Review Article

Nutritional status and muscle dysfunction in chronic respiratory diseases: stable phase versus acute exacerbations

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Abstract: Nutritional abnormalities are frequent in different chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), interstitial fibrosis and lung cancer, having important clinical consequences. However, nutritional abnormalities often remained underdiagnosed due to the relative lack of awareness of health professionals. Therefore, systematic anthropometry or even better, assessment of body composition, should be performed in all patients with chronic respiratory conditions, especially following exacerbation periods when malnutrition becomes more accentuated. Nutritional abnormalities very often include the loss of muscle mass, which is an important factor for the occurrence of muscle dysfunction. The latter can be easily detected with the specific assessment of muscle strength and endurance, and also negatively influences patients' quality of life and prognosis. Both nutritional abnormalities and muscle dysfunction result from the interaction of several factors, including tobacco smoking, low physical activity-sedentarism, systemic inflammation and the imbalance between energy supply and requirements, which essentially lead to a negative balance between protein breakdown and synthesis. Therapeutic approaches include improvements in lifestyle, nutritional supplementation and training. Anabolic drugs may be administered in some cases.

Keywords: Nutritional abnormalities; low body weight; muscle mass; muscle dysfunction; diet; exercise; prognosis; lung diseases

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Introduction

Many different and prevalent chronic respiratory disorders, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), non-CF bronchiectasis, idiopathic pulmonary fibrosis (IPF) and lung cancer, not only target the lungs but are often associated with systemic manifestations (1-5). The latter can be magnified by the concomitant presence of aging, comorbidities or unhealthy lifestyle habits. Nutritional abnormalities stand out amongst the systemic manifestations present in chronic respiratory conditions. When these nutritional abnormalities become very severe, with marked weight and muscle mass loss, they constitute a complex metabolic syndrome, known as cachexia. However, it should be kept in mind that the earliest stages of nutritional abnormalities do not necessarily involve evident body weight loss. Diagnosis and stratification of patients with impaired nutritional status is important to decide the appropriate therapeutic approach. In fact, it has been clearly demonstrated that therapeutic interventions, even with only moderate increases in body weight or lean mass, can improve the prognosis of respiratory patients with nutritional abnormalities (6). Therefore, medical professionals should be able to detect these deficiencies early.

Although the clinical impact of nutritional abnormalities

has been extensively studied in COPD, similar deleterious effects have also been reported in other chronic respiratory diseases. In the particular case of COPD, impairment in nutritional status has been associated with poor prognosis, deterioration of the quality of life, a higher exacerbation rate and an increased mortality (6,7). Similar negative impact has also been described in other respiratory conditions (3,8), which in addition can be associated with COPD in specific mixed phenotypes (COPD-bronchiectasis, -fibrosis, -asthma) (1).

One of the most important clinical consequences of nutritional deficiencies in patients with chronic respiratory disorders is the loss of muscle mass and functional impairment (2,4,9). However, nutritional deficiencies not only affect muscle mass and function, but can also have a negative impact on bone and fat tissues, reaching a state of severe cachexia in the more advanced situations. Moreover, malnutrition also targets patient's immunocompetence, facilitating infections and exacerbations, which reciprocally will contribute to worsen nutritional status.

Muscle dysfunction is defined by the loss of strength (i.e., the ability to develop a maximal effort) and/or endurance (i.e., the ability to maintain a submaximal effort through time) (10,11). This functional impairment can be relatively stable (this is known as 'muscle weakness') or temporary (denominated 'fatigue', which is reversible with rest) (10,11). Muscle dysfunction can involve peripheral (limb) as well as respiratory muscles, and can appear in acute or chronic respiratory diseases due to different causes. However, the loss of muscle mass is probably the main one, at least for limb muscles, having deleterious consequences on patients' prognosis (12,13). The term 'loss of muscle mass' is generally used to express a decrease in global muscle proportion or weight, but at a cellular level it actually indicates the loss of fibers or more frequently, a reduction in their size. The loss of muscle mass is mainly because of a decrease in muscle contractile protein content through different mechanisms, including the activation of the ubiquitin-proteasome system, autophagy and apoptosis (14). Global muscle mass and fiber size are the main factors contributing to muscle strength, although other components such as fiber type proportions and muscle length also play a relevant role (12). Therefore, a loss in either muscle mass or fiber atrophy will involve a decrease in contractile strength. On the other hand, endurance depends mostly on the muscle aerobic capacity, which in turn is a subrogate of the percentage of fibers with a predominant aerobic metabolism ('slow-twitch' fibers), capillary and mitochondrial density, and the capacity of oxidative enzymes on metabolic pathways (12).

The presence of limb muscle dysfunction can even limit normal walking, leading to a reduction of patient daily activities and social life, with a strong negative impact on prognosis, quality of life, and utilization of social and health resources (3,7,8,15-18). Respiratory muscle dysfunction in turn is associated with increased dyspnea (10,11,19), a worse ventilatory response to both exercise and exacerbations (19-21), and can even lead to severe respiratory failure, as well as weaning difficulties in patients submitted to mechanical ventilation (22,23).

Etiology

The loss of body weight, as well as that of muscle mass and function is the result of the interaction of different etiological factors, which interestingly have different relative weights for each particular patient. These factors include toxic and lifestyle habits, as well as metabolic and hormonal imbalances (*Figure 1*).

Smoking and alcohol abuse

Tobacco has a clear anorectic effect and can induce nutritional abnormalities and muscle dysfunction by different mechanisms, which include systemic inflammation, release of leptin, induction of an imbalance between protein synthesis/breakdown, and the blockade of neuromuscular transmission (24-28). As a consequence of all these phenomena, smokers show early fatigability and reduced muscle resistance (25,29,30). Enolism, frequently associated with smoking (31), can also induce loss of body weight and lean mass as well as a specific myopathy (32,33).

