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REVIEW

Co-morbidities in people with COPD: a result of multiple diseases, or multiple manifestations of smoking and reactive inflammation?

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Abstract

There has been increased awareness and recognition of COPD in both developed and developing nations. As people with COPD are identified and treated before they reach end-stage lung disease, the multiple morbidities associated with COPD have been recognised.[1,2] These morbidities affect many areas of the body and currently are often treated with numerous different drugs. This poly-pharmacy, and the need for therapy by multiple organ-specific specialists, is not optimal and often not feasible for patients with COPD. New information on many of the common multiple morbidities suggests that it may be possible to explain – and in the future control or treat – these multiple morbidities, by addressing one common trigger and a common final pathway of inflammation. This review outlines some of the reasons why it is time to consider a 'whole body' approach to COPD, rather than clinicians continuing to address the lungs first and then each additional organ one at a time.

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Contents

Introduction

Interest in earlier and effective diagnosis of chronic obstructive pulmonary disease (COPD) is prominent around the world. Earlier diagnosis – i.e. before the patient has end-stage lung disease – has focused awareness on the multiple non-pulmonary morbidities that often accompany COPD. As generalists working in primary care, we are often called upon to address these multiple problems and to try to integrate the therapy recommended by multiple specialists into care for the whole person. Generalists often look for a common pathway or common factors to explain many conditions, while the specialist often concentrates on a single organ system. In fact, the widespread "multiple morbidities" associated with COPD have triggered specialists and researchers to consider universal triggers or response mechanisms that would link the multiple organ system damage from COPD. One common

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irritant – tobacco smoke – and one common response – inflammation – may underlie many of the multiple morbidities seen in people with COPD.

In this review, we present information that supports the link between smoking and inflammation and COPD, as well as the link with cardiovascular disease, musculo-skeletal disease, cognitive deficits and depression. This link should become the basis for future investigation of COPD management, including COPD-associated multiple morbidities. The frequent association of these problems with the toxic effects of cigarette smoke and inflammation may provide us with a new, more targeted, approach to the disparate but multiple morbidities which occur with COPD.

The pathology of COPD and the effects of smoking

Most patients with recognised COPD are over the age of 50, have smoked for 20 to 30 years, and have altered their life styles to deal with increasing breathlessness and activity limitation. Cigarette smoking is associated with over 80% of all cases of COPD, and a smoker is 10 times more likely to die of COPD than a non-smoker.[1] COPD is more common among women who smoke and those who have a strong family history of COPD.[2] Smoking irreversibly changes the structure of the lungs and accelerates the decline in lung function that normally accompanies ageing. Currently no tests can predict which smoker will develop COPD but all smokers are candidates for smoking cessation. Furthermore no primary care physician should reasonably assume that a long-term smoker will develop only lung disease. Smoking affects many organ systems in addition to the lungs, including the heart, other parts of the cardiovascular system, the musculoskeletal system, the skin, the brain and the genitourinary system;[3-6] therefore, it is reasonable to assume that one or more of these systems will also have been adversely affected by prolonged exposure to tobacco smoking. The lung serves as a filter for toxic substances, preventing their entrance into the blood stream. For tobacco and biomass fuel smoke, the lung is able to filter out only a portion of those toxins, leaving others to circulate throughout the body – thereby affecting everything from the gut to the heart and the brain.

However, the likelihood of co-morbidities may also be associated with the inflammatory response of the body to tobacco products or other inhaled toxins. In the lungs, chronic inflammation of the small airways and gradual destruction of the alveoli characterises COPD.[1,4] Chronic inflammation results in fibrosis, which in turn leads to narrowing of the airways. Neutrophils are involved in the inflammation observed in COPD.[1] Various protease enzymes released by neutrophils damage the elasticity and destroy the supporting tissues of the alveoli. These problems are aggravated by excessive mucus, which clogs the airways, resulting in spasm of the muscles that surround them. Terminal bronchioles collapse or are blocked by mucus plugs, and air becomes trapped in the distal airways, causing hyperinflation. Alveolar dead space (alveoli that are ventilated but not perfused) is increased. Hyperinflation, in combination with narrowed airways and reduced gas exchange from loss of alveoli, leads to breathlessness, exercise intolerance, and hypoxia.[4]

COPD and its consequences have direct effects on organs other than the lungs. For example, hypoxia increases pulmonary vascular resistance, causing pulmonary hypertension and (in severe cases) right-sided heart failure.[5] Defects in cognitive function have been noted to be more common in patients with COPD, even prior to hypoxic stress confirmed by lowered oxygen saturation measures.

