Review Article

Systemic manifestations in chronic obstructive pulmonary disease*

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ABSTRACT

Chronic obstructive pulmonary disease is progressive and is characterized by abnormal inflammation of the lungs in response to inhalation of noxious particles or toxic gases, especially cigarette smoke. Although this infirmity primarily affects the lungs, diverse extrapulmonary manifestations have been described. The likely mechanisms involved in the local and systemic inflammation seen in this disease include an increase in the number of inflammatory cells (resulting in abnormal production of inflammatory cytokines) and an imbalance between the formation of reactive oxygen species and antioxidant capacity (leading to oxidative stress). Weakened physical condition secondary to airflow limitation can also lead to the development of altered muscle function. Chronic obstructive pulmonary disease presents diverse systemic effects including nutritional depletion and musculoskeletal dysfunction (causing a reduction in exercise tolerance), as well as other effects related to the comorbidities generally observed in these patients. These manifestations have been correlated with survival and overall health status in chronic obstructive pulmonary disease patients. In view of these facts, the aim of this review was to discuss findings in the literature related to the systemic manifestations of chronic obstructive pulmonary disease, emphasizing the role played by systemic inflammation and evaluating various therapeutic strategies.

Keywords: Pulmonary disease, chronic obstructive/complications; Nutritional status; Exercise tolerance; Neuromuscular manifestations

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable respiratory disease characterized by partially reversible chronic airflow obstruction. This obstruction is progressive and is characterized by abnormal inflammation of the lungs in response to inhalation of noxious particles or toxic gases, especially cigarette smoke. Although COPD primarily affects the lungs, there are diverse systemic manifestations related to this infirmity.[1] The local and systemic manifestations of COPD are summarized in Figure 1.

Airway inflammation and destruction of lung parenchyma are the changes that are characteristic of COPD and contribute to airflow limitation, which is a functional marker of the disease. However, the clinical profile and the repercussions on the overall patient heath status suffer the influence of the chronic manifestations of COPD and reinforce the need for a multidimensional approach that takes into consideration all of the components of the disease.[2]

In addition to airway inflammation, there is evidence of systemic inflammation in patients with COPD, although the relationship between local and systemic inflammation has yet to be established.[2-3] There is also evidence of an imbalance between the formation of reactive oxygen species and antioxidant capacity, leading to oxidative stress in the lungs. This imbalance is involved in the pathogenesis of the disease and can cause cell damage, mucous hypersecretion, antiprotease inactivation and increased pulmonary inflammation through the activation of transcription factors.[4]

There is recent evidence of changes similar to those affecting the lung. Oxidative stress and inflammation might be involved in the mechanisms of development of the systemic effects of COPD.[4] Patients with COPD present weight loss, which is an independent indicator of disease outcome.[5] Loss of lean body mass also results in peripheral muscle dysfunction, reduction in exercise tolerance and lower quality of life, alterations that are important determinants of prognosis and survival among patients with COPD.[6-7] Therefore, indices that include local and systemic manifestations of COPD might be more appropriate for determining the survival rate of these patients. In fact, the evaluation of and measures to improve nutritional status and exercise tolerance are included in the recommendations of the Global Initiative for Chronic Obstructive Lung Disease.[8]

In view of the negative repercussions that the systemic manifestations of COPD have on exercise tolerance, prognosis and patient survival, the aim of this review was to discuss the main findings in the literature regarding the systemic manifestations of COPD. We will address nutritional depletion, peripheral skeletal muscle dysfunction and other effects related to the comorbidities generally observed in patients with COPD. In addition, the role of systemic inflammation will be discussed, as will therapeutic strategies. The Medline and Lilacs databases were reviewed using the keywords related to the topics of the present study, and the searches were limited to studies published within the last fifteen years.