Sedentarism and low level of physical activity

This factor is very common in chronic respiratory diseases due mainly to ventilatory limitation, muscle dysfunction due to other factors and reactive depression, as well as Western lifestyle (34-36). It contributes to the presence of nutritional abnormalities and muscle dysfunction (especially of the lower limbs) and also results in cardiovascular deconditioning, having a negative impact on exacerbations and mortality (36-38). The main molecular mechanisms explaining some of the negative effects of reduced activity are an increase in the level of systemic inflammation and a decrease in muscle protein synthesis (39).

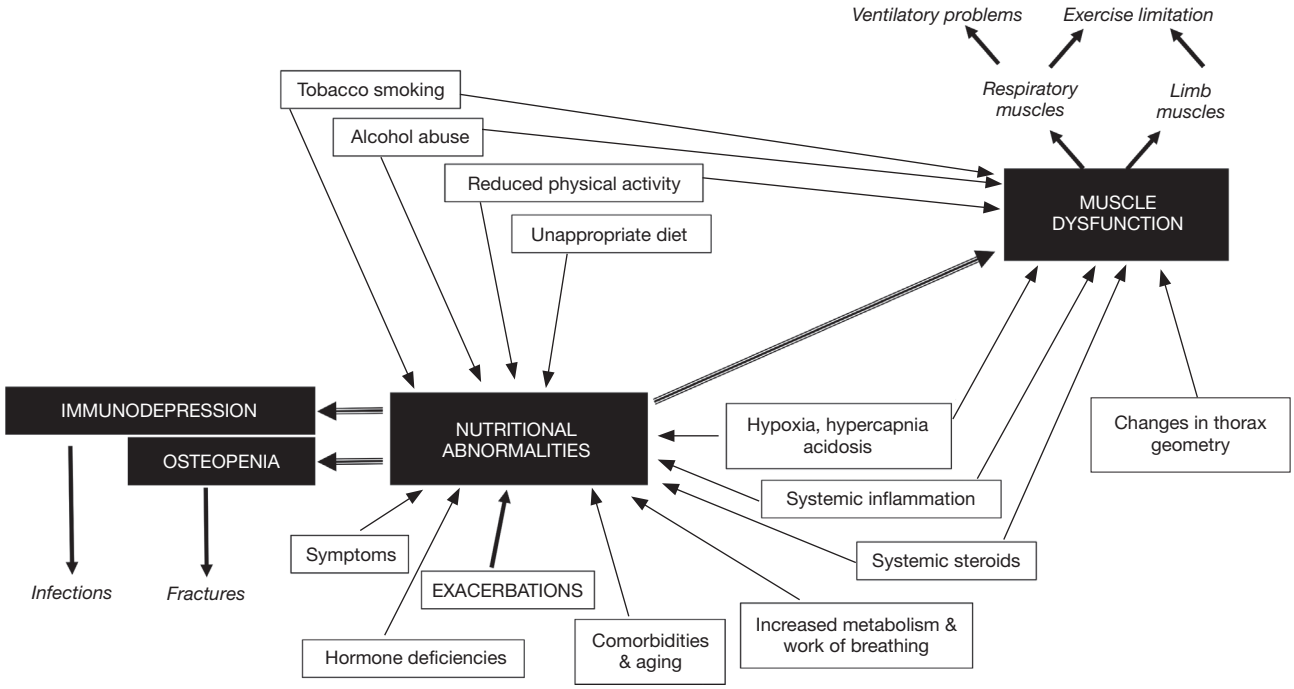

Figure 1 Different factors that contribute to nutritional abnormalities and/or muscle dysfunction. Note the relevant role of exacerbations, when many of the factors involved in nutritional abnormalities increase their influence. The most relevant clinical consequences of nutritional abnormalities and muscle dysfunction are also shown.

Inappropriate diet, anorexia and malabsorption

The caloric intake of patients with chronic respiratory disorders is often inadequate, not matching their energy requirements. More specifically, it has been shown that they consume less carbohydrates, proteins, different vitamins and omega 3 fatty acids than healthy subjects (40,41). In addition, those patients with CF also add malabsorption due to the associated impairment in exocrine pancreatic function (42). A relevant symptom that frequently appears in chronic respiratory diseases is anorexia (43-45), defined as a reduction or loss of appetite. This symptom can be related to the lung disease itself but also to the treatment and/or the accompanying emotional distress, and can worsen nutritional abnormalities. The biological mechanisms of anorexia are not fully understood but recent evidence suggests a major role for neurohormonal and inflammatory cytokine systems (46-48). Closely related to the reduction in caloric intake is the coexisting imbalance with energy expenditure. A hypermetabolic status occurs in many patients with chronic respiratory conditions as a result of different metabolic disarrangements and increases in the work of breathing (49-52). All these elements result in a negative nutritional and energy balance that would also lead to a loss of muscle mass and muscle dysfunction.

Systemic inflammation

It is well known that many inflammatory mediators are capable of inducing anorexia and an increase in the degradation of intracellular proteins either through the direct activation of proteolytic pathways or development of oxidative stress (53,54). A relative low level of systemic inflammation has been demonstrated in blood and other extrapulmonary tissues in different chronic respiratory diseases, such as COPD, IPF or bronchiectasis, even in periods of clinical stabilization (55-59). Although it is probable that the initial inflammatory process taking place in the lung becomes disseminated through systemic circulation reaching other organs ('spill over' theory), in non-CF bronchiectasis and IPF (55,60), systemic inflammation can also be the result of the direct action of the same etiological factors involved in lung disease. This is probably the case in COPD (26,61) and CF (62). Certainly, both mechanisms can coexist in many cases, as it can reasonably be assumed for lung cancer (63). In either

case, the resulting systemic inflammation seems to be a significant contributor to nutritional abnormalities and muscle dysfunction occurring in some chronic respiratory disorders (e.g., COPD or bronchiectasis) (2,9,12), and may be a cofactor in others (e.g., IPF).