What are the co-morbidities in COPD?

Data on multiple morbidities in people with COPD is limited[4] and the morbidities may even mask the impact of COPD on morbidity and mortality. For example, a cardiovascular death is rarely attributed to cor pulmonale. In fact, most COPD patients are reported to die of extrapulmonary diseases, including cardiac ischemia, cardiac arrhythmias, and heart failure. Others die of complications like pneumonia or septicemia that may not have developed or have been fatal without the burden of COPD.[7] In the Towards a Revolution in COPD Health (TORCH) trial, 35% of deaths were adjudicated to be due to pulmonary causes, 27% to cardiovascular disease, and 21% to cancer. Ten percent were attributed to other causes, whereas the primary cause of death could not be determined by the clinical end-point committee in 7% of cases.[8] The actual percentage of deaths listed as cardiovascular that were a direct result of hypoxic- (COPD-) induced cardiac strain are unknown.

COPD develops over many years. It is common to find co-morbidities – if one seeks them – within the first year of diagnosis. Soriano and colleagues[9] found many other conditions with frequencies of at least 1% at the time of COPD diagnosis. These included angina, cataracts, osteoporotic fractures, osteoporosis, pneumonia, and respiratory infections, the highest being angina with a prevalence of 4.0%. Compared to the person without COPD, patients with COPD were at increased risk for pneumonia (relative risk [RR] = 16.0), osteoporosis (RR = 3.1), respiratory infection (RR = 2.2), myocardial infarction (RR = 1.7), angina (RR = 1.7), fractures (RR = 1.6), and glaucoma (RR = 1.3) [all $p < 0.05$] over the duration of the diagnosed COPD.[9]

Smoking as a link

There are many conditions that are affected by cigarette smoke. The commonest, of course, is asthma. Cigarette smoke, like many other irritants, worsens asthma and may increase resistance to the effects of therapy, especially inhaled corticosteroids.[10] In the subgroup of asthma patients with uncontrolled or poorly controlled asthma, this can result in 'remodeling,' in which the basement membrane thickens and the airway constriction becomes fixed, functionally looking like COPD. The pathology of this fixed airway asthma is different from the alveolar destruction, hyper-inflation and neutrophillic inflammation of COPD, but when added to COPD it increases morbidity and mortality as well as the total burden of lung disease.[11,12]

Other lung diseases such as lung cancer,[13] pulmonary hypertension,[14] pulmonary emboli, and sleep apnoea, are also independently associated with tobacco smoking and co-exist with COPD. Respiratory infections are often precipitated by upper respiratory infections[15] and influenza.[16] Influenza vaccinations have been shown to decrease exacerbations that occur more commonly in those who continue to smoke.

As shown by the Framingham study, COPD is a risk factor for cardiovascular disease (CVD) and is the best predictor of CVD mortality risk. Whilst the cigarette smoke confers a direct increase in the CVD risk, smokers with COPD versus those with no COPD have a higher risk of CVD such as myocardial infarction (MI), arrhythmias, and congestive heart failure. This risk increases with increased severity of COPD and is highest among people hospitalised for COPD.[17-19]