NUTRITIONAL STATUS

Weight loss has been described as a clinical sign in the evolution of patients with COPD since the 1960s, and it has been associated with poor survival rates.[9] The prevalence of malnutrition varies, ranging from 26% to 47% among patients with COPD.[10-11] Retrospective studies have indicated that reductions in body weight, resulting in values below 90% of the ideal weight and in low body mass indices, are negative prognostic factors, independent of the severity of the disease.[5] Body mass index and survival are inversely related in patients with COPD.[5,12] In all of the groups, weight loss is associated with increased mortality. In addition, patients with severe COPD and body mass indices lower than 25 kg/m^2 present better survival rates after gaining weight.[13]

Several etiologies have been proposed for the nutritional deficiency observed in patients with COPD. However, the mechanisms involved have yet to be well elucidated.[14] Imbalance between energy intake and energy expenditure, due to decreased intake or increased expenditure, seems to be the factor involved in most cases.[15] The possible mechanisms involved in weight loss in patients with COPD are schematically presented in Figure 2.

Elevated levels of pro-inflammatory cytokines have been related to weight loss and wasting.[16] The results of clinical and experimental studies suggest that the liberation of inflammatory mediators can contribute to the development of

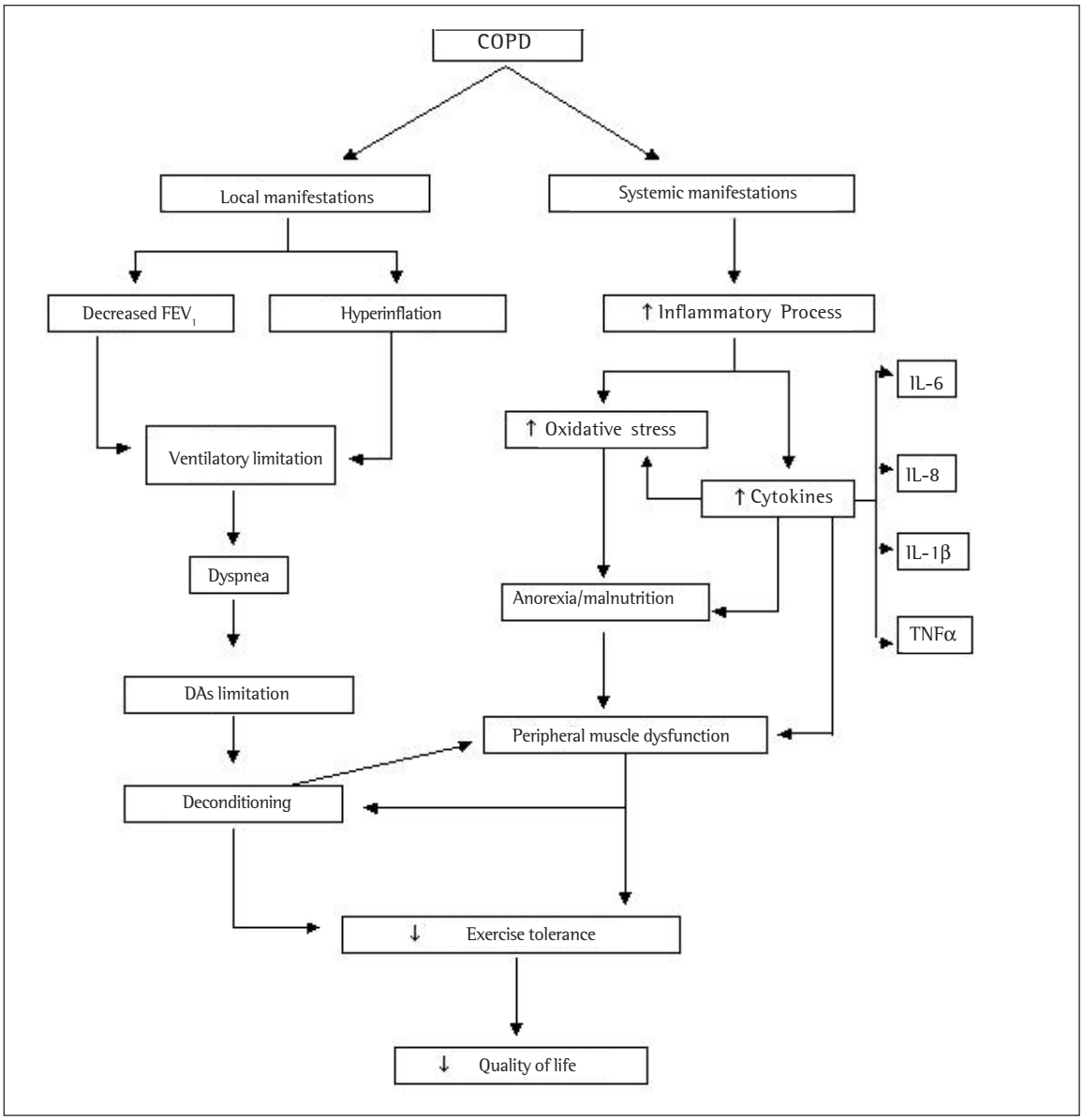

Figure 1 - Physiopathology of the local and systemic manifestations of chronic obstructive pulmonary disease

hypermetabolism, to reduced energy intake and to an inadequate response to caloric intake, leading to the nutritional alterations observed in patients with COPD. Cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin (IL)-1B can cause anorexia and proteolysis, the latter related to the activation and acceleration of the enzyme ubiquitin, a proteasome present in the peripheral skeletal muscles. Alterations in the leptin metabolism might also be involved in the development of nutritional changes in patients with COPD. Leptin is a signal for cerebral and peripheral tissue alterations as well as regulating caloric intake, basal energy expenditure and body weight. The results of the few studies that have been conducted on the topic suggest that inflammation can alter the leptin metabolism in patients with COPD. However, the role that leptin plays in the development of nutritional changes in these patients is unknown, and further studies are needed in order to understand it.[17]