Systemic oxidative stress

Oxidative stress is directly linked with systemic inflammation. Reactive oxygen species (ROS) and nitric oxide (NO) are normally present in different tissues including skeletal muscles, playing different physiological roles. However, when there is an increase in oxygen or nitrogen reactants and/or the antioxidants are unable to counterbalance their effects, oxidative and/or nitrosative stress may occur. These phenomena lead to structural and functional abnormalities (64,65). In this regard, free radical stress is believed to be involved in the pathogenesis of different chronic lung diseases, as well as in their systemic manifestations (27,66,67).

Hypoxemia, hypercapnia and acidosis

Ventilation-perfusion mismatching present in chronic respiratory conditions frequently results in chronic hypoxia, with or without hypercapnia and acidosis. Moreover, respiratory muscle dysfunction can induce some degree of hypoventilation, also contributing to gas exchange abnormalities. Conversely, hypoxia can result in nutritional abnormalities, muscle dysfunction and exercise limitation (68,69). This is probably the consequence of different phenomena such as systemic inflammation, which in turn deteriorates both tisular metabolism and the action of some peptides and hormones (i.e., leptin, ghrelin and AMP-activated protein kinase) involved in either appetite mechanisms or the maintenance of muscle, bone and fat masses. As a result, deleterious phenomena such as muscle autophagy and apoptosis, reduced mitochondrial synthesis (biogenesis), impaired proteostasis and regeneration, as well as metabolic limitations in the aerobic pathways develop within the muscle (70-73). Hypercapnia and acidosis in turn may also induce a decrease in energy stores, impaired muscle proteostasis and defective contractility (74-76).

Hormonal deficiencies

The effect of anabolic hormones can be altered in different chronic respiratory diseases. This is the case with COPD, where hypogonadism and low levels of androgens appear to be relatively prevalent, at least in those patients with loss of muscle mass (77). Some reports also indicate that COPD patients can show either a decrease in the levels of growth hormone (GH) or the inefficiency of its anabolic axis, which also includes the GH releasing factor (GRF) and the insulin-like growth factor 1 (IGF-1) (12,78). Moreover, the prevalence of diabetes mellitus (DM) is increased in different chronic respiratory diseases. In COPD patients, for instance, it almost doubles (19%) that observed in the general population (79). This has been explained by the presence of cigarette smoking, obesity, reduced physical activity, systemic inflammation, corticosteroid exposure and hypoxia (80). The prevalence of DM is even higher in adults with CF (close to 50%), due in this case to pancreatic atrophy and some of the factors already mentioned for COPD (81). Conversely, patients with DM are more susceptible to pulmonary infections (including tuberculosis) (82), which can facilitate bronchiectasis. IPF also shows an increased prevalence of DM type II (10–33%), which persist after exclusion of patients treated with systemic steroids (83,84). Diabetes can lead to nutritional derangements, with loss of body and muscle weight, and muscle dysfunction. The mechanism for the latter probably involve insulin resistance, hyperglycemia, muscle fat infiltration and peripheral neuropathy (85).

Lung cancer, and particularly small cell lung cancer (SCLC), relatively frequently induces paraneoplastic syndromes, which are mainly caused by the production of cytokines by the neoplasm or as an immune response to cancer. The most common paraneoplastic expressions of lung cancer are fatigue and cachexia, as well as neurological, hematological and endocrine syndromes. Regarding the latter, lung tumors can synthesize and secrete peptides or hormones that cause a variety of endocrine syndromes. Some of them can be related with nutritional abnormalities or muscle dysfunction. This is the case of hypercalcemia (2–12% of lung cancers), inappropriate antidiuretic hormone secretion (SIADH, 7–16% in SCLC), ectopic Cushing's syndrome (2–5% of SCLC, generally resulting from extrapituitary secretion of ACTH), and hypoglycemia (usually caused by the tumor production of IGF). All these disorders can induce muscle weakness and fatigue (86). Patients with lung cancer can also show low serum testosterone that is probably secondary to inhibition of follicle-stimulating hormone (FSH) (87). Other non-endocrinological paraneoplastic syndromes that can induce muscle dysfunction are the Lambert-Eaton myasthenic

one (a presynaptic disorder of neuromuscular transmission) and polymyositis/dermatomyositis (an autoimmune-based systemic inflammatory myopathy), both leading to muscle weakness (86).

Vitamin D deficiency

A significant number of patients with chronic respiratory disorders also show decreased levels of both vitamin D and calcium (88-91). This circumstance, which can be partially related to a poor diet intake but also to a reduction in outside physical activities, may induce loss of bone and muscle mass, contributing to muscle dysfunction (89). Vitamin D insufficiency ranges between 40–77% in COPD patients (89), 40% in patients with bronchiectasis (88), and 60% in adults with CF (90) (reaching 90–95% in North American children with this disorder) (92). The prevalence of hypovitaminosis D in patients with lung cancer is close to 50% (91), reaching 90–95% in advanced disease; and remains very high even following supplementation therapy (93). Finally, vitamin D deficiency is also frequent in IPF, and a prevalence of 20–40% has been reported (94,95). Interestingly, it has been suggested that vitamin D deficiency can contribute to a worse prognosis in both lung cancer and IPF (96,97).

Drugs

Although other pharmacological treatments can have a negative impact on nutritional status, muscle structure and/or function, systemic corticosteroids should be specially highlighted (10). These drugs can induce both chronic and acute myopathies (98). The former, characterized by weakness of proximal muscles, can appear even following low doses if they have been taken for a long period (99). By contrast, acute myopathy does not target specific muscle groups, appearing a few days after drug administration. In addition, systemic steroids can reduce synthesis of structural proteins and enhance protein degradation (100,101).

Comorbidities and aging

Other chronic disorders are commonly associated to chronic respiratory diseases. In many cases this is simply because they share some of the etiological factors. Chronic heart failure, DM and cancer are among the most frequent comorbid conditions observed in respiratory medicine. By themselves they can also contribute to nutritional deficiencies and muscle dysfunction (7,9,12,102,103). Moreover, aging alone can also induce loss of body weight, sarcopenia (loss of muscle mass associated with senescence), and muscle dysfunction (104). Therefore, special attention should be paid to elderly and comorbid patients.

