Tuberculosis and its incidence, special nature, and relationship with chronic obstructive pulmonary disease

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Abstract: Tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) carry a significant burden in terms of morbidity and mortality worldwide. This review article focuses on different aspects of Tuberculosis in terms of the relationship with COPD such as in the development of chronic airflow obstruction as a sequel to active TB and reviewing the key role of cigarette smoking in the pathogenesis of both conditions. Patients diagnosed with TB may often have extensive co-morbidity such as COPD and the effect of an underlying diagnosis of COPD on outcomes in TB is also reviewed.
Keywords: Tuberculosis, COPD, airflow obstruction

Introduction

Despite many advances in modern medicine, mankind's old adversary tuberculosis (TB) remains a significant public health problem both in developed countries as well as in developing world. Similarly, chronic obstructive pulmonary disease (COPD) carries a significant burden worldwide in terms of morbidity and mortality (Celli et al 2004). COPD is defined as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (Pauwels et al 2001). This article focuses on the inter-relationship between TB and COPD, describing the development of chronic airflow obstruction as a sequel to TB, examining the significance of tobacco smoking in the pathogenesis of TB and COPD and reviewing the role of immunological mediators common to both conditions in addition to exploring the nature of active TB in an individual with co-existing COPD.

Comparing the burden of tuberculosis and COPD

The etiological agent in tuberculosis is the bacillus *Mycobacterium tuberculosis* which represents one of many in the family of mycobacteria. The mode of spread among humans is via aerosol droplet transmission hence the lungs are often the focus of tuberculous disease although TB may present with disease in any organ system. In the 1998 survey of TB cases in England and Wales, 62% were noted to exhibit pulmonary involvement (Rose et al 2001). In that survey, 38% had sole extra-pulmonary involvement and this figure appeared to be increasing when compared to previous surveys undertaken in the same region (Kumar et al 1997; Rose et al 2001).

Up to 2 billion people, representing a third of the world's population, have been infected with the tubercle bacillus ie, have latent TB infection (Dye et al 1999). In immunocompetent individuals with latent infection, 10% will develop active TB

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during their lifetime, a figure that climbs to 50% in the immuno-compromised (Dye et al 1999; Raviglione et al 2003). Unsurprisingly, the re-emergence of TB as a major threat to global health has gone hand in hand with the worldwide epidemic of human immunodeficiency virus (HIV). There is increasing evidence that co-infection with TB accelerates the progress of HIV in an individual and up to a third of AIDS related deaths worldwide have been attributed to TB (Cahn et al 2003). In addition, individuals with impaired cell mediated immunity often have false negative result with tuberculin skin testing and active TB with HIV co-infection progresses more rapidly as well as presenting with atypical clinical presentations and radiological appearances. Poor compliance with anti-tuberculous medications not only results in inadequate treatment potentially causing considerable individual morbidity and mortality but may also lead to infection of close contacts as well as promoting the spread of multi-drug resistant disease. Multi-drug resistant (MDR) TB, defined as resistance to at least 2 first line anti-tuberculous drugs rifampicin and isoniazid, often a difficult problem in immunocompetent patients, carries a significantly increased mortality in the immunocompromised (Drobniewski et al 2002).These problems has been tackled in many different ways such adopting a Directly-Observed-Treatment Strategy or DOTS (Uplekar et al 1999; Lienhardt et al 1999). However, the burden of TB is not limited just to developing countries. In many developed countries such as the United Kingdom (UK), TB has again undergone resurgence as a significant public health problem driven by a number of factors including an increasing immigrant population from high TB prevalence areas, the impact of HIV and a previously complacent attitude amongst healthcare and governmental organisations towards the disease.

Unfortunately, both COPD and tuberculosis share certain similarities in terms of carrying a considerable burden to the health of populations. Despite this, management strategies of both conditions have, in the past, suffered from a lack of political commitment and initiative. However, in 1993, the world health organisation (WHO) declared tuberculosis a "global emergency" (Kochi et al 1991).Worldwide, 8 million new cases of active TB are reported (Dye et al 1999; Raviglione et al 2003).

