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Comorbidities of COPD as a function of age: evidence and practical recommendations

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Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic condition with a dramatic impact on the health status that is evident even in milder stages of the disease. However, deaths due to respiratory causes account for only a fraction of mortality in COPD. Thus, comorbid conditions as potential co-determinants of the effects of COPD on both health status and survival have received much attention in the last years. COPD is almost invariably associated with other diseases, and three mechanisms most likely underpin this association. First, COPD is an age-related diseases, and as such tend to be associated with other age-related diseases. Second, COPD shares its most important risk factor – cigarette smoking – with several other diseases, in particular cardiovascular diseases. Third, COPD, or COPD treatment, may impact other systems or organs, as is the case of COPD-associated anemia or osteoporosis. The aim of this article is to provide an overview on the comorbidities of COPD that are most relevant for the elderly, providing information relevant for patients' management. COPD is a highly prevalent chronic condition, the only one whose prevalence is steadily rising in western countries [1]. Currently the sixth, it is expected to rank the third cause of death by 2020 [2]. Furthermore, it dramatically impacts the health status and the personal independence [3]. However, deaths due to respiratory causes account for only a fraction of mortality in COPD [4], whereas health status is frequently impaired even in the milder stages of the disease [5]. This fact has switched the attention to comorbid conditions as potential co-determinants of the effects of COPD on both health status and survival.

Key words: Chronic obstructive pulmonary disease, Comorbidity, Aged, Aged 80 and over, Frail elderly

The original concept of comorbidity refers to diseases coexisting with the "main" disease. In elderly people, this is an elusive concept as the main disease may change over time and may be difficult to recognize. Indeed, in the majority of elderly people several chronic conditions contribute in a comparable manner to impair the health status. This is especially true of COPD patients: coexisting cardiac, skeletal, cognitive and affective problems are frequantly responsible for impaired health status in a comparable way. To overcome the conceptual limitation of the classical definition of comorbidity, the concept of multimorbidity has been proposed, which refers to the coexistence of multiple conditions with no implicit separation between a "principal" disease and associated diseases. The concept of multimorbidity goes beyond this, however, because it has been shown that some chronic disease tend to cluster in the population. In a sample of people with 75 years or more, COPD clustered with coronary artery disease and thyroid dysfunction and, less strictly, with hypertension, congestive heart failure, atrial fibrillation and other cardiovascular diseases [6]. Studies based on the classic concept of comorbidity (usually performed in younger populations) have shown that compared with people without COPD, people with COPD have about a four-fold increase in risk for cardiovascular diseases, and increases in risk between 50% and 100% of having infective, psychiatric, renal, neurological, gastro-intestinal, and metabolic diseases [7]. Thus, COPD is almost invariably associated with other diseases, and three mechanisms most likely underpin this association. First, COPD is an age-related diseases, and as such tend to be associated with other age-related diseases. Second, COPD shares its most important risk factor – cigarette smoking – with several other diseases, in particular cardiovascular diseases. Third, COPD, or COPD treatment, may impact other

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systems or organs, as is the case of COPD-associated anemia or osteoporosis.

The exposure to cigarette smoking is an important risk factor for cardiovascular and cerebrovascular diseases as well as for female osteoporosis [8-10]. Furthermore, systemic inflammation and a prothrombotic state are highly prevalent in COPD and might promote atherosclerosis [11 12]. The rapid decline of physical capabilities and, then, daily physical activity secondary mainly to dyspnoea makes the COPD patient at risk of sarcopenia, osteoporosis and fractures besides having unfavourable metabolic and cardiovascular effects [13 14]. Further complicating the issue of comorbidity in COPD is the possibility that bronchodilating and topical anti-inflammatory therapy cause arrhythmas/myocardial hypertrophy and osteoporosis respectively [15 16].

It has been suggested that systemic inflammation may be the link between COPD and comorbidities [17]. However, two alternative theories about the origin of that inflammation have been produced: for many authors the lung is still the centre of the disease with some systemic "spill-over" of disruptive and reparatory inflammatory mediators, for some others the pulmonary manifestations are one expression of an originally systemic inflammatory state and must be considered within a multiple organ disease [18].