Chronic respiratory disorders

Although a very detailed description of nutritional abnormalities and skeletal muscle dysfunction in all chronic respiratory diseases goes beyond the purposes and extension of the present review, it focuses on those entities that are especially targeted by these alterations.

COPD

Nutritional abnormalities frequently associate with COPD both by excess or fault. On the one hand, nutritional deficiencies seem to range between 15% and 50% (105,106) in COPD patients from North America and Northern-Central Europe, being lower (3% to 20%) in the Mediterranean area (107,108). This wide spectrum of data has been explained by differences in lifestyle but also in patients' selection and diagnosis criteria for malnutrition (techniques, variables and thresholds) (104). It is worth noting that nutritional deficiencies have been specifically associated with the emphysematous phenotype (pink puffer) of COPD as well as with alpha-1 antitrypsin deficiency, and are closely linked to muscle dysfunction (10). However, most of the recent COPD classifications undervalue the significance of nutritional abnormalities (1,109), a circumstance that can be the explained by the absence of a well-defined treatment. In fact, only the BODE index and its derivates include body mass index (BMI) among variables used to determine the severity and prognosis of the disease (110). In agreement with these nutritional data, muscle dysfunction is also very frequent in COPD patients. This is the case for both limb (prevalence 20–30%) and respiratory muscles (prevalence 20–45%) (111-114). While nutritional abnormalities and deconditioning play a key role in the impairment showed by the former group, respiratory muscle dysfunction is mainly the result of geometrical changes occurring in the thorax as a direct result of the lung disease (10,11).

In the particular case of patients with alpha-1 antitrypsin deficiency, not only nutritional status, but also muscle mass and strength, and exercise capacity become impaired as well (115,116).

However, a significant percentage of COPD patients

exhibit obesity (defined by a BMI >30 kg/m^2, 20–30% of individuals) or overweight (BMI 25.0–29.9 kg/m^2, reaching around 40% in some of the studies) (117). Obesity can also be diagnosed by considering body composition [thresholds for fat mass index (FMI) are ≥6.6 kg/m^2 in men and ≥9.5 kg/m^2 in women, and for the percentage of body fat ≥25% for men and ≥35% for women] (118). The causes of obesity and overweight in COPD are similar but probably more pronounced than those causing these nutritional abnormalities in Western populations, and would include an inappropriate diet and low level of physical activity (117), as well as hormonal changes and some treatments that are also present in these patients.

It is worth noting that obesity does not necessarily involve maintenance of muscle mass, since the latter is often replaced by fat, mostly in female patients. Sarcopenic obesity is the term used for the association of obesity and muscle wasting. Although the loss of muscle mass can lead to all the negative functional consequences discussed above (117,119), mild to moderate obesity has also been associated with lower mortality in COPD patients (120,121). This has been attributed to the presence of energetic storages linked to obesity, which under acute circumstances would partially counterbalance the increased catabolism characteristic of severe or critical conditions. However, it must be taken into account that obesity also leads to cardiovascular and metabolic comorbidities and potentially to hypoventilation syndromes (119). Although there is a lack of consensus for clinical management of obesity in COPD patients, it seems logical to recommend a moderate weight reduction along with prevention of metabolic and cardiovascular complications.

Non-CF bronchiectasis

Bronchiectasis, defined as the abnormal and irreversible dilation of the bronchi, are frequently observed even in general population, especially since the wide use of the high-resolution computed tomography (122). Although bronchiectasis can be the result of different processes, they are currently classified in those linked to CF and those that are independent of such a genetic alteration (non-CF), being the latter much more prevalent (123-125). Moreover, the above-mentioned advances in image techniques have allowed for the identification of a variable number of COPD patients who also have bronchiectasis to a greater or lesser extent (1). Although the most common clinical presentation of non-CF bronchiectasis is the presence of daily cough with abundant sputum and repeated infections (123,124), nutritional abnormalities are also frequent (2). Since many of the deleterious factors present in COPD are also present in non-CF bronchiectasis (local and systemic inflammation, exacerbations, ventilatory limitation, deconditioning, etc.) (126,127), it could be speculated that muscle dysfunction would also be frequent in this case. However, the actual prevalence of this disorder in non-CF bronchiectasis remains unclear. Respiratory muscle dysfunction has only been occasionally described in this lung disease (2,126,128,129) and, so far little attention has been given to the eventual presence of limb muscle malfunctioning. In fact, only isolated reports suggest that this latter abnormality is common in non-CF bronchiectasis (130,131) and exercise tolerance can also be reduced (126).

CF

Nutritional abnormalities and peripheral muscle weakness are prevalent in adult and children with CF, being an independent predictor of mortality (132). Moreover, wasting associates with an impairment in muscle mass (5,133), and a mean decrease of 25–35% in quadriceps strength (5,133,134). This suggests that nutritional abnormalities also play a key role in this case (135), although other factors such as deconditioning, systemic inflammation or drugs may also participate (5,136-138). Regarding respiratory muscles, their function can either be impaired, as is the case in the diaphragm, or preserved, as it appears to be the case in expiratory muscles. Both phenomena may be explained by the increase in loads undergone by the respiratory system, which would mainly affect the length and capacity to generate force in the former muscles but would generate a training effect in the latter (133,135).

IPF

This is a fibrosing interstitial pneumonia of unknown etiology (139). Interestingly, it is worth noting that some COPD patients also associate fibrosis (1), and probably may constitute a specific phenotype of these disorders. In fact, close to 30% of IPF patients show some degree of concomitant emphysema (140,141), which as previously mentioned frequently associates nutritional abnormalities and muscle dysfunction. Although many other comorbid conditions (cardiovascular, hormonal and digestive, among others) have been reported in IPF, the prevalence of nutritional abnormalities and skeletal muscle

dysfunction have received poor attention. The prevalence of nutritional abnormalities in hypoxemic IPF patients has been estimated at around 30% (142), Moreover, in a series of IPF candidates for lung transplantation, as much as 56% showed severe lean body mass depletion (143). However, body weight can occasionally be maintained due to a relative abundant fat mass (144). Interestingly, the nutritional status is a prognosis factor in IPF (3). Moreover, the weak relationship between exercise capacity and lung function observed in this disorder suggests the presence of additional factors. Some reports also suggest an impairment in peripheral and respiratory muscle function in IPF patients (145-147), leading to limitations in daily physical activities with a relevant impact on patients' life (145,147). Moreover, this impairment seems to be partially reversible with training (145,146,148), suggesting that in addition to the above mentioned nutritional abnormalities, there is a role for deconditioning and other factors such as treatment with systemic steroids (145).