The prevalence of COPD is, however, difficult to determine with precision due to under diagnosis as the symptoms may only become apparent only after a considerable loss of lung function (Pena et al 2000). This is coupled with the fact that spirometry (which is fundamental in order to diagnose COPD) may not be readily available in all regions. In a UK study, the overall prevalence of COPD diagnosed in primary care had progressively increased from 1990 to 1997, particularly in the female population (Soriano et al 2000). In a large study from Spain, the prevalence of COPD was estimated at 9.1%; only 21.8% of cases had been previously diagnosed (Pena et al 2000). The global prevalence of COPD in adults aged 40 years or over as defined by spirometry was estimated at 9%–10% (Halbert et al 2006). In terms of global mortality, TB is responsible for 2 million deaths annually (Dye et al 1999; Raviglione et al 2003). Worryingly, the death rate from COPD in the USA was shown to have increased by 163% from 1965 to 1998 whilst deaths from coronary artery disease and stroke fell by 59% and 64% respectively (Pauwels et al 2001). COPD is currently the 5th leading cause of death worldwide and projected to rise to become the 3rd leading cause of death by 2020 (Pauwels et al 2001; Murray et al 1997). This ranking is the result of the increasing prevalence of tobacco smoking and changes in population demographics resulting in an increased population of elderly (particularly female) smokers susceptible to loss of lung function with its clinical sequelae. Today, 1.1 billion people smoke and this appears set to increase to 1.6 billion by 2020 (Pauwels et al 2001) In essence, the world is facing a growing threat from tuberculosis as well as COPD due to various factors in relation to each condition such as the epidemic of HIV, increasing immigration, a rise in cigarette smoking and an attitude of complacency both by politicians and health care professionals.

In terms of health economics, 24 million working days are lost due to COPD in the UK (Calverley et al 1998). In the UK, the overall annual cost to the national health service (NHS) was estimated at £846 million in 1996 (National Health Service Executive 1996). A US study concluded that the total cost of COPD morbidity and morality amounted to $23.9 billion in 1993 (Sullivan et al 2000). In 1999, COPD was estimated to be the 12th leading cause of disability adjusted life years (DALYs) worldwide and it is predicted to rise to become the 5th leading cause by 2020 (Lopez et al 1998; Michaud et al 2001). The economic impact of TB is no less important. Tuberculosis predominantly affects a young working population in developing countries at the prime of life compared to COPD which tends to affect an older population. This is highlighted in a paper from India evaluating 304 patients with TB where the total cost per individual was estimated at $171 per person representing a significant financial burden to the population of many developing nations (Rajeswari et al 1999). The mean age of the study population was 37.8 years with 69% of males and 84% of females

falling in the "economically productive" age group (15–49 years).Tuberculosis ranked 7th in leading cause of death and disability worldwide in 1990 and is projected to remain 7th by 2020 contributing to 42.5×10^6 DALYS (Lopez et al 1997; Michaud et al 2001).

Susceptibility of an individual to the development of active tuberculosis and COPD involve a complex interaction between genetic and environmental factors which is currently poorly understood. A pattern of Mendelian susceptibility to TB has been described both in the paediatric as well as in the adult population (Casanova et al 2002; Alcais et al 2005). For example, in a Moroccan study of 96 families each containing 2 siblings presenting with active pulmonary TB, susceptibility was linked to a region of chromosome 8q12–q13 (Baghdadi et al 2006). Genetic and host factors play an important role in the development of COPD illustrated by the fact that not all smokers go on to develop airflow obstruction (Lundback et al 2003). Currently, the only known genetic abnormality pre-disposing to disease development is that of severe alpha-1-anti-trypsin deficiency or PiZZ phenotype (Rennard et al 1998). However, even outside the context of alpha-1-anti-trypsin deficiency, siblings of COPD patients have been shown to be more susceptible to develop abnormal lung function and familial clustering of COPD has been described (McCloskey et al 2001). Other candidate genes are currently being investigated such as those orchestrating the matrix metalloproteinase (MMP) system, tumour necrosis factor (TNF-α) and Interleukin-13 among others (Molfino et al 2004). However, a key limitation with some genetic studies lie in a failure to achieve reproducible data due to the relatively small number of patients studied in the presence of a heterogeneous study population eg, differences in ethnicity and lifestyle. Clearly, further research in this important area is needed.