Patients with COPD were studied in a retrospective cohort study in longitudinal health care databases maintained by the government of Saskatchewan, Canada, to assess the prevalence of cardiovascular diseases.[20] Subjects were diagnosed with COPD during 1997-2000, were 40 years of age or older, and were symptomatic, having received two or more prescriptions for bronchodilators within six months of diagnosis. Each subject was matched by age and sex to two controls without COPD or asthma. The prevalence of all cardiovascular diseases including arrhythmias, angina, acute MI, congestive heart failure, stroke, and pulmonary embolism, as well as the risk of hospitalisation, were elevated in the COPD group. The risk ratio for cardiovascular mortality was 2.07 (CI: 1.82-2.36) and all cause mortality was 2.82 (CI: 2.61-3.05). Some early studies suggest that bronchodilator treatment for smoking-induced COPD might aggravate the other diseases associated with smoking such as CVD. However, several studies using salmeterol and formoterol for COPD therapy have shown no increased risk for cardiovascular event or death,[21] except when there is a preceding history of hypoxemia and cardiac arrhythmia. Keeping the doses of medication within conventional dosing ranges can decrease this risk.[22] Neither beta-agonists, anti-cholinergics, or short-acting bronchodilators appear to have any significant adverse cardiovascular effects.[23]

Osteoporosis and osteoporotic fractures are a significant problem in patients with advanced COPD.[24] The aetiology for the bone loss is diverse and likely includes the direct effects of smoking and the life style of smokers (vitamin D deficiency), but also factors that are considered to be co-morbidities of COPD such as low body mass index, hypogonadism, sedentary lifestyle, and the use of glucocorticoids. Fractures are often the first recognised sign of osteoporosis. Therefore, screening for osteoporosis, especially in women with COPD who continue to smoke, may reduce fracture-related morbidity and mortality; however, when identifying treatment candidates, Katsura and colleagues[25] found that any age-matched women receiving equivalent doses of corticosteroids for asthma and COPD differed in their rates of osteoporosis. Women receiving steroid treatment for COPD had higher rates of osteoporosis suggesting a synergistic effect of COPD and smoking.[25] In men, bone density was correlated with COPD severity and arterial pH, but men with COPD were not more likely than age-matched men without COPD to have osteopenia or osteoporosis.[26] Effective strategies for prevention or treatment of osteoporosis include smoking cessation, calcium and vitamin D treatment, hormone replacement when indicated, calcitonin, and bisphosphonate administration.[27-29]

COPD and its accompanying dyspnoea often results in sedentary lifestyles characterised by a downward spiral of symptom-induced inactivity, leading to deconditioning and muscle weakness,[30] resulting in a further decrease in activity.[31] But muscle weakness may not just be a result of inactivity but is rather believed to be a co-morbidity of COPD, usually involving both respiratory and skeletal muscles.[32,33] Peripheral vascular disease due to smoking may also lead to further muscle weakness. The amount – and site – of muscle weakness varies from person to person and involves multiple suspected aetiologies, including tobacco smoking.[34,35] Treatments including pulmonary rehabilitation and smoking cessation are important, since leg weakness can be as limiting as breathlessness for patients.[36,37]

Lowered levels of testosterone have been seen in men with COPD and are positively related to quadriceps muscle weakness, but not necessarily to exercise intolerance.[38,39] The relationship between smoking and testosterone levels and function have been somewhat inconsistent in the literature.[40] Male patients are defined as being hypogonadal when androgen deficiency is combined with otherwise unexplained fatigue or diminished energy, vitality, or a sense of well-being. Hypogonadism itself does not seem to worsen respiratory symptoms, quality of life, or respiratory or limb muscle performance and exercise capacity in COPD.[38,39]

Testosterone replacement may increase lean body mass and strength in men with severe COPD and low testosterone levels. This effect is improved by an active resistance exercise program.[41] Other potential benefits – such as the effects on bones and the bone marrow – compared with the potential adverse effects of prostatic hypertrophy and the risk of prostate cancer must be balanced before testosterone replacement can be recommended as a treatment in such patients.[41,42]

The association between gastro-oesophageal reflux disease (GORD) and tobacco smoking is clear.[43] However, the association of GORD with COPD is less clear.[44] There is a higher prevalence of GORD symptoms in patients with COPD compared to control subjects, the prevalence of GORD symptoms increase with COPD severity, and more patients with COPD use anti-reflux medications compared to control subjects (50% vs. 27%, respectively; p=0.008).[45] Oxygen desaturation coincided with episodes of increased oesophageal acidity in 40% of patients with GORD in one study, questioning the role of GORD in exacerbations.[46,47] Smoking cessation may improve GORD.