Lung cancer

The development of cachexia is a common manifestation in advanced cancer, and is inversely related with time to survival (4). It constitutes a complex syndrome, which also includes anorexia. However, nutritional abnormalities may occur much earlier in lung cancer (149), predating clinically evident cachexia (150). In fact, people with lung cancer who are candidates for surgical lung resection (i.e., those with a still localized neoplasm) perceive physical weakness as the most important and undesirable symptom (151). Nutritional abnormalities associated to lung cancer are related to anorexia but also to a hypermetabolic status, where the host and the tumor compete for nutrients. These nutrients can come from diet but also from the patient's own metabolism. This is especially dramatic in the case of proteins since their synthesis is decreased and breakdown is increased in cancer. Since skeletal muscles account for around half of the entire body protein content, it is easy to anticipate that muscle mass would be affected, leading to muscle dysfunction (4). This muscle mass reduction and the subsequent muscle weakness appears to be the most relevant clinical event induced by cancer cachexia (152), since they result in significant impairment in quality of life, exercise capacity, physical functions and mortality (153-155). As for different muscle groups, patients with thoracic cancers have been shown to have lower quadriceps strength than healthy controls (156). Regarding etiology for the preceding abnormalities, most of the factors already mentioned for other respiratory conditions are also present in lung cancer, which in addition is frequently associated to COPD. These factors include, not only nutritional abnormalities but also a low level of physical activity and muscle deconditioning, tobacco exposure, systemic inflammation (most likely, cytokines such as TNF-alpha or IL-1) and oxidative stress, aging, comorbidities and cancer treatments (4,157,158). Respiratory muscle function in turn will also be influenced by changes undergone by thorax mechanics as a result of the neoplasm and underlying disorders.

Aging in particular is a factor that can contribute in a relevant way to sarcopenia and muscle dysfunction in patients with lung cancer. In fact, as many as half of the newly diagnosed neoplastic patients are older than 70 years in developed countries (159), and of them, 50% show nutritional abnormalities (160-163), with the vast majority (around 70%) also exhibiting altered physical capacity (161).

Lung cancer treatment, which can include surgery, chemotherapy, radiotherapy and immunotherapy, is an additional factor that can contribute to nutritional and skeletal muscle abnormalities. Radiotherapy for instance can induce esophagitis-dysphagia and anorexia, whereas chemotherapy can cause nausea and vomiting, both affecting the ability to achieve an adequate dietary intake (164,165). As to surgical resection it involves the loss of lung function and respiratory symptoms, which in turn can lead to a reduction in physical activities as well as to cardiovascular and skeletal muscle deconditioning. Finally, all these treatment regimens can increase the anxiety-depression symptoms linked to the diagnosis of lung cancer, also leading to a reduction in physical activity and social life. Interestingly, a systematic review indicates that dietary counseling or nutritional supplements can improve protein intake in patients undergoing chemotherapy (166). The same review shows that these measures are able to maintain the nutritional status in lung cancer patients receiving radiotherapy (166).

Exacerbations

These periods, characterized by the impairment of symptoms, can be present in different chronic respiratory conditions. Although they are more characteristic of COPD, CF and non-CF bronchiectasis, they can also contribute to the deterioration of patient performance in IPF and lung cancer. Exacerbations bring together many of the different factors that can contribute to nutritional

abnormalities and skeletal muscle dysfunction (9).

COPD

Exacerbations increase the level of local and systemic inflammation markers (see previous sections) (12,167) as well as those of leptin. Moreover, anorexia, fever, reduced physical activity, a negative energy balance, increases in the work of breathing and use of systemic steroids are often added to this adverse metabolic picture, which negatively impacts on nutritional status and muscle function (9,168-170). It should be noted that muscle wasting and dysfunction can develop early in acute episodes, lasting for a relatively long time (9). In fact, many authors consider that exacerbations are one of the factors that contribute the most to these abnormalities (9,12). In close agreement with this idea, muscle dysfunction has been shown to reach a prevalence of 80–90% in patients with multiple hospital admissions due to exacerbations (114). Conversely, those patients with muscle dysfunction show an increased risk of hospital admission due to these acute events (114,171).

Non-CF bronchiectasis

Acute exacerbations are also frequent in this disorder, being accompanied by many of the factors that are also present in COPD (dramatic decrease in physical activity, increase in lung and systemic inflammation, metabolic derangement between energetic requirements and offers, drugs with potential negative effect on muscle tissue, etc.) (172).

CF

Weight loss is so important in CF exacerbations that it has been included in its definition (173), having also specific therapeutic measures that have been incorporated in the guidelines (173). As in other chronic respiratory disorders acute episodes are characterized by a marked catabolic state combined with reduced appetite and physical activity, and inflammatory events. Moreover, insulin-requirements can be dramatically increased during CF exacerbations (173). As a result of these factors, quadriceps maximal strength decreases acutely during the episode (174,175), although it generally recovers in the follow-up (174).

IPF

The natural history of this disorder is highly variable, but some patients show acute deteriorations among periods of relative stability (176). Although little is known about the pathophysiology of these acute events, it has been shown that systemic inflammation levels become increased (60). As in the other disorders included in the present review, this factor would be added to a greater reduction in physical activity, impairment in gas exchange, and a worse nutritional balance.