In terms of treatment, it should not be forgotten that tuberculosis is a largely curable condition with anti-tuberculous medications representing the cornerstone of management. At a simplistic level, cure may be achieved provided an individual has access to basic healthcare facilities capable of diagnosing the condition (often requiring only sputum analysis and chest radiography with an appropriate history) and is able to gain access to and comply with regular anti-tuberculous chemotherapy. Unfortunately, the greatest impact of Tuberculosis is felt in developing countries where conversely, many lack access to any such healthcare facilities and essential anti-tuberculous medications**.** On the other hand, COPD is characterized by its progressive nature; patients often presenting to a health care professional with symptoms only after a considerable degree of impairment to lung function has already been sustained. Reversal of the underlying insult is not possible at such a stage thus outlining the importance of identifying individuals with COPD at an early stage of the disease process by means of spirometry so that smoking cessation will achieve the greatest impact as well as promoting greater public awareness of COPD. In essence, the only interventions shown to influence mortality in COPD to date are smoking cessation, long term oxygen therapy (LTOT) and, lung volume reduction surgery (LVRS) in a selected subgroup of individuals (Pauwels et al 2001). Table 1 summarizes some key issues examining comparisons between COPD and Tuberculosis.

The role of cigarette smoking in the pathogenesis of TB and COPD

Tobacco smoking is a major aetiological factor in the development of COPD. The association between cigarette smoking, accelerated loss of lung function and COPD is well established (Fletcher et al 1977). Susceptible smokers have an accelerated decline in FEV_1 over and above any age related changes seen in non-smokers. Eventually over years, this loss of lung function leads to progressive airflow obstruction, development of disability and symptoms such cough, wheeze and breathlessness initially on exertion then ultimately at rest. Such a disease spiral is accompanied by deterioration in gas exchange and worsening respiratory failure, Cor Pulmonale and death. Smoking cessation has been shown to reduce this accelerated decline in FEV_1 hence preventing or delaying the onset of significant disability.

Controversy exists regarding the exact role of tobacco smoking in Tuberculosis. Several early studies supported an association between tobacco smoking and the tendency to develop TB. A large study from England in 1967 examined over 76,000 subjects undergoing chest radiography (Adelstein et al 1967). The rate of tuberculosis infection was reported as being over 3 and 4 times higher for men and women respectively who were over 35 and smoking more than 20 cigarettes daily. These findings were consistent with previous studies published in the 1950s illustrating an increased risk of tuberculosis with the greater number of cigarettes smoked (Lowe et al 1956; Edwards et al 1957). However, a major methodological limitation to these early studies lay in the fact that socio-economic status was not taken into account. More recently, a questionnaire based study from America conducted between 1988–90 examined 151 TB patients and 545 controls concluding that there was a 2.6 fold (95% CI 1.1–5.9) increased risk of developing TB in those with a

Table 1 Key comparisons between tuberculosis and COPD

	Tuberculosis	COPD
Epidemiology	Increasing incidence noted worldwide contributed by epidemic of HIV among other factors; in western world, incidence higher in immigrants originating from high prevalence areas (Dye et al 2006);	Worldwide prevalence in adults ≥40 years estimated at 9–10% (Halbert et al 2006); prevalence increasing due to rise in cigarette smoking (particularly in females) and an increasing elderly in population hence resulting greater susceptibility to loss of lung function
	Predominantly affects young adults	Predominantly affects older adults (usually over 40 years)
Burden: *Current and future ranking in disability adjusted life years (DALYs)*	7th leading cause of DALYs in 1990 projected to remain 7th in 1990 (Murray et al 1997; Michaud et al 2001)	12th leading cause of DALYs in 1999; (Michaud et al 2001); estimated to the 5th leading cause in 2020 (Lopez et al 1998)
Burden: *Current and future mortality*	Currently 7th leading cause of death worldwide; will remain the 7th leading cause in 2020 (Murray et al 1997)	Currently 5th leading cause of death worldwide; Projected to become the 3rd leading cause of death by 2020 (Murray et al 1997)
Disease susceptibility and inheritance	Evidence of genetic susceptibility with a Mendelian pattern of inheritance (Casanova et al 2002; Alcais et al 2005; Baghdadi et al 2006)	Interaction between host, genetic and environmental factors (McCloskey et al 2001; Pauwels et al 2001)
	Complex interaction between genetic and environmental factors; some evidence that cigarette smoking may alter clinical presentation of TB (Shprykov et al 1994; Leung et al 2003) as well as increasing risk of developing active disease (Maurya et al 2002; Davies et al 2006)	Environmental factors central to disease development eg, cigarette smoke, biomass fuels in developing countries (Pauwels et al 2001) Genetic factors eg, alpha-1 anti-trypsin deficiency interact with environmental exposure; familial clustering reported (McCloskey et al 2001)
Pathogenesis	Involvement of matrix metalloproteinase (MMP) system among others resulting in characteristic parenchymal destruction (Hrabec et al 2002; Price et al 2003; Elkington et al 2005; Elkington et al 2006) Sequelae of tuberculosis include development of chronic airflow obstruction and bronchiectasis (Grancher 1878; Jones et al 1950; Bromberg et al 1963; Frame et al 1987; Nicotra et al 1995; Hnizdo et al 2000; Park et al 2001; Palwatwichai et al 2002; Lee et al 2003; Ramos et al 2006; 67–76)	Involvement of matrix metalloproteinase (MMP) system resulting in parenchymal destruction although many other factors involved at this and at the airway level (Braunhut et al 1994; Finlay et al 1997; Frankenberger et al 2001; Imai et al 2001; Mao et al 2003; Vernooy et al 2004; Higashimoto et al 2005)
Treatment	Curable in the majority of cases with appropriate anti-tuberculous chemotherapy; Potential for development of chronic airflow obstruction and bronchiectasis among sequelae	Not curable; To date, only smoking cessation and LTOT shown to influence mortality with LVRS in a selected sequelaesubgroup (Pauwels et al 2001)

