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REVIEW ARTICLE ON SYSTEMIC EFFECT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

SANKET K . LANGORE[1*] , Dr. KALYAN R. LANGORE [2], MAYUR K. KOLHATKAR [3], PROF. GAURAV WADURKAR [4]

[1] DEPARTMENT OF PHARMACOLOGY, HSBPVT , GROUP OF INSTITUTION FACULTY OF PHARMACY , KASHTI , SHRIGONDA , AHMEDNAGER, MAHARASTRA , INDIA , 414701

[2] DEPARTMENT OF PHARMACOLOGY, HSBPVT , GROUP OF INSTITUTION FACULTY OF PHARMACY , KASHTI , SHRIGONDA , AHMEDNAGER, MAHARASTRA , INDIA , 414701

[3] DEPARTMENT OF PHARMACOLOGY, HSBPVT , GROUP OF INSTITUTION FACULTY OF PHARMACY , KASHTI , SHRIGONDA , AHMEDNAGER, MAHARASTRA , INDIA , 414701

[4] DEPARTMENT OF PHARMACOLOGY, HSBPVT , GROUP OF INSTITUTION FACULTY OF PHARMACY , KASHTI , SHRIGONDA , AHMEDNAGER, MAHARASTRA , INDIA , 414701

ABSTRACT:

Chronic obstructive pulmonary disease (COPD) is a significant and increasing burden worldwide. Classically, COPD was considered only as a respiratory disease mainly caused by smoking. However, COPD has important extrapulmonary manifestations, or so-called systemic effects. These include unintended weight loss, skeletal muscle dysfunction, increased risk of cardiovascular disease, osteoporosis and depression. Low-grade chronic systemic inflammation is one of the main mechanisms of these systemic effects. Because these extrapulmonary manifestations of COPD are common and/or can significantly affect patient well-being and prognosis, they require systematic screening and appropriate treatment to provide optimal medical care.

INTRODUCTION :

In the latest update of the GOLD guidelines, chronic obstructive pulmonary disease (COPD) is defined as “a preventable and treatable disease with significant extrapulmonary effects that may contribute to the severity of individual patients” (1). This definition represents a very significant change from the traditional view of the disease, which mostly focused on chronic airflow obstruction. This new understanding of the disease has implications for patient care. Here, we review the scientific evidence behind this change and discuss its clinical implications and significance.

SYSTEMIC EFFECT OF COPD :

The pathogenesis and clinical manifestations of COPD are not limited to pneumonia and structural remodeling. Rather, this disease is associated with clinically significant systemic changes in biochemistry and organ function. Systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute phase proteins. Indeed, endogenous oxidant-antioxidant imbalances have been reported in patients with COPD exacerbations, and others have observed changes in circulating levels of several cytokines and adhesion molecules in patients with stable disease. As with other chronic inflammatory conditions, patients with COPD often experience weight loss, muscle and tissue wasting. Patients with COPD exhibit selective wasting of fat-free mass with impaired respiratory and peripheral muscle function and reduced exercise tolerance. Indeed, weight loss may directly contribute to a poor prognosis in patients with COPD. The mechanisms behind weight loss and muscle loss are not fully understood, but are likely to involve an imbalance in the ongoing processes of protein breakdown and replacement. This may include changes in the relative levels or activity of endocrine hormones such as insulin, growth hormone, testosterone and glucocorticoids. In addition, chronic systemic inflammation involving cytokines such as interleukin-1 and tumor necrosis factor-α may be associated with these hormonal changes and muscle wasting in COPD patients. This review discusses the mechanisms of protein metabolism/catabolism in skeletal muscle fibers, the potential roles of endogenous cytokines in protein loss, and the possibility that new drugs that inhibit cytokine signaling may be useful in reducing muscle wasting and cachexia, improving prognosis and quality of. life in patients with COPD.