We should also take into consideration that patients with COPD frequently present hypoxemia,

especially in the advanced stages of the disease. Some data in the literature suggest that hypoxemia could stimulate the production of inflammatory mediators and participate in the development of the nutritional changes seen in patients with COPD.[18]

Malnourished patients present more intense dyspnea, lower quality of life and lower exercise tolerance.[19-20]

Body mass index and weight loss are risk factors for hospitalization due to the exacerbation of the disease, are indicative of a poor prognosis in the evolution of the exacerbation and can be determinants of the need for mechanical ventilation.[21] In addition, survival time after the exacerbation has been found to correlate, in an independent way, with body mass index, and low body mass index has been found to correlate with an increase in postoperative morbidity in patients submitted to lung volume reduction surgery.[23] Nutritional depletion has also been associated with the higher mortality rates and greater frequency of hospitalization among patients with COPD on prolonged home oxygen therapy.[25]

Therapeutic strategy

Recently, the Cochrane Library published a meta-analysis in which the available studies of nutritional supplementation in patients with COPD were re-evaluated.[25] The authors found that food supplementation had no effect on anthropometric measurements, pulmonary function or exercise tolerance. However, recent studies have shown that food supplementation provides benefits for certain subgroups of COPD patients and for those presenting less accentuated nutritional changes.[26]

Despite their side effects, anabolic steroids might be an option for increasing muscle mass and improving function in patients who do not respond to traditional nutritional therapy.[26] In one study, it was shown that patients with COPD who receive anabolic steroids for short periods present an increase in lean body mass without any significant side effects.[26] However, the authors of that study found no improvement in exercise tolerance or dyspnea. Among the principal risks of androgen administration, specifically in women, are masculinization, skin reactions, altered plasma