20 year or greater smoking history (Buskin et al 1994). An interesting case-control study from Spain examined 46 cases of active TB comparing these to 46 "control" subjects who were defined as having a positive tuberculin skin test in the absence of any clinical or radiological features of active TB (Alcaide et al 1996). Smoking history was obtained by means of questionnaires and reinforced by patient interview and urinary cotinine levels were also measured with subjects being divided into active smokers, passive smokers and non-smokers. The Odds Ratio (OR) for active cigarette

smoking and the development of TB was 3.6 (1.5–2.2) and was deemed statistically significant ($p < 0.01$). The authors clearly showed an increase in risk with a greater number of cigarettes smoked. The association between passive smoking did not however reach significance in this study.

A 1996 study from Hong Kong examined 851 patients from the TB notification registry (Leung et al 2003). The OR for ever smoking in both men and women diagnosed with active tuberculosis was greater than 2 when compared with healthy population controls. Socio-economic status was taken into account in this study with no significant differences noted between smokers and non-smokers diagnosed with TB in terms of socio-economic status as well as ethnicity and body weight. In addition, several reviews of this subject taking these and other studies into account concluded that cigarette smoking increased the risk of developing active tuberculosis, perhaps between three and five fold in a recent article (Maurya et al 2002; Davies et al 2006).

There is some data to suggest that tobacco smoking may also appear to alter the clinical presentation of TB. In the paper by Leung et al having ever smoked increased the likelihood of having cough and dyspnoea as presenting symptoms of TB (Leung et al 2003). Radiologically, TB patients who had ever smoked were more likely to exhibit cavitation, miliary disease and upper zone involvement. Although the likelihood of a positive sputum smear was also higher in this group, smoking did not appear to affect susceptibility to anti-tuberculous chemotherapy. The authors concluded that there was more aggressive lung involvement found among those who had ever smoked. Other authors also seem to reach a similar conclusion demonstrating that TB in smokers takes on a more severe disseminated course, more extensive lung involvement and less cavity closure (Shprykov et al 1994).

