Effects of aging and comorbidities on nutritional status and muscle dysfunction in patients with COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a prevalent, complex and debilitating disease which imposes a formidable burden on patients and the healthcare system. The recognition that COPD is a multifaceted disease is not new, and increasing evidence have outlined the importance of its extra-pulmonary manifestations and its relation to other comorbid conditions in the clinical course of the disease and its societal cost. The relationship between aging, COPD and its comorbidities on skeletal muscle function and nutritional status is complex, multidirectional and incompletely understood. Despite this, the current body of knowledge allows the identification of various, seemingly partially independent factors related both to the normal aging process and to the independent deleterious effects of chronic diseases on muscle function and body composition. There is a dire need of studies evaluating the relative contribution of each of these factors, and their potential synergistic effects in patients with COPD and advanced age/comorbid conditions, in order to delineate the best course of therapeutic action in this increasingly prevalent population.

Keywords: Aging; comorbidities; nutritional status; muscle dysfunction; chronic obstructive pulmonary disease (COPD)

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent, complex and debilitating disease which imposes a formidable burden on patients and the healthcare system (1). The recognition that COPD is a multifaceted disease is not new, and increasing evidence have outlined the importance of its extra-pulmonary manifestations and its relation to other comorbid conditions in the clinical course of the disease and its societal cost (2). In particular, the association between COPD and skeletal muscle dysfunction/ nutritional status anomalies has long been recognized, and the deleterious synergistic effects of their co-occurrence on clinical prognosis have been well established (3-10) (*Figure 1*). However, the fact that COPD is frequently associated with other conditions that also alter muscle function and nutritional status such as older age and chronic comorbid diseases intensify the need for a better understanding of the individual pathophysiological processes at play and their inter-relationships, in order to
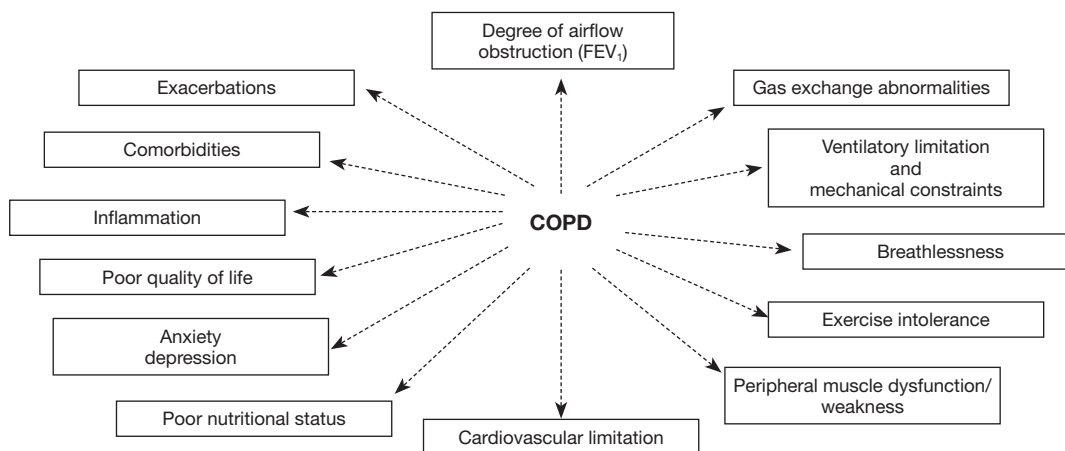
S1356

Dubé and Laveneziana. Nutritional status and muscle dysfunction in COPD

Figure 1 The different levels of impairment in chronic obstructive pulmonary disease (COPD). All these factors are keynote features in COPD and play an important role in disease progression and prognosis. FEV_1, forced expiratory volume in 1 second. From reference (11) with permission.

provide better clinical care (*Figure 1*). It is now evident that aging and comorbidities such as chronic heart failure (CHF) and chronic kidney disease (CKD), along with cigarette smoke, systemic inflammation, exercise, exacerbations, anabolic insufficiency and drugs play a relevant role in contributing to nutritional status and muscle dysfunction in patients with COPD (*Figure 2*). All the above factors modify the nutritional status and the phenotype of the muscles, through the induction of several biological phenomena in patients with COPD (*Figure 2*).