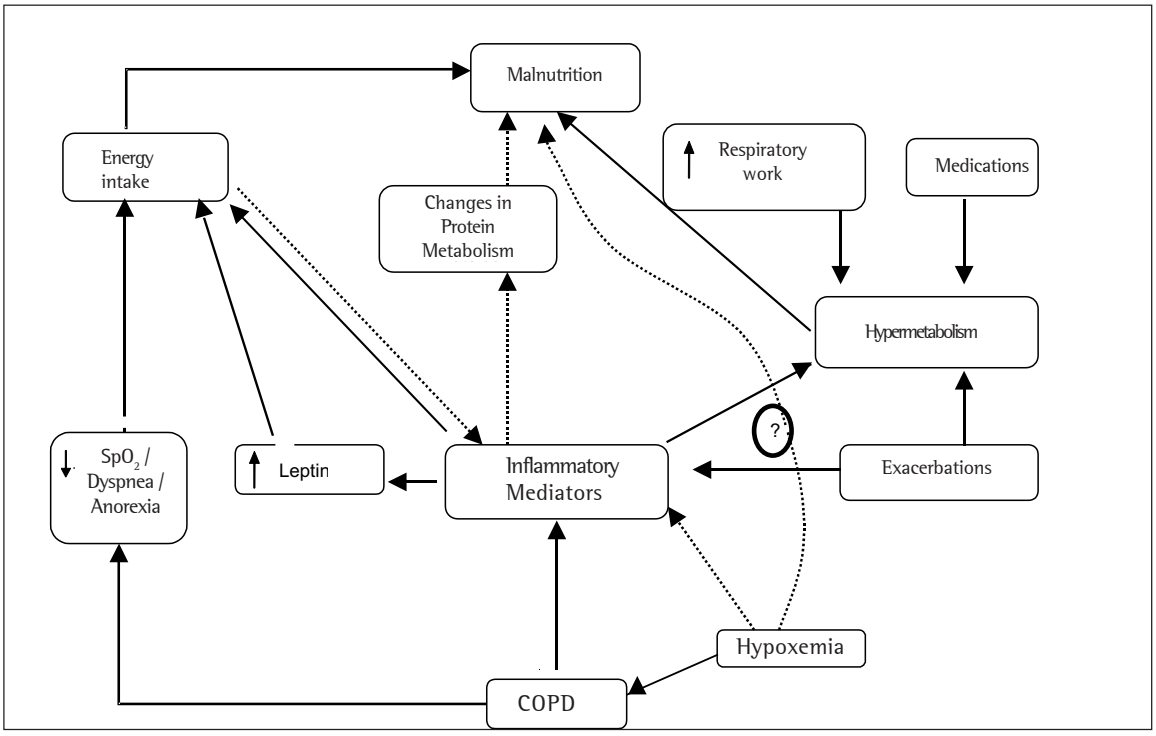

Figure 2 - Mechanisms of weight loss in patients with chronic obstructive pulmonary disease

lipids and behavioral changes.[27] Prolonged androgen therapy can increase the risk of cardiovascular events due to the decrease in HDL cholesterol levels. The literature presents inconsistent data regarding the correlation between androgen supplementation and the development of breast cancer.[27]

Further studies are needed in order to investigate the additional benefits of anabolic steroid therapy in terms of exercise tolerance and quality of life. In addition, the type of exercise combined with the anabolic therapy must be investigated since strength training has a greater influence on the metabolism of testosterone and amino acids.[28]

CHANGES IN RESPIRATORY MUSCLE FUNCTION

Patients with COPD frequently present weakness and decreased respiratory muscle endurance. The factors that can deteriorate muscle function and structure can be classified into two groups: intrinsic and extrinsic.[29] Among the extrinsic factors are geometric changes in the chest wall, changes in lung volume, and systemic metabolic factors. As intrinsic factors, changes in muscle fiber size, sarcomere length, muscle mass and muscle metabolism have been reported.[29]

Pulmonary hyperinflation is one of the factors that affect muscle function. Hyperinflation changes the shape and geometry of the chest wall and leads to a chronic reduction in the diaphragm apposition zone.[30] In addition, the flattening of the diaphragm reduces fiber length, which is an important determinant of the force-generating capacity of a muscle.