Common mediators in the pathogenesis of TB and COPD

The development and subsequent disease progression seen both in TB and COPD result in characteristic destructive parenchymal lung changes. A common link to the pathogenesis of both conditions may lie in the destruction of the pulmonary extra-cellular matrix (ECM) comprised of collagen and elastin which is key to the structural integrity of the lung (Elkington et al 2006). In particular, the role of matrix metalloproteinases (MMPs) deserves special mention. MMPs are a family of naturally occurring protease enzymes capable of degrading the ECM. In conditions where there is altered or unregulated activity of MMP enzymes, there exists the potential for re-modelling and subsequent damage to the lung architecture. The antigenic wall component of mycobacterium tuberculosis, lioparabinomannan (LAM), stimulates the release of MMP-9 as well as up regulating genetic expression of MMP-1 and MMP-9. This not only results in the breakdown of collagen in the ECM but is also stimulates further lung damage by activation of other immune mediators such as Interleukin-8 and other cytokines. This process may be central to the development of cavitatory parenchymal lung damage often complicating active tuberculosis that is familiar to the clinician. Hrabec et al demonstrated that MMP-9 levels were three times higher in the serum of tuberculosis patients compared with controls with increasingly elevated levels seen in those patients exhibiting advanced disease compared to limited disease (Hrabec et al 2002). Elkington et al found increased expression of MMP-1 and MMP-7 in the granulomas of patients with active TB compared with controls as well as increased MMP-1 secretion from the airway epithelial cells adjacent to these granulomas (Elkington et al 2005). Furthermore, this study also showed that activity of the specific inhibitor of MMP-1, tissue inhibitor of metalloproteinase 1 (TIMP-1), was suppressed resulting in unchecked MMP-1 activity and the potential for significant destruction of the ECM. TNF-alpha, which plays an important role in the formation of tuberculous granulomas, has been demonstrated to stimulate MMP-9 secretion from granulomas cultured from patients with active tuberculosis (Price et al 2003).

Many studies have demonstrated an association between MMPs and the development of structural lung damage complicating tobacco related COPD. Finlay et al compared the expression of MMPs from alveolar macrophages taken from broncho-alveolar lavage (BAL) samples in 10 COPD patients and 10 control subjects (Finlay et al 1997). The group found significantly more MMP transcription, in particular MMP-9, in the COPD group. Other studies have similarly found elevated levels of MMP-8 and MMP-9 in induced sputum and BAL samples taken from COPD patients (Vernooy et al 2004). Imai et al compared lung parenchyma samples taken from 23 patients with COPD with 8 normal controls (Imai et al 2001). This study showed an increased level of MMP-1 RNA activity in the COPD group which was not present in the control subjects. Furthermore, this group demonstrated that the source of such activity may originate from Type 2 pneumocytes in the lung parenchyma. In contrast to that seen in TB patients, a recent study showed elevated serum TIMP-1 levels in COPD patients compared to controls (Higashimoto et al 2005).

The clear message from the literature is that increased expression of certain MMPs is associated with re-modelling of the pulmonary ECM and structural changes in the lung seen in both TB and COPD. Strictly, the above changes to the extra-cellular matrix would be expected to predominantly involve the lung parenchyma as opposed to the airways. Further studies are needed to correlate the degree of structural impairment related to the MMP system with physiological indices of pulmonary function focusing on airway physiology, both in TB as well as COPD. Furthermore, the challenge remains whether pharmacologically targeting the matrix metalloproteinase network and other such mediators in these two conditions will result in clinically significant outcomes. (Braunhut et al 1994; Frankenberger et al 2001; Mao et al 2003).

The impact of COPD as a co-morbidity in tuberculosis

There is little information in the literature about the impact of COPD co-morbidity in terms of prevalence, treatment outcomes and prognosis in TB. A study from Turkey which reviewed 5480 cases of active pulmonary and pleural TB found that COPD was the second most common co-morbid condition (Aktogu et al 1996). In that study, 6% of patients (331 cases) had a diagnosis of COPD which was second only to diabetes mellitus (8% of cases) and higher than narcotic abuse and alcoholism. Wang et al studied 461 cases of culture positive pulmonary TB in a tertiary referral centre in Taiwan (Wang et al 2005). In terms of concomitant non-malignant diseases, a formal diagnosis of COPD was found in 31 cases again ranking second highest behind diabetes mellitus and ahead of renal failure, liver failure and HIV. In a study of tuberculous pleurisy cases by Liu et al COPD was again the 2nd most common co-morbid condition (found in 23% of cases) behind diabetes mellitus (Liu et al 2005). In that study, a diagnosis of COPD was not associated with case fatality. Furthermore, in a Romanian study, COPD was documented in 10.6% of cases of relapsed TB (Didilescu et al 2000). Perhaps not surprisingly, the prevalence of COPD as a co-morbid condition varies according to the age group studied. COPD has been found to be much more common in elderly patients diagnosed with TB. In a study from Pakistan, in terms of associated medical problems, COPD was found in 24.3% of elderly patients diagnosed with TB compared with only 3% of young cases (Rizvi et al 2003).

