REVIEW

TB meets COPD: An emerging global co-morbidity in human lung disease

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SUMMARY

Chronic obstructive pulmonary disease (COPD) is emerging as the third largest cause of human mortality worldwide after heart disease and stroke. There is growing evidence of a co-morbidity between COPD and tuberculosis (TB), the leading cause of death globally due to respiratory infection. Thus, the increase in the burden of COPD over the coming decades, as predicted by the World Health Organisation, is of concern with respect to the control of TB. A better understanding of the interactions between these two diseases is essential for the design of complementary preventive and control strategies. In this review, some of the known risk factors that are common to both diseases are discussed. Furthermore, we examine how impairment of the innate immune system, and corticosteroid therapy, in COPD patients may increase the risk of TB manifestation. Conversely, we review how TB lung pathology may heighten susceptibility to subsequent development of COPD, even after completion of effective TB treatment. Growing evidence appears to point towards a bi-directional relationship between these two lung diseases where each may act as an independent risk factor for the other. This has important implications for the respective long-term management of TB and COPD.

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Contents

1. Introduction .......................................................... 659
2. Shared risk factors between TB and COPD ......................................................... 660
3. COPD, its treatment and the risk of mycobacterial lung infections ........................................ 660
4. TB and subsequent COPD susceptibility ............................................................... 661
5. Potential mechanistic relationships between COPD and TB immunopathology ........................................ 662
6. Conclusions and future perspectives ................................................................. 662
Funding ......................................................................................................................... 662
Competing interests .................................................................................................... 662
Ethical approval ........................................................................................................... 662
References .................................................................................................................... 662

1. Introduction

Tuberculosis (TB) is the leading cause of mortality due to respiratory infection worldwide, killing approximately 1.5 million people each year [1]. Multi-drug resistant tuberculosis (MDR-TB), resistant to at least rifampicin and isoniazid, has reached 480,000 cases per year and in some countries accounts for more than 25% of new TB cases [1]. The convergence of TB with HIV/AIDS has been well established [2–6] with an estimated 1.1 million of the 9 million people who developed TB in 2013 being HIV-positive. Other well-recognised co-morbidities associated with TB include diabetes [7–9] and alcohol misuse [10,11]. An association with
chronic airflow limitation is less well known. The aim of this review was to appraise common risk factors associated with both COPD and TB, as well as epidemiological and potential mechanistic links between these two diseases. A qualitative examination was performed of the published literature up to August 2015 using databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (http://scholar.google.com) for reports where obstructive airway disease and mycobacterial respiratory infection have been investigated.

In 2010, a population-based study of 115,867 in-patients, aged ≥40 years, from hospitals in Sweden between 1987 and 2003 found that the relative risk of developing active TB was 3-fold higher in patients with chronic obstructive pulmonary disease (COPD) than in controls (hazard ratio, HR, of 3.0 [95% confidence interval: 2.4–4.0]) [12]. In addition, the study reported that COPD patients who developed active TB had a 2-fold increased risk of death from all causes within the first year following TB diagnosis compared to other TB patients (odds ratio, OR of 2.2 [95% CI: 1.2–4.1]). Conversely, a recent meta-analysis found a significant association between a previous history of TB and the presence of COPD in adults aged ≥40 years (pooled OR of 3.05 [95% CI: 2.42–3.85]) that was especially pronounced in high TB incidence countries [13]. Such data have raised the worrying prospect that the growing burden of COPD globally could potentially fuel the incidence of active TB and vice versa. COPD kills over 3 million people worldwide each year according to the World Health Organisation (WHO) [14] which predicts an increase in COPD mortality in the coming decades [15]. Hence, as noted by Inghammar and colleagues, the factors underlying the increased TB risk in COPD patients need to be elucidated [12] as do the reasons for a greater likelihood of COPD development following TB disease.

