are a family of calcium-dependent zinc-containing endo-peptidases [82] that mediates tissue remodeling in tuberculosis [83] the degrading components of ECM, the alveolar wall scaffold, are implicated in the pathogenesis of both tuberculosis and COPD. In mycobacterial infection, various MMPs have different roles. In the development of healthy granuloma, MMP-9 helps to suppress the infection. Reactivation of latent TB, however, leads to secretion of MMP-1. MMP-1 is responsible for alveolar degradation and tuberculosis cavitation. [84]. Finlay et al [85] found in the emphysematous lung, alveolar macrophages are as an important source of MMPs. In BAL fluid of COPD patients, they found significant quantities of MMPs especially MMP-9 compared to normal healthy volunteers. Similarly, Imai et al [86] found increased MMP-1 expression in COPD patients ' lung parenchyma relative to normal controls. It is the pneumocyte of type II which makes MMP-1 and is involved in lung destruction. MMPs are therefore a common mediator that can bind the two disorders. Nevertheless, further studies are needed to clearly elucidate the role of MMPs in tuberculosis and COPD pathogenesis. Singh et al [87] studies the Impact of various anti-mycobacterial agents on levels of MMP in patients with tuberculosis. In the broncho-alveolar lavage fluid of patients with tuberculosis, levels of MMPs such as MMP-1, −2,-3, −7, −8 and −9 are elevated and correlated with tuberculosis-associated tissue damage. Different anti-mycobacterial agents such as rifampin, moxifloxacin, and azithromycin showed an immune-modulatory effect by decreasing the expression and secretions of MMPs in the epithelial cell gene. More study is needed to examine whether anti-tubercular therapy can prevent future development of COPD by inhibiting expression of MMPs in the epithelial cells of the airway.

3.2 Bronchiectasis

Post-tuberculosis bronchiectasis is common in developing countries, particularly in patients with recurrent tuberculosis history. [88] Palwatwichai et al [89] in a prospective study from Thailand found Tuberculosis history in 32% of 50 bronchiectasis cases, making it the most common underlying bronchiectasis etiology. Bronchiectasis is a major cause of chronic airflow obstruction due to endobronchial obstruction or peri-bronchial fibrosis or obstruction due to enlarged lymph nodes. [90] Bronchiectasis is termed tractional bronchiectasis within areas of scarring. Patients with tuberculosis may also experience broncho-stenosis and narrowing of the airway. Chae et al [91] reported Atelectasis (84%) and bronchiectasis emphysema (89%) as the most common CT findings in patients with tuberculosis.

4. COPD's Effects on Tuberculosis:

COPD patients also have an increased risk of tuberculosis. Inghammar et al [92] studied the effect of COPD on incidence and mortality of tuberculosis. A maximum of 115,867 patients over 40 years of age who were discharged from the Swedish hospital with COPD diagnosis were tested for risk of tuberculosis. The risk of developing tuberculosis in COPD patients was 3-fold higher than controls, and the incidence of tuberculosis was inversely related to the value of FEV1. However, the risk of death from all causes was 2-fold higher in the first year following the diagnosis of tuberculosis in COPD patients with active tuberculosis relative to those with tuberculosis under general population control. Lee et al [93] studied the risk factors for COPD patients with pulmonary tuberculosis. Cox regression analysis identified COPD as independent risk factors for tuberculosis with a hazard ratio of 2.47 among 23 594 COPD cases and 47 188 non-COPD subjects. Further oral corticosteroids and oral β-agonists were obtained by COPD patients who developed tuberculosis. The use of inhaled corticosteroids was also associated with a higher risk of tuberculosis and the risk was greater with the use of a high dose of inhaled corticosteroids equal to or greater than 1000 mg / d fluticasone. [94] Hence, in endemic countries with tuberculosis, it should be compulsory to rule out infection / disease with tuberculosis before using high-dose corticosteroid inhaled. Through inducing immune suppression, corticosteroids increase the risk of tuberculosis. [95]. Shang et al [96] studied the Immunological reaction in cigarette smoke exposed mice to M. tuberculosis. Lung and splenic macrophages and dendritic cells expressed lower levels of IL-12 and TNF-α in cigarette smoke-exposed mice. Cigarette smoke exposure thus changes the defensive immune response to M. tuberculosis. For patients with combined pulmonary tuberculosis and COPD,

immune deficiency is much greater than each single disease. [97] Tang et al [97] measured different cytokines In 152 cases of pulmonary tuberculosis-COPD combined in the peripheral blood, 150 cases of pulmonary tuberculosis patients, 157 cases of COPD patients and 50 cases of healthy volunteers. The combined patients with tuberculosis-COPD had a significantly lower proportion of CD4 + T cells than the non-COPD patients with tuberculosis. In the control group, patients with tuberculosis had a significantly higher percentage of CD8 + T cells. In COPD patients with tuberculosis, cytokines such as sIL-2R, IL-6, TNF-α, IFN-α levels were significantly higher than in COPD patients without tuberculosis. High levels of these cytokines can cause progression of tuberculosis in patients with COPD by generating an exuberant inflammatory response. COPD patients themselves develop alveolar macrophage dysfunction independent of steroids, posing an additional tuberculosis risk. [98] [99] Macrophages are one of the most important cells in tuberculosis and also play a role in healing and resolution of wounds. [100] they can trigger airway remodeling. Mycobacteria in the lungs can lead to unregulated activation of wound-healing macrophages, leading to airway remodeling and persistent obstruction of the airflow. [101]

5. Treatment For TOPD:

Treating TOPD does not vary from treating COPD alone. Yum et al [102] studied the efficacy of inhaled tiotropium bromide on 29 patients with tuberculosis damaged lungs for duration of 2 months. The performance of FEV1 and FVC over baseline with tiotropium therapy has been significantly improved. Lee et al [20] found that the patients with chronic airflow obstruction due to tuberculosis have shown improved bronchodilator response. Despite all these results, it should be noted that COPD treatment is not variable depending on the origin etiological factors.

6. Future Prospects:

At the moment, there are several areas that are still unexplored. First of all; to prove the causality between tuberculosis and COPD, we need a broad population-based case control study of tuberculosis patients and an asymptomatic healthy population. We need to examine the variations in medical, biological, radiological, airway inflammation and treatment response between TOPD and COPD. We need to know if there are any variations between children and adults with pulmonary tuberculosis in the production of airflow obstruction. For addition, unraveling these areas would definitely give better ideas about the TOPD situation.

7. CONCLUSION:

Past history of tuberculosis is a significant risk factor for COPD, and tuberculosis in COPD patients is also common. Chronic airflow obstruction development may be associated with specific risk factors or lung damage associated with tuberculosis. Both COPD and tuberculosis in developing countries are a major health issue. For increasing the potential burden of COPD, early diagnosis and implementation of appropriate tuberculosis care should be emphasized. To order to prevent future development of both tuberculosis and COPD, focus should also be placed on avoiding common risk factors such as cigarettes and exposure to biomass fuel smoke.

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