It is debatable whether the presence of COPD as a co-morbid condition represents a risk factor for mortality in cases of TB. In a UK study of 209 cases of culture positive pulmonary TB, 19 patients died before completion of treatment. 8 of these deaths were attributed to TB whilst 11 were from co-morbid conditions. Furthermore, 6 of these 11 deaths were as a result of COPD, all in white Caucasians with a male: female ratio of 4:2 (Ormerod et al 2002). In a 1990 study, COPD was listed as a concomitant disease in 5% of death certificates in patients dying from pulmonary TB (White et al 1996). In a cohort study of 139 patients treated for TB in the United States, 10% of patients had an underlying diagnosis of COPD (Oursler et al 2002). The authors concluded that the presence of COPD was an independent risk factor for death along with diabetes mellitus, renal disease and HIV infection. However, in a study from Baltimore, USA, a diagnosis of COPD was not associated with death from TB on multi-variate analysis (Fielder et al 2002). In this study of 174 patients diagnosed with TB, 23 cases had underlying COPD whilst 42 patients died whilst receiving anti-tuberculous chemotherapy.

A diagnosis of COPD may also be relevant in sicker TB patients eg, with drug resistance or those requiring intensive care unit (ICU) support. A Russian study of 309 civilians and 291 prisoners found a prevalence of isoniazid resistance of 60.2% and further suggested that this may be linked to an underlying diagnosis of COPD at an odds ratio of 2.1 (95% confidence interval 1.0–4.3; $p = 0.042$) (Ruddy et al 2005). However, in a paper from Spain studying 276 cases of TB (24 drug resistant cases) over a 6 year period, COPD was not associated with the emergence of drug resistance on multi-variate analysis (Arevalo et al 1996). There were 33 patients with COPD in the entire group but only 2 of these patients had drug resistant disease. Regarding TB patients requiring ICU support, a study of 58 patients with TB admitted to a German ICU between 1990 and 2001 found that 6 of this group had an underlying diagnosis of COPD (Erbes et al 2006). 15 of the 58 patients died (4 of whom had COPD) compared with 43 who survived (2 of whom had COPD). Here, this difference in COPD prevalence was statistically significant on uni-variate analysis ($p = 0.03$). However, there is comparatively little data on these sub-groups of TB patients in terms of associations with COPD and this area warrants further more detailed study.

The conflicting results from the above data examining the presence of underlying COPD as a risk factor for increased morbidity and mortality from TB may be due to the difficulty in adequately controlling for cigarette smoking. This is itself a risk factor for increased morbidity during the course of TB treatment as well as for the development of airflow obstruction (Leung et al 2003; Shprykov et al 1994). There is still less data in the literature on whether a diagnosis of COPD alters the clinical presentation

of pulmonary TB. This is in contrast to data on other diseases affecting the outcome of TB such as diabetes mellitus despite COPD evidently being present in a substantial number of patients diagnosed with TB (Bacakoglu et al 2001).

The development of chronic airflow obstruction as a sequel to pulmonary tuberculosis

Obstructive abnormalities in lung function may complicate pulmonary tuberculosis, particularly in long standing disease and if the extent of parenchymal involvement is extensive. Although, earlier studies regarding this issue were performed in developed countries, the main burden is now felt in developing countries where there is both a high incidence of cigarette smoking and patients are more likely to present with extensive parenchymal lung destruction secondary to inadequately treated TB.

A major limitation in the interpretation of the early literature is due to the fact that such studies lacked an adequate control group making it difficult to distinguish the effects of cigarette smoking from tuberculous infection in terms of effect on lung function measurements. In 1959, in a study of 1,533 patients, Gaensler et al showed that 61% had evidence of airflow obstruction (defined as an FEV_1/FVC <70% and VC >80% predicted); 50% of patients had respiratory symptoms (64). Snider et al studied 1403 patients admitted to a Chicago Municipal TB Sanatorium over a 2 year period between 1964 and 1966 (Snider et al 1971). 23% were noted to exhibit airflow obstruction. Airflow obstruction was more commonly noted among white Caucasian males more of whom also showed the most severe diminution of FEV_1 to less than 50% predicted. The development of airflow obstruction was linked to the presence of morning expectoration with 58.8% of males with expectoration having obstructive spirometry compared with 42.4% without expectoration. There was no significant association noted between smoking history in terms of pack years and the FEV_1/FVC ratio. Abnormal spirometry was also not associated with the duration of active disease prior to presentation and only weakly with age. Meanwhile, a study from Sweden published in 1966 examined 488 patients with TB admitted to hospital over a 5 year period (Birath et al 1966). All patients underwent spirometry and chest radiography. A reduction of FEV_1 as well as Vital Capacity (below 2 Standard deviations of predicted) was noted in 78 cases whilst a sole reduction in FEV_1 was noted in 52 patients. The greatest frequency of respiratory symptoms (in terms of cough, expectoration, wheeze and allergic symptoms) was seen in those patients who had the greatest reduction in FEV_1. Abnormalities in lung function were significantly associated with increased duration of disease and age over 40. 12–15% of those defined as having "short" duration of disease (<1year) had abnormal lung function compared to 33–37% of those where disease duration was defined as "long" (>10 years). In addition, the prevalence of airflow obstruction was significantly greater in those patients labelled as having "generalized" tuberculous disease (defined as lesions due to TB involving 75% or more of the chest radiograph). There were no gender related differences noted but the influence of cigarette smoking was not taken into account in this study.

