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EDITORIAL

FRAILTY, COMORBIDITY, AND COPD

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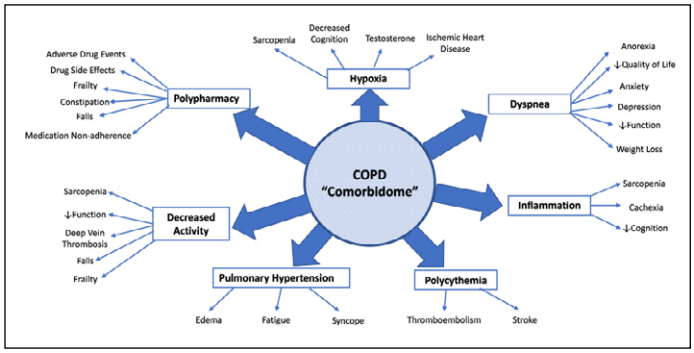
Chronic Obstructive Pulmonary Disease (COPD) is the third most common cause of mortality in the U.S.A. (1). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (2). COPD can directly lead to or accelerate co-morbidities through hypoxia, dyspnea, polycythemia, pulmonary hypertension, and decreased activity (Figure 1). Older age and decreased cognition may lead to incorrect inhaler techniques (3). Persons with COPD have an average of 7 co-morbidities compared to 3 for other persons (4). The existence of comorbidities is strongly related to COPD exacerbations and symptoms (5). The Body Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity (BODE) Index is a simple index predicting the risk of death in patients with COPD (6). Using the Frailty Index, a co-morbidity index of multiple morbidities, 56.6% of persons with COPD were found to be frail in the National Health and Nutrition Examination Survey (NHANES) (7). Not surprisingly, many of these persons had some functional disability. Patients with COPD are more likely to be frail than other patients (8). A meta-analysis found that patients with COPD were twice as likely to be frail (9).

Physical frailty has been defined as "a medical syndrome with multiple causes and contributor that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (10). It should be distinguished from disability. The concept of a physical frailty phenotype was originally described by Fried et al (11). Their criteria were unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity using the Fried criteria in persons with COPD, there was an increase in frailty with persons with a higher GOLD score (12). Table 1 provides the prevalence of the physical frailty phenotype in persons with COPD (12-17). In frail persons undergoing pulmonary rehabilitation 61.3% were no longer frail and had better exercise performance following pulmonary rehabilitation.

Figure 1
The COPD "Comorbidome"



FRAIL (fatigue, resistance, ambulation, illnesses and loss of weight) is a rapid screen for frailty that has been shown to identify persons at risk for functional deterioration,

Table 1
Prevalence of Physical Frailty Phenotype in COPD

Author	Year	n	Prevalence	Comments
Galizia et al (13)	2011	489	49%	Increased mortality
Singer et al (14)	2015	395	28%	Increased disability and mortality
Mittal et al (15)	2015	30	17%	Improved with pulmonary rehabilitation
Valenza et al (16)	2016	212	63%	-
Lahousse et al (17)	2016	402	5%	Increased mortality
Maddocks et al (12)	2016	816	26%	Increased mortality
Improved with pulmonary rehabilitation				

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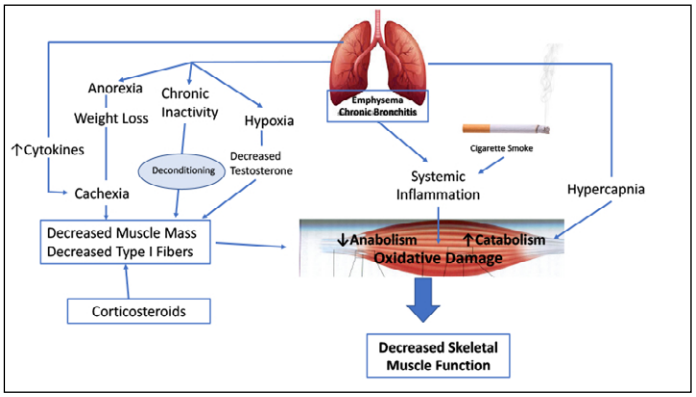
hospitalization and mortality (18-23). Limpawattana et al (24) found that using the FRAIL scale frailty was present in 6.6% and prefrailty 41.3% in persons with COPD. Fatigue was the most common component of the FRAIL scale present in persons with COPD. In persons with COPD who were assessed by the Edmonton Frail Scale, severely frail patients were more likely to be readmitted to hospital within 90 days than were nonfrail patients (25). Using the Kihon index to determine frailty in persons with COPD, frailty was found to be strongly related to patient reported outcomes but not to lung function measurements (26).