Some of typical comorbidities of COPD are of particular importance for the elderly and deserve special attention because they are relevant for disease management in these patients.

As previously stated, heart disease is frequently associated with COPD, mainly due to the effect of smoking of both the lungs and the heart. Indeed, the linear association between FEV1 and cardiovascular events is more evident in smokers compared with non-smokers [19]. The presence of cardiovascular disease has important prognostic implication, as cardiovascular events are the major cause of death in COPD patients [4], and ECG signs of ischemic heart disease or right ventricular hypertrophy or overload are significantly associated with mortality [20]. The coexistance of heart disease and COPD makes the interpretation of dyspnea difficult, as this symptom is the hallmark of both conditions. The BNP essay may be of help for the differential diagnosis, as even in people with pre-existing heart failure its concentration does not increase during COPD exacerbations [21]. However, many different conditions including renal failure, that is frequently associated with COPD, may cause an increase of BNP and reduce its diagnostic value [22].

Renal insufficiency is frequently associated with COPD. Once again, cigarette smoking seems to play an important role in this association, as it is associated with worsening renal function and faster course of glomerulopathies [23]. Heavy metals (especially lead, strontium and cadmium) and aromatic hydrocarbons contained in smoke can promote oxidative stress which damages the glomerulus and proximal tubule, and cause proteinuria and immuno-mediated glomerulonephritis [24 25]. Furthermore, nicotin may induce renal fibrosis [26] and contribute to mesangial proliferation and extracelluare matrix deposition [27 28]. The Extrapulmonary Consequences of COPD in the Elderly (ECCE) study showed that the prevalence of GFR < 60 ml/min/1.73 m^2 with or without increased serum creatinine was 43% in COPD patients over 64 years and 23.8% among non-COPD controls [29]. Other studies, however, have reported lower prevalence (9.6% in females and 5.1% in males) [30]. Differences in age and COPD severity of the study populations and in methods for diagnosing renal insufficiency are the most likely explanation of this discrepancy. It has been shown that the association between COPD and reduced GFR is especially evident in the emphysematous phenotype of COPD [31]. This is of particular importance because this phenotype is associated with loss of muscle mass, and therefore with reduced creatinine production. In this situation, the serum concentration of creatinine may be normal even in presence of reduced GFR, a condition referred to as "concealed" renal failure. In COPD patients, this condition is present in about 20% of patients, that is the same prevalence of overt renal insufficiency in the same population [29]. In other words, for each COPD patient with abnormal concentration of serum creatinine, there is another patient with normal serum creatinine but reduced GFR. The recognition of this condition is of particular importance, as many drugs used to treat COPD or COPD exacerbations (e.g., antibiotics) are cleared by the kidney and may need dose titration in presence of renal insufficiency.

Osteoporosis and fractures are associated with COPD, regardless of sex, and the risk for spine or hip fractures in these patients is increased by about tenfold [32]. A review based on 13 clinical studies [33] reported a prevalence of osteoporosis in COPD ranging from 9 to 69%, with difference mostly due to different definitions of osteoporosis. In this study, the major correlates of osteoporosis were forced expiratory volume in the first second (FEV1), fat-free mass, and body mass index (BMI). Beside the role of systemic corticosteroids, the relationship between COPD and osteoporosis may also be mediated by low physical activity, as it has been shown that the bone mineral density is directly correlated with daily physical activity and inversely correlated with the COPD Assessment Tool (CAT) score [34]. Since vertebral fractures may not only worsen quality of life of these patients, but also respiratory functions [35], a screening for osteoporosis using DeXA is probably warranted in all COPD patients. Furthermore, all patients

with COPD should be referred to a physical rehabilitation program, that is effective in reducing the risk of falls and fractures, improves quality of life and functional status. With respect to pharmacological prevention and treatment of COPD-associated osteoporosis, it has not been specifically studied, and the same strategy used for corticosteroid-induced osteoporosis is usually suggested: bisphosphonates and teriparatide as first-line, and denosumab as a second-line choice.