It has been 7 years since a research seminar have been totally devoted to this topic (11); since then, numerous researches have been undertaken to try to elucidate the effects of aging and comorbidities on nutritional status and muscle dysfunction in patients with COPD.

This review proposes to examine the current knowledge pertaining to the alterations in skeletal muscle function and nutritional status induced by COPD itself, and to compare them to those observed in physiological aging and in frequent chronic diseases associated with COPD, in order to delineate the independent and possibly additive contributions of each condition to the overall status of these patients.

Aging and skeletal muscular function/nutritional status in patients with COPD

In this section, we will focus on the effects of the aging process on skeletal muscle function and morphology and on the nutritional status, with a particular emphasis on the recent data supporting the consideration of COPD as a

disease of accelerated aging.

Physiological consequences of the aging process on skeletal muscles

Sarcopenia (loss of muscle mass associated with a decline in function) is common in the elderly (12) and is characteristic of the physiological aging process (13,14). Changes in muscle morphology are therefore frequently observed with increasing age and relate to changes in muscle fibre composition, size and number (15,16). Numerous studies have investigated the changes in muscle fibre distribution in the skeletal muscles of elderly subjects, with sometimes contradicting results: an increase in the proportion of type 1 (slow-twitch) muscle fibres has frequently been described (17-21), although others report a relative stability (22-29), or even a decrease (30) in the proportion of type I fibres. These differing descriptions are possibly related to intrinsic differences in the studied populations and the influence of important factors such as nutritional status, physical activity levels, comorbidities and biopsied muscle. Skeletal muscle fibre atrophy is also a hallmark of the physiological aging process and mainly seems to affect type II (fast-twitch) fibres (18-20,22-25,31). Alterations in muscle metabolism are also prevalent, with a decrease in the activity of oxidative and glycolytic enzymes being frequently observed with advancing age (19,29,31). Together, these changes will translate into a progressive loss of muscle strength in elderly subjects (32). This phenomenon has important clinical consequences as muscle weakness is a hallmark feature of
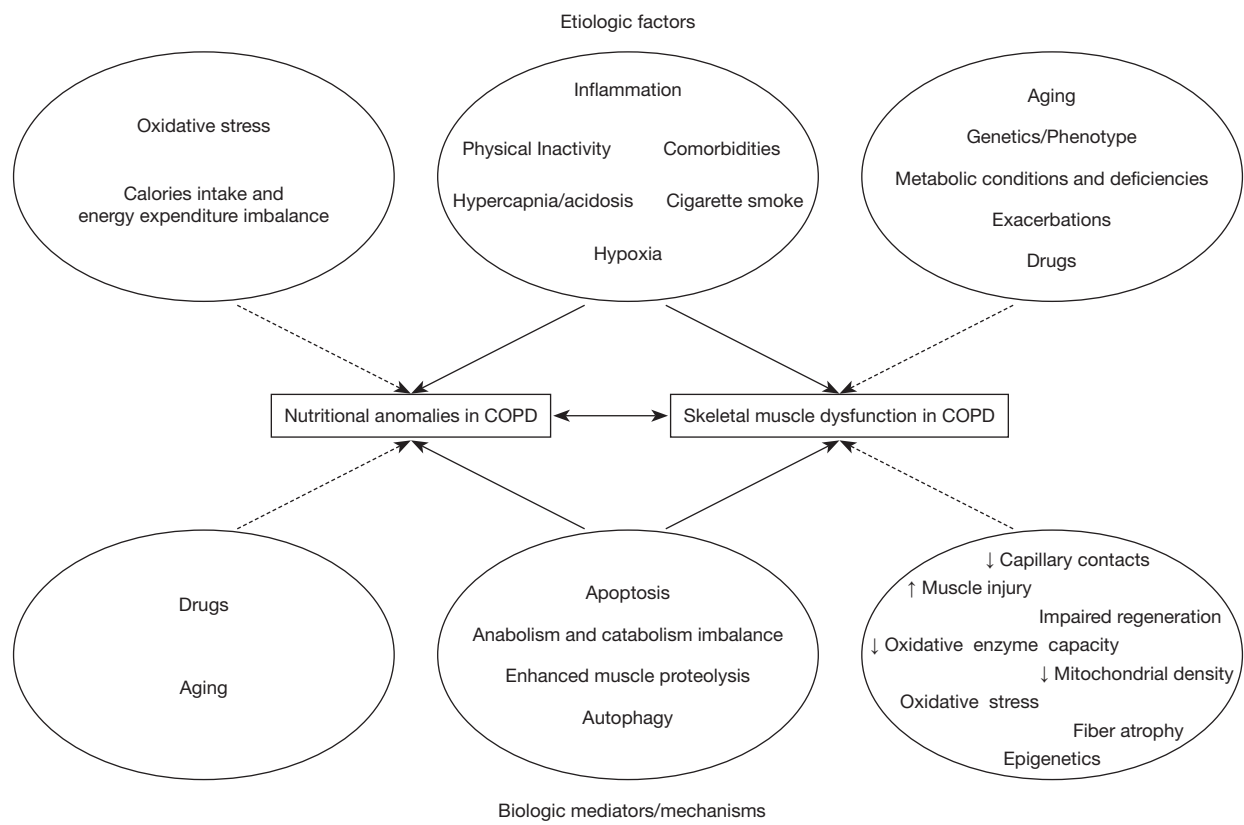
Figure 2 A schematic representation of the potential relationships, similarities, and differences regarding etiologic factors (upper panel) and biological mediators/mechanisms (lower panel) involved in skeletal muscle dysfunction and nutritional anomalies in COPD. Dotted line—etiologic factors and/or biological mediators/mechanisms concerning only skeletal muscle dysfunction; solid line—etiologic factors and/or biological mediators/mechanisms concerning both nutritional anomalies and skeletal muscle dysfunction; discontinued line—etiologic factors and/or biological mediators/mechanisms concerning only nutritional anomalies.