Both depression and COPD are more common in smokers. The depression in COPD may be related both to the lower quality of life associated with moderate to severe COPD, and with smoking.[48,49] These psychological factors can impose an additional barrier to effective symptom control, further reduce quality of life, and require pharmacological and non-pharmacological treatment strategies for effective management. The limited marginal effectiveness of antidepressants in people with COPD[50] may suggest the need for additional or alternative therapy such as cognitive behavioral therapy.[51] The additive effect of smoking cessation has not been assessed.

Inflammation and multiple organ system morbidity

Over the past 15 to 20 years, inflammation has become recognised as a common reaction of the human body to irritants, to foreign materials and, in some cases, to the body's own organs. Early studies of inflammation resembled the blind men and the elephant; each organ system appeared to have unique mediators of that site's inflammation. But as we have become more sophisticated and able to look more closely, many of those mediators appear to be present in the inflammatory response or inflammatory cascade of multiple organ systems. Tumour necrosis factor-alpha (TNF-alpha), or cytokines such as interleukin-8 (IL-8) or IL-5 are not unique to the lung or the gut or the brain. In this section, we review the progress made in terms of our understanding of inflammation in many chronic diseases, and we present an overarching hypothesis that these inflammatory responses may all be linked, perhaps partially through a reaction to the toxins of tobacco and biomass fuel smoke. The continued presence of inflammatory mediators like C-reactive protein (CRP), even 10 to 20 years after a person stops smoking, may partially explain the development of COPD in former smokers – again, this links the smoking and inflammatory basis of COPD with COPD co-morbidities.[52]

Like the gut, the lung is an entry and an exit site for our vascular systems. Not only does the lung provide oxygen and remove toxins, it brings toxins into the vascular system. In addition, cells and other biological mediators produced within the pulmonary tissue are released into the vascular system to spread throughout the body. The irritated or inflamed lungs of a person with COPD produce multiple types of inflammatory and pro-inflammatory cells from cytokines to TNF-alpha. The 'spill over' of these local airway inflammatory cells into the systemic circulation is hypothesised to be a contributor to other inflammatory conditions such as CVD.[53] Such pro-inflammatory mediators may help explain the aetiology of many of the multiple morbidities associated with COPD.[54]

Cardiovascular disease is often associated with COPD. The CVD may be a direct result of the toxins inhaled from cigarette or biomass fuel smoke and which are passed through the lungs into the circulatory system. As mentioned above, those toxins can have direct adverse effects on cardiac muscle and cardiac vessels such as the coronary arteries. However, CVD is also known to have an inflammatory basis.[55-58] For example, elevated CRP is a clinical marker of inflammation, and a direct participant in vascular inflammation in CVD.[59] Circulating activated platelets also may link CVD and COPD through inflammatory mediators.[60] People with COPD often experience chronic heart failure (CHF). Inflammatory cytokines such as interleukins have been shown to be present in COPD and appear to contribute to the development and progression of CHF.[61] Cardiovascular studies are often ahead of research into other multiple morbidities in part due to the much greater funding resources for CVD research (at least in the U.S.). Several of these studies have linked CVD and depression on the basis of inflammation.[62-64]

Research that addresses the impact of inflammatory cytokines on vascular smooth muscle and remodelling may also lead to work on remodelling in pulmonary smooth muscle.[65,66] Researchers have discussed the role of the potential skewing of Th1/Th2 cytokine balance in the role of such vascular problems as abdominal aortic aneurysms.[66] Similar studies of pulmonary vascular remodelling due to inflammatory mediators suggest the importance of exploring this same phenomenon in lung remodelling.[67]