In patients with COPD, the diaphragm works under an increased mechanical load due to the airflow limitation and the geometric changes to the thorax resulting from pulmonary hyperinflation. In addition to the mechanical disadvantage, other changes, such as altered electrolytic status, as well as effects on proinflammatory mediators and growth factor, can interfere with respiratory muscle function. The diaphragms of such patients preserve the intrinsic capacity to generate pressure, but muscle function can be affected by the extrinsic factors.[31] There are also changes in the diaphragm structure. Those changes are characterized by an increase in the percentage of type I fibers and a reduction in the percentage of type II fibers, as well as by an increase in the oxidative capacity of all fibers.[32] These adaptations indicate aerobic adaptation of the diaphragm in response to the disease. However, that adaptation is insufficient to restore strength and endurance to their normal values.

CHANGES IN PERIPHERAL SKELETAL MUSCLE FUNCTION

Patients with COPD who use the resources of the health services approximately twice a year present significantly greater quadriceps strength than do those who use these services more frequently.[33] A cross-sectional area of the thigh, evaluated through tomography, of less than 70 cm2 has been implicated as the principal predictor of mortality and as the point at which catabolism prevails over anabolism in patients with COPD.[6,34] These results suggest that the structure and function of the peripheral muscles have a significant impact on the overall health status of patients with COPD. The muscles of patients with COPD can present changes in strength, mass, morphology and bioenergetics, which are described below.

Muscle strength and mass

Muscle weakness is proportional to loss of muscle mass.[29] There is evidence that patients with COPD present a significant reduction in upper and lower limb strength when compared to matched controls.[35] In addition, the cross-sectional area of the thigh is significantly smaller in patients with COPD.[35]

Reduction in muscle strength is predominant in the lower limbs. Among the possible explanations for this are the fact that activities related to gait development are usually avoided by patients with COPD due to the sensation of dyspnea, as well as the predominance of upper-limb use in the performance of daily activities and the great number of scapular girdle muscles responsible for the elevation of the arms participating concomitantly in the accessory respiration. These are the mechanisms that are most responsible for upper limb muscle strength being relatively preserved in patients with COPD.[29,35]

Muscle morphology

Reduction in the muscle contractile activity influences tropism, as well as affecting the balance between muscle synthesis and muscle

degradation.[37] As a consequence of prolonged disuse and immobilization, there is a predominance of slow-twitch muscle fibers in healthy individuals. This muscle fiber profile has been identified in patients with COPD.[38]

In addition to the muscle fiber redistribution observed in patients with COPD, there is evidence that the cross-sectional area of all (slow-twitch and fast-twitch) muscle fibers is significantly reduced in patients with COPD.[38]

Muscle bioenergetics

In studies that used material collected through vastus lateralis muscle biopsies, it was observed that patients with COPD present a significant reduction in oxidative enzymes,[39-41] together with a lack of a reduction in glycolytic enzyme levels,[29,39-41] or even an increase in the same.[29,41] Another bioenergetic change reported in patients with COPD is the reduction in the metabolism of muscle phosphocreatine,[29] one of the main factors involved in the lactate anaerobic metabolism.[42]

In summary, patients with COPD present low oxidative capacity, normal or increased glycolytic capacity, and decreased lactate anaerobic metabolism.[39,41] A slowing of the anaerobic lactate metabolism,[29] which is responsible for high-intensity, short-duration activities,[42] concomitant with a reduction in oxidative activity, reinforces the predominance of the anaerobic lactate system in patients with COPD,[43] which results in early-onset lactic acidosis and exercise intolerance.[29]

ETIOLOGY OF PERIPHERAL SKELETAL MUSCLE DYSFUNCTION

Figure 3 summarizes the main etiological factors of peripheral skeletal muscle dysfunction in patients with COPD. Changes in skeletal muscles have been related to various factors, including decreased physical conditioning, metabolism of amino acids, systemic inflammation and oxidative stress. The different mechanisms are briefly described herein.