Diagnosis

Nutritional abnormalities

The actual prevalence of nutritional deficiency in chronic respiratory conditions is relatively high, although precise rates depend mainly on the criteria used for the diagnosis. These are commonly based on anthropometric variables [body weight, percentage of ideal body weight (%IBW), or BMI, ratio between weight in kg and height in square meters] or, even better, data from the analysis of body composition [such as fat free mass index (FFMI)] (*Figure 2*). The simplest but less specific is to obtain direct or derived anthropometric variables. Values under 80% in %IBW or 18–18.5 kg/m^2 in BMI are commonly considered as the diagnostic thresholds for impaired nutritional status (177,178). BMI can also be used to stratify such a deficit in mild-moderate (16–18 kg/m^2), severe (15–15.9 kg/m^2) and very severe (below 15 kg/m^2) (178). Other traditional anthropometric determinations are triceps skinfold or thigh circumference, but they have been progressively abandoned in the clinical setting. However, anthropometric measurements can be poorly sensitive to mild-to-moderate nutritional abnormalities. A more appropriate approach is to determine body composition using bioelectrical impedance or dual-energy X-ray absorptiometry (DEXA) (7,179). Both methods provide an accurate approximation of fat free mass, which in the case of the latter technique can even offer compartmentalization in different body parts such as trunk, upper or lower limbs. FFMI is the body composition variable most widely used to assess nutritional status. Values lower than 16–18 kg/m^2 in men, and 14.5–15 kg/m^2 in women (105,180) are indicative of muscle mass loss. It should be noted that diagnosis of nutritional deficiencies can be especially difficult in female patients, since they can show loss of muscle mass even though body weight remains relatively stable, showing significant discrepancies between BMI and FFMI (105). Other methods that can also be used to assess nutritional status are imaging techniques (computed tomography, magnetic resonance

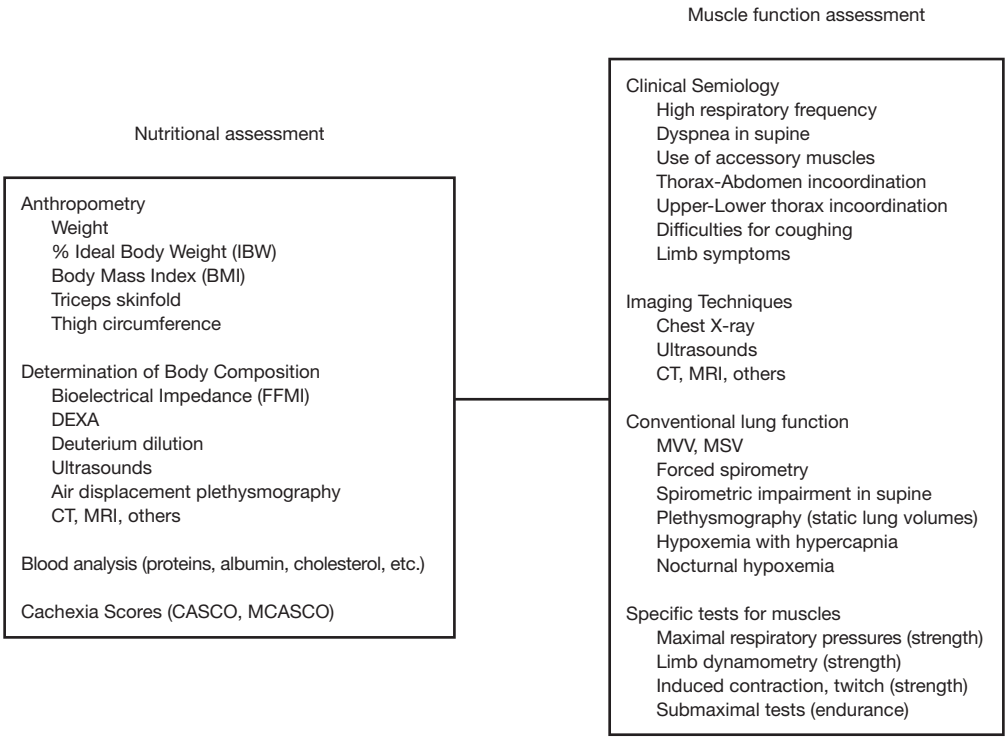

Figure 2 Techniques and the most relevant variables used for nutritional and muscle function assessments. Note that both abnormalities are closely related since the presence of malnutrition often contributes to the occurrence of muscle dysfunction. FFMI, fat-free mass index; DEXA, dual-energy X-ray absorptiometry; CT, computed tomography; MRI, magnetic resonance imaging; CASCO, CAchexia SCOre; MCASCO, mini-CASCO score; MVV, maximum voluntary ventilation; MSV, maximum sustainable ventilation.

and ultrasounds), air displacement plethysmography (ADP), deuterium dilution, and isotopic techniques (7,11,179,180). Blood determinations of serum total proteins, albumin fraction, cholesterol and prothrombin time can also be useful to complete the assessment of nutritional status (7). An interesting 'CAchexia SCOre' (CASCO) has been recently validated and can be useful in chronic respiratory conditions. It includes several domains (body weight loss and composition, inflammation/metabolic disturbances, immunosuppression, physical performance, anorexia and quality of life), and classifies patients from 'non-cachectic' to 'with severe cachexia' (181). Since this score involves multiple variables, a simplified version (miniCASCO or MCASCO), which only involves body weight-lean mass, blood analysis and a short questionnaire, has also been recently developed for clinical purposes (182).

Muscle dysfunction

Although closely related, nutritional deficiencies and muscle dysfunction are not always associated. Thus, specific methods should be used to directly assess muscle function (12,13) (*Figure 2*).