Muscle wasting in COPD is poorly understood. Certainly inadequate nutritional intake can affect weight loss and loss of muscle mass. Recent studies suggest that intake of certain nutrients such as fresh fruits and vegetables can decrease the expression of key inflammatory genes and therefore inflammation.[68] People with COPD often eat little, and may find shopping for fresh foods especially difficult, resulting in reduced intake and increased expression of inflammatory modulators. However, the total caloric intake and muscle wasting are not always parallel. Studies of chronic muscle dysfunction suggest that chronic inflammation has a significant role in musculoskeletal disorders that results from simple repetitive acts.[69] How this may relate to the muscle dysfunction seen in the context of the chronic inflammation in people with COPD is still speculative.[69] Other studies show that cytokines crossing the blood-brain barrier may induce appetite suppression.[70]

Depression has recently been found to have an inflammatory basis, with increased levels of such factors as interleukin (IL-6) that are also common in COPD.[71-73] Cytokines play a key role in the hypothalamic-pituitary-adrenal axis activation seen in depression.[70,74] Work in community populations demonstrates significant increases in pro-inflammatory chemokines such as IL-8 in adults with chronic stress, chronic illnesses and depression.[64] Some of this work even suggests that depression associated with an inflammatory condition such as COPD may not respond to therapy with anti-depressants without also treating the inflammation,[70] a fact supported by the few studies on the treatment of depression in people with COPD.

Cognition can decrease with hypoxia. However, cognitive decline has been shown to be present in people with COPD who are not hypoxic and do not have measurable levels of depression.[6] This may also be an adverse outcome of the chronic inflammatory state found in people with COPD.[75] Peripheral cytokines penetrate the blood brain barrier and contribute to cognitive impairment via cytokine-mediated interactions between neurons and glial cells.[70]

While the results of the TORCH study remain the topic of debate, the decline in all cause mortality in those using daily inhaled corticosteroids must be considered again in view of the head-to-toe inflammatory state that can be associated with the passage of COPD-related inflammatory cells outside the lung and into the systemic circulation. Treatment with inhaled corticosteroids (ICS) also provides a low dose of systemic corticosteroid. Is that low level of ICS sufficient to affect the role of the pro-inflammatory as well as the inflammatory mediators on other organ systems? Can ICS reduce the risk for inflammatory-mediated CVD[55-58] or muscle wasting or depression?

Another type of therapy that may improve outcomes for all the multiple morbidities (e.g. all-cause mortality rates) associated with COPD is the group of phosphodiesterase (PD) E4 inhibitors. Currently these drugs are being tested for their effects on inflammation-associated asthma and COPD.[76] However, they might provide treatment for all the inflammatory-related issues resulting in the multiple morbidities of COPD.

In summary, the multiple morbidities found in those patients with COPD could simply be the result of statistics. With ageing comes the risk of multiple diseases, from diabetes to heart disease to Alzheimer's disease. However, the association between COPD and its co-morbidities may be more than just the effect of age. The multiple morbidities of COPD are directly related to the increased risk of vascular and heart disease associated with chronic exposure to the toxins of tobacco and biomass fuel smoke. But these co-morbidities may also be a result of the chronic inflammatory state – which is spread throughout the body – that occurs in people who develop COPD. Genetic predisposition to the pro-inflammatory state may help explain why some smokers develop COPD and others don't. And it may play an important role in determining the multiple morbidities which occur in those who do develop COPD.

Conclusion

One common irritant – tobacco smoke – and one common response – inflammation – may underlie the multiple morbidities seen in people with COPD. In this review, we have outlined the common co-morbidities present in patients with COPD. We have presented some of the work used to link smoking and inflammation with COPD, cardiovascular disease, musculo-skeletal disease, cognitive deficits and depression. In the future, this work may allow the general practitioner/family physician to anticipate and to screen appropriately for these conditions, hopefully resulting in better patient outcomes and quality of life. It may also allow future research to assist in developing treatments and preventions for these co-morbidities – treatments that will address the inflammatory process more broadly yet more selectively than corticosteroids, and which may address and even prevent the addiction of tobacco smoke.

Conflict of interest declaration

None declared.

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