Decreased conditioning

When exposed to repetitive dynamic situations, patients with COPD present an increase in the ventilatory demand, which forces them to avoid these activities and, as a consequence, they suffer from chronic sedentary behavior.[29] This, in turn, reduces strength and muscle mass, as well as aerobic capacity, resulting in an even more intense ventilatory demand for the same dynamic activities, closing the dyspnea-sedentary lifestyle-dyspnea cycle.[29] Due to this knowledge and to findings in the literature, it became necessary to investigate the changes in muscle function that might be responsible for the exercise intolerance seen in patients with COPD.[15,29]

Muscle fiber redistribution (with an increase in the percentage of type I fibers, a decrease in oxidative enzymes and the maintenance of glycolytic enzymes commonly found in patients with COPD) has been related to hypoxemia.[15] However, various authors have reported that muscle fiber redistribution is a consequence of immobility, a situation that principally affects type I fibers. In addition, the fact that the functional, morphological and bioenergetic changes are totally reversible after appropriate reconditioning programs[39] reinforces the participation of chronic reduction in conditioning as the main mechanism of the peripheral skeletal muscle dysfunction.

The bioenergetic changes found in patients with COPD are explained, in part, by the chronic reduction in conditioning frequently present in these patients. In normal individuals, during periods of inactivity, there is initially a reduction in the aerobic capacity due to the reduction in the

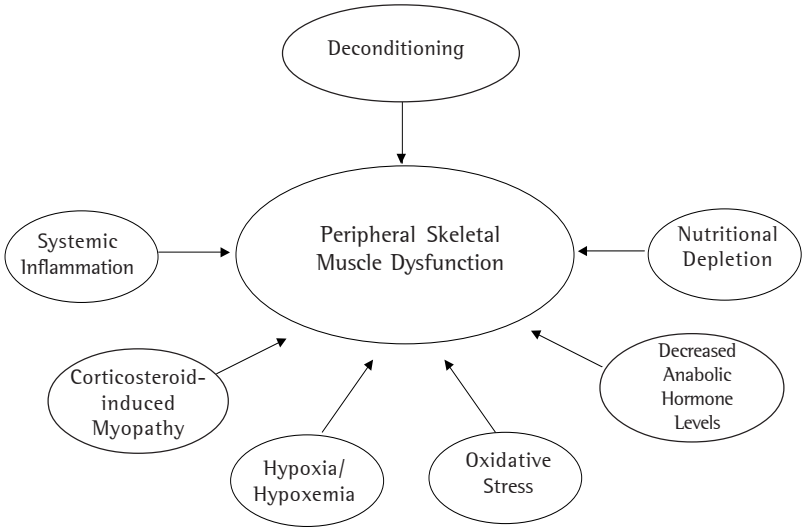

Figure 3 - Physiopathology of musculoskeletal dysfunction in chronic obstructive pulmonary disease

systolic volume and in the cardiac index and, subsequently, there is a reduction in the capacity to extract oxygen.[42] In normal individuals, the mitochondrial density can be increased, doubling its value over five weeks of training. However, a week of inactivity is responsible for the loss of 50% of what was achieved in five weeks of training.[42] Three or four weeks of reconditioning are needed for the mitochondrial density to recover its previous density.[42]

Similarly, in biopsies performed on the anterior tibial and deltoid muscles,[44,45] no enzyme changes were observed in the vastus lateralis. In a study evaluating the anterior tibial enzyme profiles of patients with COPD who were not treated with corticosteroids (n = 15), patients under treatment with prednisolone (n = 14), and homogeneous controls (n = 10), the results presented no evidence of changes in the enzyme profiles of the two groups of patients with COPD. Similarly, other authors[45] evaluated the enzyme and muscle fiber profiles in patients with COPD and in homogeneous control individuals through deltoid biopsies. Those authors found no differences between the groups. There was no redistribution of muscle fibers, and the concentration of citrate synthase was found to be similar between the group of patients with COPD and the control group.

The evidence of unchanged enzyme and muscle fiber profiles in postural and upper limb muscles implicates disuse as the main cause of muscle changes in patients with COPD. First, the anterior tibial muscle plays a role in posture maintenance. Therefore, it is essentially comprised of type I fibers and is constantly active. Second, most of the daily activities are performed using the upper limbs, and this propitiates almost constant activity for the deltoid. The high degree of activity of these muscles probably guarantees the preservation of muscle function, structure and bioenergetics.