Functional evaluation of respiratory muscles can be addressed with different approaches from clinical semiology to instrumentalized techniques. On the one hand, muscle dysfunction can be suggested by the presence of different symptoms and signs such as a very high respiratory rate with small tidal volume, a relevant worsening of dyspnea when lying in supine, the use of accessory muscles for ventilation, thoraco-abdominal or upper-lower chest incoordination, and difficulties in effective coughing (11). Imaging techniques, such as conventional chest X-ray and ultrasounds, can also be useful to suggest the presence of respiratory muscle dysfunction (183,184). From a functional point of view, a marked impairment in forced vital capacity (FVC), a 25% reduction in this parameter when changing from sitting to the supine position, as well as a decrease in static lung volumes [such as total lung capacity (TLC) or functional residual capacity (FRC)], and hypoxemia

with hypercapnia (especially at night) can be the result of respiratory muscle dysfunction (11,185). More specific are those techniques that allow determination of maximum respiratory pressures as an expression of muscle strength. Their measurement at the mouth, using dynamic or static maneuvers (i.e., with or without concomitant airflow, respectively), is the most commonly used procedure in clinics. While maximum inspiratory pressure (MIP) is usually determined from residual volume (RV), maximum expiratory pressure (MEP) is commonly measured from TLC (186). However, both can also be determined from FRC. MIP and MEP values can be expressed in absolute and relative terms since validated references exist for both variables (186,187). Values below 80 cmH_2O or 65% of the reference are considered as indicative of respiratory muscle dysfunction (13,188). Alternatively, maximum pressures can be determined on the nostrils during a maneuver of forced inhalation [sniff nasal inspiratory pressure (SNIP)] (189,190), and values lower than –60 or –70 cmH_2O are accepted as suggestive of inspiratory muscle dysfunction (13). Validated reference values are also available in this case (191,192). Since all the above-mentioned measurements are valid only in the presence of normal upper airways, it may be necessary to perform a more invasive technique in some patients. In this case, maximal esophageal pressure (Pesmax, which closely reflects pleural pressure) (193) and/or transdiaphragmatic pressure (Pdimax) should be determined (194,195). A Pesmax lower than –70 or –80 cmH_2O or a Pdimax above 50 (women) or 75 (men) cmH_2O are highly suggestive of inspiratory muscle dysfunction (11,13,194). A common limitation to all these procedures is the need for patient collaboration. When this is not possible, maximum muscle contraction can be induced by supramaximal electrical or magnetic stimulation ('twitch') (9,196,197). The latter is better tolerated since the former is uncomfortable and can even be painful (11,197). Approximations to reference values with twitch stimulation of the diaphragm have also been published (13,198,199). Values lower than 50–60 cmH_2O in men and 35–40 cmH_2O in women are considered as indicative of diaphragm dysfunction, and below 15 cmH_2O would evidence a serious muscle malfunction (11,13). Less extended is determination of those variables that reflect muscle endurance. The simplest are maximum voluntary ventilation (MVV) and maximum sustainable ventilation (MSV), although they are both very unspecific (11). A good alternative is determination of the time elicited by the patient sustaining a percentage of the maximum respiratory pressure until task failure (Tlim) (200-203).

Functional assessment of peripheral muscles in turn, can also be approximated by clinical semiology. In this case, the presence of lower limb symptoms during even mild-to-moderate exercise or an evident loss of muscle mass are both suggestive of limb muscle dysfunction (204,205). Those techniques used to assess body composition, which have been detailed previously, can also help in the suspicion of an impairment in muscle function. However, as occurs for respiratory muscles, there are specific tests to assess limb muscle function. The strength can be determined by dynamometry, generally using a maximal isometric maneuver. Handgrip is most often used for assessing upper limb strength, whereas quadriceps isometric contraction is usually employed for lower limbs (11). Quadriceps strength can also be determined by measuring the peak torque at fixed joint angle speed (206,207), although this technique requires more experience. Reference values are available for both handgrip and quadriceps dynamometers (208-212). In the case of handgrip, values below 80–85% pred. have been proposed as suggestive of upper limb muscle dysfunction, whereas the threshold for quadriceps muscle is more controversial (213,214). As in the case of respiratory muscles, electrical or magnetic stimulation can be used in subjects unable to participate in the maneuver (215,216), and reference values are also available (11,217). Limb muscle endurance can also be approximated using procedures and variables very similar to those used with respiratory muscles (e.g., Tlim) (218-221).

Therapy

As so many factors can contribute to nutritional abnormalities and muscle dysfunction in chronic respiratory disorders, the therapeutic approach should be multidimensional (*Table 1*). Unhealthy lifestyle must be modified and patients should increase their physical activity, improve the quality of their diet, and abstain from tobacco smoking and alcohol. It is also important to prevent and appropriately treat exacerbations and avoid, or at least, reduce treatments with drugs that are deleterious to nutritional status and muscle function.

When these measures become insufficient, dietary supplements or anabolic drugs can be used. Similarly, training programs would contribute to reconditioning not only of the skeletal muscles but of the cardiovascular system.

Table 1 Therapeutic measures for nutritional abnormalities and muscle dysfunction. Most of them act on both problems

Healthy lifestyle
Avoid smoking and alcohol
Maintain good level of physical activity
Balance diet
Ensure healthy aging
Diet supplements (if healthier lifestyle is not enough)
Optimize the control of the underlying respiratory disease and its comorbidities
Bronchodilators, inhaled steroids or oxygen if necessary
Avoid Exacerbations and optimize their management: vaccines, antibiotics, enriched diet (+ supplements?) & early mobilization. Training?
Avoid systemic steroids if possible
Treat and monitorize comorbidities
Training (potentiates nutritional actions)
Exercise training, interval training, resistance training
Respiratory muscle training (if indicated)
Stimulated training (patients unable to collaborate)
Anabolic drugs (only selected cases)
Androgens, SARM
GH, GH secretagogues, growth factors
Other drugs
Antioxidants and anti-inflammatory (no clear effects)
Appetite enhancers (?)
Potentiators of muscle contraction (calcium sensitizers)
Rest (if there is a fatigue component): mechanical ventilation

SARM, selective androgen receptor modulators; GH, growth hormone.

Avoid tobacco smoking

This simple measure is able to improve nutritional status and muscle mass and function through different positive effects (222). On the one hand, it will eliminate the anorectic effect of tobacco, improving diet quality (223). On the other, systemic inflammation and oxidative stress, as well as protein synthesis/breakdown imbalance will be reduced, with improvements in body weight, as well as in muscle mass and function (224-227).