A more recent paper from South Africa attempted to examine the impact of multiple episodes of treated TB on lung function (Hnizdo et al 2000). In this study, pulmonary function tests were performed on 27,660 black South African gold miners. 2137 of the sample had previously suffered from at least 1 episode, 366 from 2 episodes whilst 96 had 3 more episodes of active TB. 18.4% of those with 1 active TB episode developed chronic airflow obstruction (defined here as FEV_1<80% predicted) compared with 27.1% with 2 episodes and 35.2% in those with 3 or more. Following one episode of TB, the loss of FEV_1 was highest 6 months post infection (326 mls) though the overall residual loss of FEV_1 at the end of a minimal 12 month follow up stabilized at 153mls. This compared to a fall in FVC by 305mls 6 months post infection which stabilized to a residual loss of 96 mls. However, again, there was no control group and the study population was not adjusted for smoking history nor were any specific effects of other dust exposure quantified. Meanwhile, a smaller study from Brazil evaluated symptomatology and pulmonary function in 50 patients with pleuro-pulmonary sequelae of TB (Ramos et al 2006). In this study, those patients with an underlying diagnosis of COPD or asthma were excluded while 54% of the study population had never smoked. An obstructive ventilatory pattern alone was noted in 22% of patients with pulmonary TB whilst 34% exhibited a "mixed" obstructive and restrictive pattern. The authors found no significant relationship between abnormalities of pulmonary function and smoking history**.** However, the study did not take into account exposure to other noxious agents eg, biomass fuels often linked to the development of COPD in developing countries (Pauwels et al 2001). The severity of lung function impairment was proportional to the degree of radiographic involvement noted on the plain film. Interestingly, the authors concluded that the presence of respiratory symptoms did not predict altered pulmonary function.

A well described sequel to active tuberculosis is the development of bronchiectasis and subsequent airflow ob-

struction (Grancher et al 1878).The exact incidence is difficult to determine with precision. In the early 19th century, prior to the advent of more non invasive diagnostic techniques, attempts to explore the incidence of bronchiectasis complicating TB relied on the analysis of autopsy material. In a study of 100 such autopsies, changes of bronchiectasis were described in 46% of cases (Jones et al 1950). Nowadays, bronchiectasis as a sequel to TB is seen less commonly in the developed world due to prompt diagnosis and improved access to anti-tuberculous chemotherapy. Nevertheless, bronchiectasis still complicates active pulmonary TB too frequently in developing countries. A prospective study from Thailand studied all patients (fifty in total) diagnosed with bronchiectasis over a 2 year period from January 1998 (Palwatwichai et al 2002). The mean age of the sample was 58 years whilst 78% had never smoked. A history of TB was noted in 32% of the study population with the authors concluding that TB represented the most common aetiological agent responsible for the development of bronchiectasis. Such data is in contrast to the findings of a retrospective review of 363 adult bronchiectasis cases over an 8 year period in Texas, USA (Nicotra et al 1995). Here, only 9.8% of cases were attributed to "granulomatous" disease but this paper did not differentiate between tuberculosis and sarcoidosis as causative factors. In that study, bronchiectasis resulting from tuberculosis was described as more likely to occur in older individuals. However, such studies may be limited by the reliance of the patient describing a previous history of tuberculosis and the authors subsequently attributing this description as the definitive aetiology leading to the development of subsequent bronchiectasis.