The influence of the metabolism of amino acids

Some COPD manifestations jeopardize the metabolism of amino acids and promote muscle loss in affected patients.[37] Patients with COPD present changes in the profile of plasma and skeletal muscle amino acids.[37] Lower serum concentrations of glutamate, glutamine and alanine have been found in patients with emphysema who suffer from nutritional depletion.[46] In addition, branched chain amino acids, especially alanine, are found in low plasma concentrations in patients with COPD. This reduction is more evident in patients with lower than normal body weight.[47]

These amino acids perform various important functions: alanine interferes with glyconeogenesis; glutamine is metabolized in the liver and in the gastrointestinal tract, energizing leukocytes and fibroblasts; and glutamate participates in all transamination reactions in the skeletal muscles.[37]

The influence of systemic inflammation

Production of insulin-like growth factor 1, which mediates the growth hormone anabolic action, is counter-regulated by TNF-a, IL-1 and IL-6.[48] In addition, elevated levels of IL-6 correlate negatively with levels of testosterone and dehydroepiandrosterone, which also have anabolic effects.[34] The negative effect that IL-6 has on the functional capacity of elderly individuals has been described by some authors.[49] Higher IL-6 levels are associated with poor survival rates and significant impairment of the functional capacity in elderly individuals.[50]

The influence of the pro-antioxidant metabolism

Some authors have suggested that the participation of the imbalance of the pro-antioxidant metabolism in patients with COPD is an important mechanism in the determination of musculoskeletal dysfunction in this population.[51-52] In 2003, some authors[51] evaluated the systemic oxidative stress caused by localized exercise of the quadriceps. The authors measured the plasma levels of thiobarbituric acid reactive substances and the production of oxygen-derived free radicals as an index of oxidative stress index and the vitamin E levels as antioxidants. Patients with COPD presented significantly lower quadriceps muscle resistance than did homogeneous control individuals. The concentration of thiobarbituric acid reactive substances was significantly higher in patients with COPD six hours after having performed the exercise. In patients with COPD, vitamin E levels were significantly lower than in the control individuals, and thiobarbituric acid reactive substances were found to correlate negatively and significantly with vitamin E, a correlation not found in control individuals.

Other authors[52] evaluated, through vastus lateralis biopsy, reduced glutathione activity and oxidized glutathione activity in seventeen patients

with COPD and five homogeneous control individuals. When the individuals were submitted to only one session of submaximal training, there were no significant differences in the reduced glutathione or in the oxidized glutathione profiles, either in the patients with COPD or in the controls. However, when the analysis was performed after an eight-week treatment regimen (five sessions per week), there was a significant increase in the reduced glutathione levels in the control group, whereas, in the individuals with COPD, there was no statistically significant difference. These findings suggest that patients with COPD are incapable of improving their antioxidant capacity after a physical conditioning regimen, in contrast to what commonly occurs in healthy individuals.

TREATMENT STRATEGIES

Aerobic exercise

Aerobic exercise is recommended for individuals with COPD and should be initiated regardless of the COPD stage at which the patient is determined to be.[8] This kind of training increases mitochondrial oxidative enzyme levels, capillarization of the trained muscles, aerobic threshold and maximum oxygen uptake, as well as decreasing creatine-phosphate recovery time, thereby resulting in greater exercise tolerance.[42]

Strength training

Since muscle weakness contributes to exercise intolerance in individuals with chronic pulmonary disease, strength training is a rational option in the pulmonary rehabilitation process.[29] Currently, there is evidence that this training can result in a significantly greater improvement of the quality of life than that provided by aerobic exercise.[53] Although researchers and health professionals debate the importance of muscle strength in the functional capacity of patients with COPD, there is no consensus regarding the implementation of strength training in pulmonary rehabilitation programs.