2. Shared risk factors between TB and COPD

Patients with COPD have been found to have a 3-fold higher risk of developing TB compared to control subjects [12]. Tobacco smoking is well established as the most important causative factor for the development of COPD [16,17]. The proportion of COPD mortality that has been attributable to smoking has been estimated to be 54% for men aged 30–69 years and 52% for men aged 70 years or more [18]. Smoking also increases the risk of TB. In a systematic review, Bates and colleagues found that smoking is a significant risk factor for both Mycobacterium tuberculosis infection and TB disease with estimated summary relative risks of 1.73 [95% CI: 1.46–2.04] and 2.33 [95% CI: 2.15–3.28], respectively [19]. The association of smoking with TB infection and disease have been corroborated by other meta-analyses [20,21]. In addition to tobacco smoke, the association of indoor air pollution, caused by smoke from the burning of biomass fuel, with COPD has been well documented [18,23]. With approximately 3 billion people worldwide exposed to biomass smoke, it is considered the next major risk factor for COPD after tobacco smoke [23]. Biomass smoke has also been reported as an independent risk factor for TB from studies performed in India and Brazil [24].

Diabetes increases the risk of active TB development by approximately 3-fold (relative risk of 3.11 [95% CI: 2.27–4.26]) and results in poorer treatment outcomes [25,26]. The role of diabetes in COPD has been examined recently and evidence suggests that diabetes can also worsen the progression and prognosis of COPD [27]. Nutritional status has been implicated as a factor in the COPD development. For example, a positive association between vitamin C serum levels and lung function, in particular FEV1 (forced expired volume of air in the first second of expiration), has been reported [18]. Malnutrition increases the risk of TB due to impairment of the immune system [24]. Vitamin D plays an important enhancing role in the innate and adaptive immune response to M. tuberculosis infection and protection against active TB disease [28]. A number of studies have shown that vitamin D supplementation, as an adjunct to anti-TB chemotherapy, can accelerate the rate of negative sputum smear conversion [28]. Interestingly, vitamin D deficiency has been linked with poor lung development [29] and COPD [30]. It is not clear, however, whether other specific nutrient deficiencies play a role in both COPD and TB development, but the vitamin D example suggests a potential etiological overlap between the two diseases at the level of host nutrition.

Thus, it is apparent that TB and COPD share a number of common risk factors (Figure 1). Such mutual risk factors may be coincidental and independent, but as outlined below, there is gathering evidence of a common mechanistic relationship between these two lung diseases.

3. COPD, its treatment and the risk of mycobacterial lung infections

As already noted, patients with COPD have a higher risk of developing TB compared to controls [12]. In further support of this, Lee and colleagues conducted a nationwide study in Taiwan involving 23,594 COPD cases and 47,188 control subjects and reported that COPD was an independent risk factor for the development of TB [31]. The hazard ratio for TB development in COPD patients was 2.47 [95% CI: 2.21–2.76] compared to controls [31]. Of particular interest was their finding that COPD patients who subsequently developed TB had received higher daily doses of oral corticosteroids (OCS) and oral β-agonists than COPD patients who did not develop TB [31]. In another Taiwanese study by Shu et al., 554 COPD patients were stratified with regard to dosage of the inhaled corticosteroid (ICS) fluticasone [32]. The study found that presentation with pulmonary TB during follow-up was especially associated (10%) with the highest dose of fluticasone treatment (>500 μg/day) compared to 3% in the lower dose group, and 1% in the no ICS treatment group [32].

The above findings highlight a concern that certain treatments for COPD may be a contributing factor in the established COPD-related risk of developing TB. The corticosteroid effect is likely to be a generic one, not limited to COPD. Thus, Jick et al., in a study performed on 497 new cases of TB and 1966 controls in the UK-based General Practice Research Database, reported an independent adjusted OR of TB development of 4.9 [95% CI: 2.9–8.3] for glucocorticoid use [33]. For the orally-administered glucocorticoid, prednisone, the adjusted OR increased with dose from 2.8 [95% CI: 1.0–7.9] for <15 mg/day to 7.7 [95% CI: 2.8–21.4] for ≥15 mg/day. Brassard et al., in a study involving 564 cases of TB in Canada, reported that current users of ICS, who are not taking OCS therapy, are at an increased risk of TB development (rate ratio, RR of 1.33 [95% CI: 1.04–1.71]) [34]. Similarly, Lee et al., in a study in Korea involving 4139 TB cases and 20,583 controls, also reported that ICS was linked, in a dose-dependent manner, to an increased rate of TB diagnosis (adjusted OR of 1.20 [95% CI: 1.08–1.34]) [35]. It has been proposed that clinicians should be aware of the increased risk of TB development in patients receiving corticosteroid treatment [35]. Pre-screening for latent TB, and/or monitoring for active TB disease, may be warranted where high dose corticosteroid COPD therapy is used, especially in high TB incidence countries.