TYPES OF SYSTEMIC EFFECT OF COPD

- BODY CELL MASS WESTING COPD

- SYSTEMIC INFLAMMATION
- TISSUE HYPOXIA
- WEIGHT LOSS AND NUTRITIONAL ABNORMALITIES
- NERVOUS SYSTEAM EFFECT

BODY CELL MASS WESTING COPD

Several studies have shown mainly a loss of muscle mass in patients with COPD, especially in the lower limbs. Based on studies with incubated muscles and muscle extracts, there is now sufficient evidence that the ATP-dependent ubiquitin-proteasome pathway is responsible for most of the increased proteolysis in various types of muscle atrophy. Several adaptations indicating activation of the ubiquitin-proteasome pathway have been found that appear to be common to many different forms of muscle atrophy. However, how most muscle proteins are ubiquitinated and degraded remains unclear. In addition, variations in the mechanisms causing muscle atrophy, especially the rate or order of degradation of individual muscle proteins and differences in the activation of ubiquitin enzymes under different catabolic stimuli, must be investigated.

A direct effect of TNFα on differentiated skeletal muscle cells was reported by Li et al32, who showed that TNFα treatment of differentiated myotubes induced a time- and concentration-dependent decrease in total protein content and loss of mature myosin heavy chain content. These changes occurred at TNF concentrations similar to those measured in patients. The TNF signal was partially transduced by NF-κB activation, and TNFα rapidly stimulated ubiquitin conjugation to muscle proteins. In addition to energy disturbances or disturbances in the balance of anabolism and catabolism, muscle wasting can be caused by a decrease in the number of fibers due to changes in the regulation of skeletal muscle regeneration or activation of apoptotic pathways. Muscle regeneration as part of the adaptive response of skeletal muscle depends on the activation of satellite cells. This is the process by which dormant progenitor cells are stimulated to proliferate and then distinguish the myogenic bHLH family of transcription factors and another class of transcription factors tightly regulated by myocyte enhancer factor-2. Guttridge et al33

recently reported that in myocyte differentiation, TNF-induced NF-κB activation inhibited skeletal muscle differentiation by repressing MyoD mRNA at the post-transcriptional level. MyoD is expressed in proliferating undifferentiated myoblasts and is important for the repair of damaged or atrophied tissue. In differentiated myotubes, a combination of TNF and interferon (IFN)γ signaling was required for MyoD silencing and skeletal muscle fibrodysfunction. Therefore, inflammatory mediators such as TNFα and IFNγ appear to affect skeletal muscle regulation in two steps: (1) by preventing the formation of new muscle fibers and (2) by degeneration of newly formed myotubes and failure to repair damaged skeletal muscle. Langen et al3 evaluated the effects of inflammatory cytokines TNFα and IL-1β on myocytes and found that TNF-induced NF-κB activation disrupted muscle protein expression in differentiating myoblasts; muscle creatine kinase activity and the amount of myosin heavy chain (MyHC) were significantly reduced after 72 h of TNFα exposure. A causal relationship between NF-κB activation and inhibition of myogenic differentiation can be clearly demonstrated. The present findings suggest that inflammatory cytokines may promote muscle wasting by inhibiting myogenic differentiation through an NF-κB-dependent pathway, and direct inhibition of NF-κB may be beneficial in reducing muscle wasting associated with cachexia.

SYSTEMIC INFLAMMATION :

It is now accepted that an excessive/inadequate pulmonary inflammatory response to various harmful inhaled gases or particles (mainly cigarette smoke) is the main pathogenic mechanism of COPD . Several studies have shown that the pneumonia response is characterized by 1) increased no. with a predominance of neutrophils, macrophages and T-lymphocytes CD8; 2) increased levels of proinflammatory cytokines such as leukotriene B , interleukin (IL)-8 and tumor necrosis factor (TNF)-α; and 3) evidence of oxidative stress caused by inhalation of oxidants (tobacco smoke) and/or activated inflammatory cells mentioned above. . Less well understood, similar inflammatory changes can also be observed in the systemic circulation of these patients, e.g. signs of oxidative stress, the presence of activated inflammatory cells and elevated plasma levels of pro-inflammatory cytokines. This concept is key to understanding the systemic effects of COPD.

TISSUE HYPOXIA :

Several findings support a possible pathogenic role of tissue hypoxia in the development of SMD in COPD. First, chronic hypoxia suppresses protein synthesis in muscle cells, causes a net loss of amino acids and reduces the expression of myosin heavy chain isoforms Second, healthy subjects lose muscle mass at high sea level (hypobaric hypoxia). Third, the skeletal muscle of patients with COPD and chronic respiratory failure is structural (reduced type I fibers) and functional (mitochondrial cytochrome c) . upregulation of oxidase) changes according to arterial hypoxemia. If tissue hypoxia plays a pathogenic role, home oxygen therapy in COPD may have a beneficial effect on SMD.