Neuromuscular electric stimulation

Neuromuscular electric stimulation has been routinely used in the rehabilitation of patients with neuromuscular and orthopedic disease. There is mounting evidence that it can also be useful in patients presenting peripheral skeletal muscle dysfunction and exercise intolerance resulting from systemic diseases.[54]

Neuromuscular electric stimulation can be especially useful in patients presenting severe COPD and significant musculoskeletal dysfunction. The benefits of this type of therapy might be particularly evident in patients with intense dyspnea, who are incapable of performing even extremely light activities. In this type of patient, neuromuscular electric stimulation might alleviate the effects of the muscle dysfunction, making it possible for them to participate in pulmonary rehabilitation programs involving physical conditioning.[55]

Antioxidant therapy

Oxidative stress plays an important role in the physiopathology of COPD. In view of this, antioxidant therapy seems to be a rational strategy for patients affected by the disease. To date, the main antioxidant available for the treatment of patients with COPD is N-acetylcysteine.[56] This antioxidant can reduce the rate of annual decrease in forced expiratory volume in one second in patients with COPD. Some authors,[56] in a multicenter study, reported no influence of N-acetylcysteine on the forced expiratory volume in one second of 523 patients who were in follow-up treatment for three years. However, the functional residual capacity was significantly decreased in the group treated with N-acetylcysteine. Further investigation is needed, especially regarding the effects that antioxidant therapy has on COPD progression, on the frequency of exacerbations and on symptom relief.

OTHER EFFECTS

Influence of the use of corticosteroids

Together with muscle dysfunction, osteoporosis is also frequent in patients with COPD. The use of corticosteroids, inhaled or systemic, can cause bone loss in these patients, although there are also studies that show decreased bone density in those who did not receive corticosteroids.[57]

Patients under treatment with corticosteroids for more than a month can present a significant decrease in testosterone levels, resulting in sexual dysfunction.[17] The corticosteroid dosage is inversely proportional to the serum levels of testosterone, probably due to corticosteroid-induced suppression

of the secretion of gonadotropin-releasing hormone by the pituitary gland.[17]

Patients with COPD who are under prolonged treatment with corticosteroids present less muscle strength than do those who are not. Studies with rats revealed that corticosteroids stimulate proteolysis, inhibit protein synthesis and hinder amino acid transport to muscle cells. Corticosteroids and acidosis activate the ubiquitin pathway, which is known to increase protein degradation, especially in those patients using corticosteroids due to exacerbations.[17]

Cardiovascular diseases

Patients presenting low forced expiratory volume in one second have a higher risk of death due to cardiovascular diseases. It has been shown that there is a association between baseline pulmonary function values and the incidence of coronary disease and cerebrovascular diseases.[58] The inflammatory process seen in patients with COPD might be the mechanism responsible for this association.[3]

Some authors,[59] in a study of 6629 patients, showed there is a correlation among airway obstruction, systemic inflammation, and the increase in heart diseases. The presence of an inflammatory process, evidenced by the increase in C-reactive protein levels, caused an up to two-fold increase in the risk of heart diseases in the group of patients with severe obstruction in comparison to the group in which there were no alterations in the spirometric tests.

Similarly, low doses (50-200 µg) of inhaled corticosteroids have been shown to reduce the risk of acute myocardial infarction in patients with COPD.[60] The present study raises the hypothesis that the anti-inflammatory effect of corticosteroids modifies the expression of genes related to the inhibition of the synthesis of cytokines such as IL-2, IL-6 and TNF-a, as well as influencing endothelial adhesion, enzyme levels and levels of other proteins involved in inflammation. However, further studies are needed in order to investigate the effects of anti-inflammatory treatment on the risk of acute myocardial infarction in patients with COPD.

CONCLUSION

According to what has been discussed above, COPD must be considered a systemic disease, and the extrapulmonary manifestations must be considered in the evaluation of its severity. In addition, the treatment of these manifestations could modify the prognosis of these patients. Further studies elucidating the systemic manifestations, especially those affecting nutritional status and peripheral skeletal muscle function, are needed for the development of new treatment strategies, which might improve the exercise tolerance and the overall health status of these patients.

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