the presence of frailty in the elderly, which is a state of decreased functional reserve strongly associated with the risk of disability and overall prognosis (12,33).

Aging and nutritional status

Undernutrition is frequent in elderly subjects, independently associated with age (34) and frequently under-diagnosed (35). Physiological anorexia, smoking, the presence of comorbid medical conditions (including COPD), alterations in smell and taste and changes in physical activity with decreased energy requirements are factors that potentially impact nutriment intake in elderly subjects (34,36-40). Importantly, the presence of malnutrition is associated with changes in body composition and the presence of sarcopenia (36), and is directly associated with prognosis in elderly patients

(34,35,41,42). As such, malnutrition can be seen as a component of the frailty syndrome (43), with several studies demonstrating that the quality of dietary intake is related to the risk of frailty (44-46).

Alterations in skeletal muscle function and nutritional status in COPD and comparison to physiological aging

Sarcopenia is one of the most recognized extra-pulmonary manifestations of COPD and has been extensively studied (47-53). Although a thorough description of the mechanisms underlying its presence in COPD patients is outside the scope of this text, we need to highlight the main characteristics of skeletal muscle changes associated with COPD in order to contrast them to the aforementioned changes induced by the aging process. Skeletal muscle fiber redistribution in COPD has been well demonstrated, with

S1358

Dubé and Laveneziana. Nutritional status and muscle dysfunction in COPD

a consistent and prominent increase in the proportion of type II fibers relative to type I fibers (54-59), associated with an atrophy of the muscle fibers (54) and alterations in enzymatic metabolism activity characterized by increased glycolytic activity, decreased aerobic metabolism (55,60-62) and an impairment in oxidative metabolism that is predominantly observable during and after exercise (63-65). These anomalies will clinically translate into a loss of muscle mass, strength and endurance in patients with COPD, especially in the lower limbs (66), with a significant negative impact on functional capacity, exercise tolerance and overall prognosis (3,4,67-75).