Pathophysiology behind the development of chronic airflow obstruction secondary to active tuberculosis

Very little exists in the literature comparing clinical and physiological characteristics of chronic airflow obstruction (CAO) secondary to TB to that seen in patients with tobacco related COPD. A South Korean study followed 21 patients with chronic airflow obstruction (CAO) secondary to TB as well as studying clinical characteristics and various lung function measurements (Lee et al 2003). All patients had parenchymal damage to more than half a lung as a result of proven TB yet had no evidence of active TB, currently did not smoke and had less than 20 pack year smoking history (mean 3.6 pack years). These data were compared with a control group of 11 patients diagnosed with tobacco related COPD whom by definition had >20 pack years smoking history (mean 44.1 pack years) with no radiographic evidence of pulmonary infiltration. There were no significant differences noted between the 2 groups in occurrence and frequency of symptoms of dyspnoea and cough though there was a trend towards a greater frequency of haemoptysis in the CAO patients. In addition, no significant differences were observed between the 2 groups regarding exacerbation episodes and hospitalizations. Bronchodilator response was also studied in the 2 groups. A positive response (defined as an increase in FEV_1 of 200 mls or 12%) was seen more frequently in the tobacco related COPD group compared to the CAO patients (82% vs 27%; $p < 0.05$). The FEV_1 seen in the CAO group following bronchodilator inhalation was also significantly lower than the COPD patients (1.15 l vs 1.37 l; $p < 0.05$). Airway resistance (Raw) was higher in the CAO group but this did not reach statistical significance.

The extent of airflow obstruction and parenchymal destruction seen as a result of TB infection may be so severe as to lead to the development of respiratory failure which may sometimes require acute ventilatory support (Park et al 2001). Several studies have highlighted the mortality associated with the development of ventilatory failure in this group of patients (Erbes et al 2006; Park et al 2001; Frame et al 1987). A study from South Korea retrospectively reviewed 38 such patients admitted to the ICU requiring mechanical ventilation (Park et al 2001). Patients were predominantly male (65.8%) and 52% of the group had never smoked. Pulmonary function measurements had been performed in 21 of these patients in the preceding 12 months. The mean FEV_1 of this group was 0.77 litres (29.3% predicted), mean FVC of 1.52 litres (41% predicted) with a mean FEV_1/FVC ratio of 55.1% suggesting that chronic airflow obstruction secondary to TB plays a major role in the development of acute respiratory failure. However, the methodology of such studies were again limited due to a lack of adequate control subjects as well as retrospective data hence making it difficult to separate the effects of tobacco smoking from tuberculosis infection as the primary cause of respiratory insufficiency. It must not be forgotten that, particularly in developing countries, a diagnosis of tobacco related COPD may be a major contributory factor in the development of acute ventilatory failure complicating tuberculous infection **(**Erbes et al 2006; Park et al 2001**).**

The pathophysiology leading to the development of airflow obstruction in TB is multi-factorial in nature (Bromberg et al 1963). Endobronchial involvement may

result in localised and generalised bronchial obstruction, fibrosis and an increased airways resistance. There may be extrinsic bronchial compression secondary to tuberculous lymphadenopathy. Parenchymal lung destruction may also affect pulmonary compliance resulting in an increased tendency for peripheral airways collapse and subsequent air trapping. This is worsened by abnormalities in the ventilation-perfusion relationships. Parenchymal and airway changes result in areas of decreased ventilation which may be adequately perfused. Conversely, mycobacteria infection may induce vascular changes in the lung leading to a scenario of decreased perfusion in areas of adequate ventilation. Unsurprisingly therefore, the net result of the above is an impairment of lung function and the development of airflow obstruction with abnormal gas exchange.

Summary

Worldwide, tuberculosis and COPD are common conditions carrying an immense burden on the health of populations and healthcare resources. The development of chronic airflow obstruction and respiratory symptoms may be preceded by one or several episodes of active TB and is more likely following extensive and severe infection, particularly if this involves large areas if lung parenchyma radiologically. Tobacco smoking is central to the development of COPD in most cases and some evidence exists to support the role of smoking in influencing the progression and clinical course of TB infection. Immunological mediators affecting the lung parenchyma have been identified that are common to the pathogenesis of COPD and TB. COPD also appears to be a common co-morbid condition in patients diagnosed with active TB though further studies are needed to determine whether the clinical presentation, disease progression and mortality from TB are affected by an underlying diagnosis of COPD.

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