CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is a highly prevalent condition that is projected to be the third leading cause of death worldwide in 2020. COPD imposes a significant economic burden in different countries as a consequence of acute exacerbations and comorbidities. In patients with COPD, skeletal muscle dysfunction is a common systemic manifestation that affects both respiratory and limb muscles and has a significant impact on exercise tolerance and quality of life (8). As a matter of fact, quadriceps muscle dysfunction, mainly characterized by reduced muscle force, is observed in one-third of all patients with COPD, even at very early stages of their disease (17). In addition, quadriceps weakness and reduced muscle mass are reliable predictors of COPD mortality (13, 18).

Although it has been well characterized that COPD muscle dysfunction is the result of the complex interaction between systemic and local factors, the etiology of muscle dysfunction remains to be fully identified. Interestingly, although hyperinflation and an increased work of breathing appear to be the main contributing events to respiratory muscle dysfunction, deconditioning seems to play a major role in the dysfunction of peripheral muscles in COPD. Other factors such as cigarette smoke, nutritional abnormalities, exacerbations, drugs, hypoxia, hypercapnia, comorbidities, and physical activity also influence muscle mass and function in patients with COPD (1–3, 5, 11, 18). In addition, derangements of key molecular and cellular processes such as redox imbalance, mitochondrial dysfunction, enhanced protein catabolism and reduced protein anabolism, structural alterations, and systemic inflammation also modify muscle phenotype and function in patients with COPD.

In the current Highlighted Topic on “Muscle Dysfunction in COPD,” renowned investigators in the field explore the most relevant mechanisms that participate in the pathophysiology of skeletal muscle dysfunction of patients with COPD. These authors from around the world review and assess the most up-to-date literature on specific topics such as motor control abnormalities (12), remodeling (10), cachexia (15), epigenetics (4), autophagy (9), and metabolic alterations including mitochondrial dysfunction (14) taking place in both respiratory and limb muscles of patients with COPD. Furthermore, the influence of exacerbations (6) and exercise training (16) on muscle mass maintenance and performance has also been described in two additional mini-reviews of this highlighted topic. A brief summary of the different aspects addressed in each of the mini-reviews is provided below.

In the first review of this series, Gea et al. (7) provide a general overview of the main molecular and cellular alterations encountered within the muscle fibers of patients with COPD and how these changes may account for the muscle contractile dysfunction and mass loss observed in COPD.

Mantilla and Sieck (12) examine to what extent alterations in different motor unit (muscle fiber) types contribute to muscle dysfunction in COPD. Moreover, they examine the potential factors and mechanisms that may impair the neuromotor control of respiratory and limb muscles and how these alterations impair muscle performance in patients with COPD.

Levine et al. (10) explore the mechanisms thought to mediate the differential remodeling features observed in the diaphragm and vastus lateralis muscles of patients with COPD. Additionally, the pathophysiology of muscle remodeling is reviewed.

Remels et al. (15) analyze the pathophysiological mechanisms involved in muscle wasting and weakness in patients with COPD. Oxidative stress, systemic inflammation, and myostatin seem to be potent inducers of muscle mass loss and wasting in COPD.

Barreiro et al. (4) review the potential implications of epigenetic mechanisms in the regulation of muscle mass maintenance and differentiation in muscles of patients with COPD. In addition, they provide an extensive review of the specific actions and processes by which epigenetic mechanisms control embryonic myogenesis, muscle proliferation, and differentiation.

Hussain et al. (9) assess recent progress involving the molecular structure and function of the autophagy-lysosome pathway within skeletal muscles in health and disease. Autophagy seems to be crucial in the regulation of muscle mass maintenance and performance. Preliminary results point toward an induction of the autophagy-lysosome pathway in peripheral muscles of patients with COPD.

Puente-Maestu et al. (14) evaluate the potential implications of mitochondrial dysfunction in both respiratory and limb muscles of patients with COPD. Mitochondrial alterations in muscles of these patients are mainly characterized by a reduction in oxidative capacity and enhanced production of reactive oxidants. Moreover, the characteristic phenotype observed in the vastus lateralis of patients with severe COPD, which renders the muscle less fatigue resistant, seems to correlate with a decrease in the number of mitochondria but an increased production of reactive oxidants within the mitochondria.
Gayan-Ramirez et al. (6) describe the pathophysiological mechanisms leading to enhanced catabolism in muscles of patients with COPD during exacerbations. The relevance of these exacerbations lies in the fact that they increase the prevalence and severity of skeletal muscle dysfunction in patients with COPD. Therefore, exacerbations have a major impact on the quality of life of these patients. The authors argue that early measures should be taken (e.g., pulmonary rehabilitation) to prevent the deleterious effects on muscle biology and function during the course of exacerbations in patients with COPD.

Ribeiro et al. (16) examine the different strategies and indications of pulmonary rehabilitation, including exercise training in patients with COPD. Furthermore, the specific beneficial effects in terms of muscle biology and physiology are also explored in their mini-review. Finally, these authors evaluate whether exercise training could have deleterious consequences in certain phenotypes of patients with COPD and/or clinical settings.

In conclusion, we hope that the mini-reviews contained in the present highlighted topic encourage research in this specific arena with the aim of enhancing current knowledge on the pathophysiology of COPD muscle dysfunction. The ultimate goal should be to better treat and cure our patients by means of novel therapeutic strategies targeted to specific key physiological and cellular processes taking place in the muscles of such patients.

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AUTHOR CONTRIBUTIONS

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