Nutritional depletion and cachexia are also frequently associated with COPD (9,76-79) and are thought to be related to a complex combination of factors that include, among others, the presence of persistent systemic inflammation (80-82), hypoxemia (83) and an increase in resting energy expenditure that is possibly related to increased respiratory work of breathing (82,84). In addition, hormonal derangements such as the decrease in leptin levels observed in patients with COPD may contribute to body wasting (85). Nutritional status and body composition (especially when evaluated using fat-free mass) in patients with COPD are related to the presence of skeletal dysfunction and sarcopenia (79), and, more importantly, to overall prognosis (7-10,86).

The prevalence of COPD increases with age (87), and as such the relative effects of both conditions on skeletal muscles and nutritional status are complex and difficult to untangle. However, the available evidence described above suggests that the relative contribution of aging and COPD to skeletal muscle dysfunction and nutritional depletion are somewhat different in nature, with aging mainly associated with a reduction of fast-twitch muscle fiber proportion and a decrease in nutriment intake related to physiological alterations in energy requirements and anorexia, while COPD is associated with a decrease in slow-twitch muscle fibers and nutritional depletion more closely related to persistent systemic inflammation and increased metabolic requirements. From a clinical point of view, this notion is supported by a large study of elderly COPD patients, in which age and COPD were respectively independently correlated with different aspects of the nutritional status, with age being related to body functionality score, while COPD was associated with body composition status (88). These findings highlight the potential negative synergistic effects of advanced age and COPD on functional capacity and prognosis and the need for an increase in clinical awareness regarding the co-occurrence of these factors.

COPD as a syndrome of accelerated lung aging

The cellular equivalent of aging is senescence, in which cells permanently cease to divide in response to various stimuli (89). The onset of physiological cellular senescence is triggered by the shortening of telomeres, which are repeated sequences of nucleotides (TTAGGG) located at the end of each chromosomes that act as buffers that protect DNA from deterioration during the replicative cycle. Premature senescence can be triggered by other stimuli such as DNA damage, oxidative stress and expression of oncogenes (90,91). The active replenishment of telomeres can be accomplished by telomerase, but this polymerase is absent from somatic cells, leading to a progressive shortening of telomeres with each cell division (92). When a critical length of telomeres is reached, a senescence signal is sent to the cell. The observation that the number of senescent cells increases with age suggests a link between cellular senescence and the physiological aging process (89,93). Increasing evidence support a relationship between the impaired tissue repairing ability induced by cellular senescence and the development of emphysema: an accumulation of senescent cells in the lung of COPD patients compared with smokers without COPD has been demonstrated in humans (94,95), subjects with COPD show shorter telomeres than age-matched controls (96), telomerase deficiency predisposes to COPD (94) and surexpression of anti-aging proteins such as sirtuin 1 protects against cellular senescence and emphysema (97).

Importantly, senescent cells are not metabolically inactive and, on the contrary, generate an inflammatory reaction characterised by the production of pro-inflammatory mediators (interleukine 1, 6, 8, CCL2, TGF-beta and MMPs) (94,98,99) that propagate a persistent inflammatory state. This senescence-associated secretory phenotype (SASP) can induce senescence in adjacent cells (99,100) and could even, if "spilled-over" to the systemic circulation, play a role in the development of the systemic manifestations of COPD. As discussed in the previous section, some evidence suggests a relationship between the presence of skeletal muscle dysfunction and/or nutritional deficiency in COPD and the presence of a systemic, persistent low-grade inflammatory state (80-82,84,85,101-105). Whether the SASP plays a direct role in the mediation of the relationship between the lung disease and the extra-pulmonary manifestations of COPD remains speculative in nature, but

provides a novel target for future research.