WEIGHT LOSS AND NUTRITIONAL ABNORMALITIES:

Unexplained weight loss is one of the most commonly recognized systemic effects of COPD. It occurs in approximately 50% of patients with severe COPD, but can also be seen in approximately 10-15% of patients with mild to moderate disease, and is largely due to decreased skeletal muscle mass . Weight loss always occurs when caloric intake and consumption do not match. The reduced caloric intake does not seem to be particularly marked in these patients, except during periods of exacerbation. Thus, it is unlikely that a significant proportion of people will be defined as unexplained weight loss. In contrast, most patients with COPD have an increased basal metabolic rate . If this is not achieved at the same time as increasing caloric intake, weight loss will occur. Systemic inflammation, tissue hypoxia and drugs used in the treatment of COPD (eg β2-agonists) may contribute to increased metabolism in COPD . The first of them is now considered to be the main pathogenic factor.

Unexplained weight loss in COPD has a poor prognosis. Interestingly, however, the prognosis is reversible if patients gain weight . More importantly, this predictive value is independent of other measures, such as FEV1 or PaO2, which assess the degree of pulmonary dysfunction. Therefore, weight loss identifies a new systemic domain of COPD that must be considered in the management of patients with COPD. The so-called BODE index (a composite score that includes body weight (according to the body mass index), the degree of airflow obstruction (expressed as FEV1 value, expressed as a percentage of the control value), the degree of dyspnea perceived by the patient (determined by the

MMRC questionnaire) and the physical load of the person (determined by the 6- with the minute walking test)) are better predictors of COPD mortality than FEV1 alone

Nervous system effects :

Different regions of the nervous system may be abnormal in patients with COPD. For example, the use of nuclear magnetic resonance spectroscopy has recently shown that cerebral bioenergetic metabolism is altered in these patients . Does this represent a physiological adaptation to chronic hypoxia as occurs at altitude 157 or can it be considered another systemic effect. COPD mediated by other unknown mechanisms is unclear. Another possible systemic effect of COPD on the central nervous system is related to the high incidence of depression in these patients . It is possible that this is simply a physiological response to a chronic debilitating illness. However, it is equally likely that there may be a link to the systemic inflammation associated with COPD, since TNF-α and other cytokines and molecules such as nitric oxide have been implicated in the pathogenesis of depression in several experimental modelS. Defining these issues may open up new treatment options for COPD.

Finally, some recent data suggest that the autonomic nervous system may also be altered in patients with COPD . Takabatake et al. showed indirect evidence of abnormal control of the autonomic nervous system in patients with COPD, especially in patients with low body weight, and associated deregulation of the normal circadian rhythm of leptin. Given that leptin has important effects on neuroendocrine function, appetite regulation, body weight control and thermogenesis in humans and that previous studies have shown decreased plasma leptin levels in COPD patients , these findings may be related to pathogenesis. SMD and weight loss in COPD.

SYSTEMIC EFFECTTIN WOMEN WITH COPD :

There has been a dramatic change in the sex ratio of COPD at the population and clinical levels. Classic textbooks recommended that doctors rule out COPD in patients with the triad of the elderly, men and smokers. Some of the large COPD randomized controlled trials (RCTs) that have been conducted in the past did not even include women.

Therefore, it was surprising to many to learn that more women than men died of COPD in the United States in 2000. Similar trends were observed in Canada, Great Britain, Finland and other countries. A demographic change has been observed as women live longer and smoke more, putting them at greater risk of developing COPD. Globally, it is worth noting that in all but three countries (Norway, Sweden and New Zealand), and only since 2003, women have never smoked as much as men. In recent population studies, women with COPD are as common as men, and recent large RCTs have had no problems enrolling women with COPD. Comorbidities specific to women, such as gynecological and peri- and postmenopausal disorders, are expected to be seen in the COPD spectrum.

CONCLUSIONS :

COPD is associated with low-grade chronic systemic inflammation, which likely underscores many of the systemic effects described so far. In clinical settings, these systemic effects frequently result in many comorbidities that have a significant impact on patient health and prognosis. Moreover, most of them are treatable, highlighting the importance of aggressive search and treatment for optimal and comprehensive management of the disease.

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