Dietary recommendations

To cope with nutritional abnormalities, it is important to emphasize the necessity of increasing the intake of proteins and polyunsaturated fatty acid-rich foods, as well as vitamins (such as A, B6, B9, B12, C, D, and E) (228-230). It also appears to be positive to increase the consumption of fibers, as this can delay the progression of some chronic respiratory diseases, perhaps through its effects on bowel microbiome (231,232).

Nutritional supplements

These can be used as an adjunct to an appropriate diet in order to achieve better results. Supplements should essentially provide an additional amount of calories, but also proteins, amino acids (especially those of branched chain), vitamins and minerals (123,168,233). Liquid supplements with high-caloric content are especially helpful in restoring body weight and skeletal muscle mass in patients with some chronic respiratory disorders (234). However, some recent reviews have not demonstrated clear benefits in others, when there is an already well-balanced diet (235). Regarding protein and amino acid content, the source of the supplement is also important. Those derived from milk or whey appear to be better absorbed and utilized than those obtained from soybean (168,236). In the case of CF, pancreatic enzyme replacement is mandatory.

Appetite stimulants

Positive results have not been demonstrated with the administration of these drugs (such as megestrol, donabiol or pentoxifylline) in underweight chronic respiratory patients (237).

Appropriate level of physical activity and training

Sedentarism, psychological symptoms, skeletal muscle dysfunction and, in some cases, ventilatory limitation, lead to reduced physical activities, which conversely will aggravate these same causes. This vicious circle should be broken by recommending an increase in outdoor physical activities (11); a simple measure that can reduce hospital admissions and improve prognosis and quality of life in COPD (238-240). Although it also appears to be able to ameliorate some of these outcomes in other chronic respiratory diseases, more studies are needed (241,242).

When physical activity is insufficient for obtaining positive results, training programs should be recommended (243). These are able to improve cardiovascular and muscle function, increasing exercise capacity and reducing anxiety and depression symptoms (11,244-250). In addition, many of the structural and metabolic abnormalities shown by skeletal muscles will erode or even disappear with training (251,252). General training has different modalities including endurance exercise training, which is crucial for obtaining an improvement in muscle function and physical capacity (11,253-255). Strength and resistance training in turn can also be helpful for specifically ameliorating these functional properties of skeletal muscles. Both the intensity of loads and the pattern of repetitions will determine improvements in strength, endurance or both (201,254). An important point is to reach an acceptable nutritional status before starting an intense training program (255). In fact, dietary measures and training potentiate each other, obtaining better results with an appropriate combination (6,52,234). It is also relevant to initiate training at a moderate level, since high intensity exercise can cause muscle oxidative stress in untrained patients (256). A negative effect that can be easily avoided with progressive increases in the effort requirements until achieving an acceptable level of cardiovascular and muscle conditioning (257). In patients with a very limited exercise capacity, who cannot follow volitional training modalities, it may be necessary to use electric or magnetic stimulation of skeletal muscles (258-261). A very interesting and still controversial point is whether it is beneficial, or not, to train patients during or immediately following exacerbations. Although there is some evidence suggesting that this procedure can prevent loss of muscle mass and function during these acute episodes (262), further studies are needed and probably, the therapeutic approach should be individualized taking into account the underlying disease and patient's condition (11,263-265).

Anabolics

These drugs are only necessary in highly selected cases, and most are hormone derivates or releasers, notably those related to androgens or the GH. Some of the former, such as testosterone or nandrolone, are able to enhance the balance between protein synthesis and breakdown, increasing muscle mass (12,78). However, they can also produce undesirable side effects, which can nonetheless be reduced with the use of selective androgen receptor modulators (SARM) (266). As for GH, it also has a powerful anabolic effect, being able to increase body weight in chronic respiratory patients with malnutrition, but unfortunately not demonstrating systematically a clear improvement in muscle function (267). The same appears to be the case for GH secretagogues (drugs that promote synthesis or release of GH) such as ghrelin, tesamorelin and anamorelin. Nevertheless, there are some reports showing functional improvements associated with the gain of body and muscle weight with these drugs (268,269).

Control of the underlying lung disorder

Naturally, a good control of the chronic respiratory disease contributes to maintaining nutritional status and muscle function (11,104). This is especially important regarding prevention and treatment of exacerbations, when many of the factors leading to nutritional abnormalities and muscle dysfunction become even more accentuated. The therapeutic measures mainly include the use of bronchodilators, vaccines and antibiotics in COPD and bronchiectasis, and the latter drugs and anti-fibrotic therapies in IPF. Although systemic steroids can be necessary, their dose and the duration of the treatment should be carefully considered. An appropriate and more caloric diet (270), as well as early mobilization of the patient are also very important. Moreover, more recently it has been suggested that initiating training during or immediately post-exacerbation can partially counterbalance the deleterious effects of these acute episodes (271,272).

Drugs with anti-inflammatory and antioxidant effect

Different substances have been tested so far in order to neutralize local and systemic inflammation and oxidative stress. This is the case of antioxidant substances and antibodies against inflammatory cytokines, their receptors, or some transcription factors. However, the evidence of positive effects is scarce and some of these therapies have also shown important side effects (273-277).

Conclusions

Nutritional abnormalities and muscle dysfunction are frequently found in patients with chronic respiratory disorders such as COPD, non-CF bronchiectasis, CF, IPF and lung cancer. These defects can appear together or separately, although they are closely interrelated and share

many different etiological factors. Diagnosis of nutritional abnormalities include anthropometry and determination of different body components (mainly obtained through bioelectrical impedanciometry), whereas that of muscle dysfunction involves determination of muscle strength and endurance. The treatment of underweight patients includes the improvement of lifestyle habits, dietary supplements and, in some particular cases, the use of anabolic drugs. These measures should be accompanied by training, especially in those patients with muscle dysfunction.

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Footnote

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