Figure 2
Mechanisms of Sarcopenia in Persons with COPD



Sarcopenia is defined as low physical function in persons with a low muscle mass (27-30). Jones et al (31) reported that sarcopenia was present in 15% of COPD patients. It was associated with less functional performance exercise capacity and health status. In the Rotterdam study, sarcopenia was present in 26.9% of COPD patients (32). Both of these studies utilized the European Working Group on Sarcopenia in Older People definition to make the diagnosis. Using the Asian Working Group for Sarcopenia definition, the prevalence for sarcopenia in COPD in Asia was 24% (33). In Brazil the prevalence of sarcopenia in COPD was 24% (34). Another study in Brazil using the Foundation of the National Institute of Health definition (FNIH) found a prevalence of sarcopenia in COPD was 12.4% (35). Patients with sarcopenia had a worse outcome. SARC-F is a rapid screen for sarcopenia which has been demonstrated to be valid and predict declining function and mortality (36-39).

There are numerous causes of sarcopenia, many of which are very common in COPD (40-42). These include weight loss (43), low testosterone (44), inflammation (45), all of which are more common in COPD than in the average patient. Hypercapnia leads to an increase in protein catabolism by activating E3-ubiquitin ligasis and atrogin-1 (46). Myostatin inhibits muscle growth (47). Myostatin levels are elevated in cor pulmonale secondary to COPD (7, 48). COPD is associated with systemic inflammation which leads to oxidative damage of muscle (49). Oxidative damage can lead to decreased function of titin (50). All these changes lead to a relative decrease in type I fibers compared to type II fibers (51). The mechanisms of sarcopenia in patients with COPD are illustrated in Figure 2.

Persons with COPD develop anorexia because they become dyspneic when eating due to hypoxia related to the thermic energy of eating (52-55). A Cochrane review by Ferreira IM et al. found that nutritional supplementation increases respiratory muscle strength, improves health related quality of life, and increase BMI and 6-minute walk distance in malnourished patients (56). Depression is also more common in COPD and it also leads to anorexia and weight loss (57-59). For these reasons all persons with COPD should be screened for anorexia using the Simplified Nutrition Appetite Questionnaire (SNAQ) (60-63). The inflammation associated with COPD further leads to muscle loss resulting in severe cachexia especially in persons with emphysema (64, 65).

The combination of comorbidities and geriatric syndromes requires an integrated disease management approach for COPD (66). Alvin L. Barach (67) and Thomas Petty (68) were the first to suggest that exercise was a key component of pulmonary rehabilitation. It has been shown that exercise together with protein supplementation is the most efficacious management for COPD (69-72). An exercise intervention prescribed in 58 frail older patients after hospital admission for acute COPD exacerbation in improved muscle strength, balance, and exacerbation (73, 74). For this reason, replacement with 1,000 IU of vitamin D daily may be reasonable in patients with COPD (73).

Palliative care is appropriate for persons with end-stage COPD (75). It is defined by the World Health Organization as "An approach that improves the quality of life of patients and their families facing the problems associated with life threatening illnesses." Table 2 provides appropriate criteria for being considered for palliative care. However, there is only a limited amount of evidence supporting the use of palliative care in COPD patients (76). There is need for a multicenter study to examine the role of palliative care in end-stage COPD patients.

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