Comorbidities and skeletal muscular function/ nutritional status in patients with COPD

Patients with COPD often present with comorbid conditions, the most frequent of which include cardiovascular diseases, cerebrovascular diseases, anxio-depressive disorders, osteoporosis, cachexia/muscle weakness, lung cancer, CKD (106-110) and several others less frequently considered (111). In a cross-sectional analysis of a large sample of subjects, patients with COPD had a mean of 3.7 comorbidities (including lung disease), compared with 1.8 in age- and sex-matched controls (112). This difference was associated with a two-fold increase in healthcare utilization in patients with COPD in the same study (112). Furthermore, the presence of comorbidities potentiates the negative effects of COPD on functional capacity, quality of life and overall prognosis (3,4,71,74,113).

Among the frequent comorbidities encountered in patients with COPD, some have also been associated with disorders of skeletal muscle function and nutritional status. In particular, CHF and CKD have both been independently associated with anomalies in body composition, nutritional status and skeletal muscle function and composition. The following section will review the main impacts of CHF and CKD on muscle function and nutritional state in order to contrast and compare them with those of COPD.

CHF and skeletal muscle dysfunction

Loss of peripheral muscle strength and endurance is more frequent in patients with CHF than in age-matched controls (74,114,115), and, as in COPD, seems to preferentially affect the lower limb musculature (116). Biopsy studies of the lower limbs muscles in this population have shown that muscle fibre atrophy is frequent and is directed mostly at type II (fast-twitch) fibres (117,118), although a decrease in type 1 cross-sectional area has also been reported (114). Most available data also support the presence of a type I to type II muscle fibre shift redistribution (118-123), as seen in COPD. From a metabolic perspective, subjects with CHF display reduced levels of fatty acid and carbohydrate enzymatic metabolism, while showing increased levels of anaerobic activity (115,117,118,120,124).

Vescovo et al. investigated the relative contribution of deconditioning to the skeletal muscles anomalies observed in CHF by comparing muscle biopsies from patients with CHF to bedridden patients and healthy controls. Muscle atrophy levels were greater in bedridden patients than CHF subjects, but the proportion of types 1 and 2 myosine heavy chains were respectively decreased and increased in CHF, while the opposite was observed in subjects with disuse atrophy. Other have similarly described differences in the skeletal metabolic enzymatic activity patterns of patients with CHF compared with age- and VO_2-matched controls, but these effects were only apparent in men (125). These results suggest that disuse alone cannot account for the myopathy observed in CHF, although further studies directly comparing detrained subjects and patients with CHF are required to further understand this relationship, especially given the fact that the control group in the study by Vescovo et al. (patients that had been bedridden for 1 year) may not be representative of the patients with deconditioning encountered in routine clinical practice.

CHF and nutritional status

Weight loss and cachexia are frequent in patients with CHF (126,127) and are likely the result of a combination of neuroendocrine and metabolic factors that induce inadequate dietary intake, excessive nutriment losses or alterations in metabolism (128-130). Pharmacological therapy such as diuretics, digoxin and angiotensin-converting enzyme inhibitors may cause anorexia (128) in these patients, and while intestinal edema inducing satiety and/or a protein-losing gastroenteropathy has often been suggested as a possible cause of anorexia in CHF, clear data supporting this hypothesis are lacking (131,132). In addition, although a certain contribution of anorexia and/or starvation to cardiac cachexia remain possible, the anomalies in body composition in CHF are not compatible with simple starvation, in which weight loss occurs at the expense of fat tissue, in contrast to what is observed in CHF patients (133), where tissue loss is apparent in muscles, fatty tissue and bones.

As in COPD, CHF can be conceptualized as a syndrome of persistent immune activation inducing a state of low-grade systemic inflammation and a preferential shift towards catabolic metabolism induced by increased levels of inflammatory cytokines (128,133,134). In addition, chronic impaired cardiac function is associated with neurohormonal changes that include, among others, an activation of the sympathetic nervous system. In a study comparing the systemic levels of inflammatory and neurohormonal mediators in CHF patients with or without cachexia, plasma levels of norepinephrine, epinephrine, TNF-alpha

S1360

Dubé and Laveneziana. Nutritional status and muscle dysfunction in COPD

and cortisol were higher in in the cachectic group, despite similar baseline values of left ventricular ejection fraction and functional class (133). These results highlight the potential role of systemic inflammation and neurohormonal activation in the development in cachexia in patients with CHF, although further studies are required to elucidate the precise mechanisms and directionality of this relationship.