The association of corticosteroid use with mycobacterial disease is not limited to TB. Hojo et al., noted a potential increased risk of non-tuberculosis mycobacterial (NTM) disease, associated with infection of Mycobacterium avium complex (MAC), Mycobacterium kansasii or Mycobacterium terrae, in asthmatic patients receiving...
long-term ICS therapy [36]. A study performed in Denmark by Andrejak et al., on 332 patients with pulmonary NTM disease and 3320 controls reported an OR of 29.1 [95% CI: 13.3–63.8] for the development of NTM disease in COPD patients on current ICS therapy compared to an OR of 7.6 [95% CI: 3.4–16.8] in COPD patients who had never received ICS therapy [37]. A recent meta-analysis reported a significant relationship between ICS use and the risk of both TB and NTM disease in patients with chronic respiratory illnesses [38].

4. TB and subsequent COPD susceptibility

Eisner and colleagues reported previously that the population-attributable fraction for smoking as a cause of COPD was generally less than 80% [18]. Hence, reducing daily smoking rates would still leave behind a population who are at increased risk of developing COPD as a significant proportion of cases occur in never smokers. Tackling non-smoking risk factors is going to need to be linked to strategies to reduce the burden of COPD. A recent systematic review by Byrne and colleagues reported in 2015 that a significant association exists between a previous history of TB and the presence of COPD in patients aged over 40 years who were adjusted for known COPD risk factors including cigarette smoking and age [13]. Of particular note was the finding that as the national TB incidence rate went above 100 cases per 100,000 population per year, the OR of COPD development was over 3 times higher in patients with a previous history of TB compared to no history of TB e.g. adjusted OR of 4.9 [95% CI: 2.6–9.1] and 6.6 [95% CI: 3.7–11.7] for South African males and females, respectively, and 6.31 [95% CI: 2.67–15.0] for adults in the Philippines [13].

As reviewed by Salvi and Barnes, nearly half of fully-treated TB patients presented with obstructive airway disease during follow-up examination, and this proportion increased with time post completion of TB treatment [23]. Furthermore, in a study performed on South African miners, there was a concomitant decrease in FEV₁ (forced expired volume of air in the first second of expiration) and FVC (forced vital capacity) with increasing episodes of TB [41]. A large, international, population-based, Burden of Obstructive Lung Disease (BOLD) study published in 2015 investigated the association of airflow obstruction and spirometric restriction with a history of TB. This study, based on 14,050 participants from 18 countries, found that a self-reported history of TB was significantly associated with both airflow obstruction (adjusted OR of 2.51 [95% CI: 1.83–3.42]) and spirometric restriction (adjusted OR of 2.13 [95% CI: 1.42–3.19]) [42]. The authors of the study concluded that a history of tuberculosis “should be considered as a potentially important cause of obstructive disease and low lung function, particularly where tuberculosis is common” [42]. It has also been reported that patients with an earlier diagnosis of NTM disease, associated with both MAC and non-MAC NTM infection, had a higher likelihood of presenting with COPD in follow-up examinations (adjusted HR of 3.57 [95% CI: 2.56–4.97] for women and 2.89 [95% CI: 2.31–3.61] for men) [48]. Furthermore, COPD patients with multiple and single NTM isolates, that included, in order of frequency MAC, Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum, and M. kansasi, were approximately twice as likely to be admitted with acute COPD exacerbations at least once a year during the follow-up period compared to COPD patients from whom no NTM were isolated [49].
5. Potential mechanistic relationships between COPD and TB immunopathology