Hypoxemic COPD is an important cause of polyglobulia. Anemia, however, is a more frequent comorbidity of COPD. Its prevalence has been estimated to be about 13% in a population with a mean FEV1 of 37% [36], and even in a population with hypoxemic COPD it is still 12% [37]. Different mechanisms may explain such a high prevalence of anemia in COPD. Chronic inflammation causes increased concentration of IL-1 and TNF-alpha which, in turn, decrease the lifespan of red blood cells and induce resistance to erythropoietin [38]. Recently, the role of hepcidin in regulating iron metabolisms has come to light. It is a 25-amino acid peptide produced by the hepatocytes, and it is an inhibitor of iron absorption in the small intestine and iron release from macrophages [39]. it has been shown that its production is stimulated by inflammatory cytokines such as IL-6, but not by the aforementioned IL1 and TNF-alpha [40]. Hepcidin concentration was found to be increased in COPD patients with a mean age of 71 years compared to controls of the same age, and it has been hypothesized that systemic inflammation and elevated values of IL-6 present in exacerbations and stabile COPD might be responsible for the increased hepcidin level [41]. Interestingly, in a younger population (mean age 60 years) the serum concentration of hepcidin was found to be reduced in participants with moderate or severe COPD compared to controls [42]. Thus, age seems to play a role in the complex interplay between COPD, systemic inflammation, and anemia.

Malnutrition, defined as a BMI below 21 kg/m^2 or fat-free mass index below 15 kg/m^2 (in women) or 16 kg/m^2 (in men), affects about one out of four patients with moderate to severe COPD [43]. There are several mechanism that may explain this high prevalence of undernutrition. A decreased energy intake has been described in COPD patients due to dietary problems (including anorexia), and is associated with lower fat-free mass [44]. At the same time, COPD patients tend to have an increased resting energy expenditure, and this increase is associated with weight loss [45]. Beside this imbalance between energy intake and expenditure, an increased production of inflammatory cytokines and an altered secretion of adipokines such as leptin or adiponectin also play an important role in the development of malnutrition in COPD [46]. In front of this evidence, several attempts have been made to improve the health status of COPD patients using nutritional supplements. A Cochrane review has shown that use of nutritional supplements in malnourished COPD patients may increase weight and fat-free mass, and may improve functional capacity and quality of life [47].

Neuropsychological problems, mainly cognitive impairment and depression, are a common comorbidity of COPD. Estimates of prevalence of depression in COPD vary according to the screening instrument used, and range between 10% and 42% [48]. Patients with COPD have a 7-fold increase of having depression [49], and the presence of depression is associated with higher mortality and worse quality of life, as measured by the Saint George Respiratory Questionnaire [50]. Patients with coexisting COPD and depression are less likely to adhere to pulmonary rehabilitation treatments, this fact, however, should not discourage the referral of patients to this treatment. In fact, in patients with severe COPD it has been shown that rehabilitation can improve depressive symptoms independently of its effects on dyspnea and quality of life [51]. Cognitive impairment, as measured by the Mini-mental State Examination (MMSE), is 2.5 times more common in patients with COPD compared to non-COPD patients. Among the different measures of COPD severity, such as FEV1 reduction or BODE index, hypoxemia shows the strongest association (OR: 5.45) with cognitive impairment [52]. It must be noted that the association between COPD and cognitive impairment may be even stronger. In fact, it has been shown that the MMSE has a poor sensitivity (55%) in detecting cognitive impairment compared to a complete neuropsychological assessment [53]. This is probably due to the fact that hypoxemic COPD patients have a peculiar pattern of impaired cognitive functions compared to other forms of dementia common in the elderly, with prevalent involvment of verbal memory and other frontal functions that are not adequately explored by the MMSE [54]. Thus, the screening for cognitive impairment in these patients should also include a tool sensitive to abnormalities in frontal functions (e.g., executive function) such as the clock drawing test. Such a screening may also be useful for prognostic purposes, since the impairment in executive function is associated with increased mortality in hypoxemic COPD patients [55].

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