CKD and skeletal muscle dysfunction

CKD is relatively frequent in patients with COPD and may be underrecognized (109,135). Although less studied than in COPD and CHF, anomalies in the skeletal muscles of patients with CKD have also been described, with skeletal muscle weakness being relatively frequently reported, especially in the lower limbs (136-141). Muscle fibre atrophy of the lower limb muscles has also frequently been reported, and preferentially affects type II (rapid-twitch) fibres (137,139,142,143). Studies evaluating muscle metabolic enzymatic activity levels in patients with CKD have been more scarce, but alterations in oxidative and anaerobic metabolism have been reported in these patients in some (140,144,145), but not all, studies (146).

CKD and nutritional status

The catabolic/anabolic balance is disturbed in CKD, especially when end-stage renal failure is present, and its mechanisms are complex and incompletely understood. Among other factors, the metabolic acidosis that is often present in CKD may play an important role in the development of body wasting by promoting protein degradation, especially at the muscle level (147-152). In fact, even small corrections of metabolic acidosis in patients with CKD improve nutritional status and muscle mass, even without nutritional supplementation (153,154).

Acidosis is thought be at the root, and to act synergistically, with others factors promoting protein catabolism (155) or anti-anabolism such as an increase in circulating glucocorticoid levels, insulin resistance, anomalies in growth hormone and leptin serum levels and increased circulating levels of inflammatory cytokines creating a chronic pro-inflammatory state (148,156-159).

Comparison of muscle dysfunction and nutritional status in patients with COPD, CHF and CKD

As reviewed, the alterations observed in the skeletal muscle

of patients with CHF and CKD are very similar to those observed in COPD with, broadly speaking, a switch to a fast-twitch fibre phenotype, loss of oxidative capacity, muscle fibre atrophy and loss of strength/endurance. Although some factors contributing to the eventual reaching of this state seem to be overlapping between these conditions (especially the presence of a persistent systemic inflammatory state and anomalies in nutritional status), the initial causative mechanisms for them vary across diagnoses, suggesting that, in practice, they may act synergistically and additively. To our knowledge, however, very few studies have focussed on the relative contribution of COPD and its comorbidities on skeletal muscle function and nutritional status. Hamilton *et al.* compared skeletal muscle function in a large group of patients according to the presence of cardiac and/or respiratory disease, and showed that patients with concomitant cardiac and respiratory diseases had lower respiratory and lower limb muscle strength than patients with cardiac disease alone, suggesting an additive deleterious effect of respiratory disease in muscle performance in patients with cardiac diseases (74). These results should be interpreted in light of the fact that a certain proportion of patients were classified in the "respiratory impairment" subgroup based on the presence of low forced expiratory volume in 1 second (FEV_1) despite normal FEV_1/vital capacity ratio, making the true prevalence of COPD in this subgroup unknown.

In a study that investigated the predictive factors of CKD in patients with COPD, the presence of muscle-skeletal disease and hypoalbuminemia was an independent risk factor for the presence of "concealed" CKD (odds ratio 2.73 and 2.98, respectively), suggesting an additive effect of the presence of both COPD and CKD on the prevalence of these anomalies.

Conclusions

The relationship between aging, COPD and its comorbidities on skeletal muscle function and nutritional status is complex, multidirectional and incompletely understood. Despite this, the current body of knowledge allows the identification of various, seemingly partially independent factors related both to the normal aging process and to the independent deleterious effects of chronic diseases on muscle function and body composition. There is a dire need of studies evaluating the relative contribution of each of these factors, and their potential synergistic effects in patients with COPD and advanced

age/comorbid conditions, in order to delineate the best course of therapeutic action in this increasingly prevalent population.

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Footnote

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S1364

Dubé and Laveneziana. Nutritional status and muscle dysfunction in COPD

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S1366

Dubé and Laveneziana. Nutritional status and muscle dysfunction in COPD

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