Questions arise as to what specific aspects of TB pathology could result in an individual becoming more susceptible to the development of COPD. Several studies have reported the effects of TB on lung structure and function. Pulmonary TB can lead to remodelling of the lung architecture and this can be manifested as extensive fibrosis, cavitation, traction bronchiectasis, bronchiectasis or parenchymal lung destruction [41,47]. In a study from South Africa, Wilcox and Ferguson reported that airway obstruction was present in 68% of subjects who had previously been treated for tuberculosis up to 16 years prior to undergoing pulmonary function assessment [43]. They concluded that “treated pulmonary tuberculosis is a cause of significant chronic obstructive airways disease” [43]. While antimicrobial chemotherapy may result in improved lung function in patients with pulmonary TB,PLIT et al. [44] reported a large proportion of patients were left with residual airflow limitation (28%) or a restrictive pattern (24%). In a study from India, 78% of obliterative bronchiolitis cases (associated with small airway obstruction) were found to be post-TB [45]. Hnizdo et al. [46], determined that the frequency of chronic airflow impairment was related to the number of episodes of TB that a patient has experienced i.e. 18.4% in patients with one TB episode, 27.1% with two, and 35.2% with three or more TB episodes. It is therefore plausible that the structural damage to the lung that occurs during episodes of active pulmonary TB is a significant factor in the subsequent development of COPD.

There is also evidence linking the underlying immunological mechanisms of COPD to an increased risk of M. tuberculosis infection. The immunosuppressant effect of therapeutic corticosteroids alone is unlikely to be sufficient to account for the higher rate of TB that is observed in COPD patients. COPD is a multi-component disease which includes mucociliary dysfunction, airway inflammation, and lung structural changes [52]. Impaired lung function in itself may be associated with an increased risk of TB in COPD patients. In a study conducted in Sweden, TB incidence was found to be inversely correlated with FEV1 [39]. In addition, impairment of innate lung defence, such as mucociliary clearance, in COPD facilitates bacterial infection of the lower respiratory tract [40]. This is seen with regard to the phagocytosis of Haemophilus influenzae and Streptococcus pneumoniae which is suppressed in macrophages isolated by bronchoalveolar lavage from COPD patients [53]. Berenson et al. reported that alveolar macrophages from patients with COPD had significantly impaired phagocytosis of clinical isolates of non-typeable H. influenzae (NTHi) compared with those from participants without COPD [54].

It is apparent that phagocytic dysregulation in COPD patients, may contribute to an increased susceptibility to lower respiratory tract bacterial infections and that this may well extend to M. tuberculosis pathogenesis. Shang et al., demonstrated cigarette smoke (CS) exposed mice infected with M. tuberculosis had thickened alveolar septal walls, and more diffuse infiltrates of macrophages, lymphocytes, and neutrophils rather than the discrete foci of inflammation observed in control mice. CS was found to suppress the protective immune response to M. tuberculosis [55]. Lower levels of lung and splenic macrophages and dendritic cells producing IL-12 and TNF-α were detected in CS-exposed mice along with a diminished influx of CD4+ and CD8+ effector and memory T cells into the lungs and spleens [55]. The authors also reported that primary human alveolar macrophages exposed to cigarette smoke (CS) were defective in controlling intracellular M. tuberculosis and that they exhibited reduced TNF-α production [55]. More recently, O’Leary and colleagues compared the immune response of human alveolar macrophages isolated from non-smokers, smokers, and ex-smokers [22]. Both smokers and ex-smokers exhibited impaired functions in macrophage function in terms of uncontrolled intracellular bacterial growth and reduced TNF-α, IFN-γ, and IL-1β production following ex vivo challenge with M. tuberculosis. While not all smokers/ex-smokers in the study had a clinical diagnosis of COPD, it is likely that an overlap exists regarding functional impairment of the human alveolar macrophage response to M. tuberculosis infection due to smoking and COPD.

6. Conclusions and future perspectives

There is now a growing realisation of a bi-directional relationship between the pathogenses of TB and COPD and that this relationship can occur independently of common risk factors such as smoking. Further research is needed to elucidate the mechanistic relationships between TB and COPD at the cellular and molecular levels. For example, the ability of primary macrophages and other immune cells, isolated from different categorised Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of both smoking and non-smoking related COPD, to mount an effective protective defence against M. tuberculosis requires study. The effect of current corticosteroid COPD therapies on immune protection against M. tuberculosis challenge also needs to be tested in cell culture and/or animal models of infection. In addition, the longer-term effect of successfully-treated M. tuberculosis disease on the immunopathology of lungs and the subsequent response to causative agents of COPD, such as cigarette and biomass smoke, warrant investigation. Such research would help underpin an improved understanding of these key respiratory diseases and lead to future improvements in measures to manage COPD and limit the long-term airway damage imposed by TB.

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References


