Research progress on the mechanism and drug treatment of chronic obstructive pulmonary disease

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Abstract: Chronic obstructive pulmonary disease is a heterogeneous lung disease, which is characterized by chronic respiratory symptoms such as cough, expectoration and dyspnea caused by abnormal respiratory tract and/or alveolar abnormalities, resulting in persistent and progressive airflow obstruction. Patients show systemic inflammatory response and impaired lung function. Failure to intervene in a timely and effective manner will directly threaten the life safety of patients. Therefore, in-depth understanding of the pathogenesis of COPD and targeted implementation of effective treatment mechanisms are essential for patients to restore health and strive for survival opportunities.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem with high morbidity and mortality, which brings huge burden to society and economy. With the aging of the population, changes in smoking habits and environmental factors, the prevalence of COPD is on the rise. Therefore, in-depth study of COPD has important public health significance and clinical value. In recent years, significant progress has been made in the field of COPD, involving disease mechanisms, treatment methods, and other aspects. However, COPD is still an incurable disease, and the quality of life of patients is seriously affected. Therefore, the research on COPD still needs to be deepened and expanded. This review aims to summarize and analyze the latest research progress in the field of COPD, focusing on the research of disease mechanism and treatment methods. It aims to provide a comprehensive perspective, contribute to the promotion of COPD research, and point out the direction for the treatment of COPD patients.

2. Overview of COPD

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive pulmonary disease (COPD), is a disease characterized by irreversible airflow limitation and progressive development. COPD is prone to occur in the elderly, but with the continuous changes of environmental pollution and lifestyle, the patients tend to be younger, and the incidence of COPD is increasing year by year. According to the existing data, the incidence of COPD in China is increasing year by year. In 2007, a large population study by Academician Zhong Nanshan showed that the overall prevalence of COPD in China was 8.2% [1].A cross-sectional study conducted by Wang Chen et al. from 2012 to 2015 showed that the overall prevalence of COPD in people aged 20 and above in China was 8.6%, of which the prevalence of people aged 40 and above was 13.7% [2]. According to the 2016 Global Burden of Disease (GBD) data, COPD ranks eighth among the top 30 major diseases that cause disability-adjusted healthy life year losses, and it has risen to fifth in China. The World Health Organization and the World Bank speculate that the fifth leading cause of disability in the world will become chronic obstructive pulmonary disease in 2030. The global burden of disease data points out that in 2015, the third leading cause of death in the world has become chronic obstructive pulmonary disease, and the number of deaths due to chronic obstructive pulmonary disease is expected to increase to 4.5 million in 2030, accounting for 8.5% of global deaths. The direct medical expenses of COPD patients in China are as high as USD 3565 per person per year, accounting for 118.09% of the per capita annual income, and the economic burden of patients is very heavy [3]. COPD seriously affects the quality of life of patients and is the third leading cause of death in China [4].Emphysema, chronic bronchitis, airway inflammation, and pulmonary parenchymal lesions were typical symptoms of COPD. Cough, progressive dyspnea, and expectoration were iconic symptoms. COPD patients have difficulty breathing, resulting in shortness of breath or fatigue. In the early stage of the disease, COPD patients have shortness of breath after activity. With the development of the disease, dyspnea or even inspiratory

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difficulty occurs, which gradually weakens the patient's respiratory function. COPD is mainly related to long-term chronic inhalation of gases containing harmful particulate matter, especially smoking, burning organic fuels such as firewood and particulate matter in haze. In addition, kitchen fuel, air pollution and some genetic factors are also associated with the incidence of COPD.

The pathogenesis of COPD mainly includes four aspects: inflammatory mechanism, oxidative stress mechanism, airway remodeling reaction and genetic factors.The mechanism of inflammation in the pathogenesis of COPD is mainly some inflammatory cells play a role including macrophages, lymphocytes and neutrophils. Neutrophils cause chronic mucus hypersecretion by releasing bioactive substances such as neutrophil elastase. In addition, the inflammatory response also involves the imbalance between protease and anti-protease, resulting in COPD. The mechanism of oxidative stress is mainly due to the increase of inflammatory factors IL-1β, IL-6, TNF-α in the blood of patients, which makes the airway wall thickened, aggravates airway obstruction and reduces airflow. The mechanism of airway remodeling mainly includes inflammatory response, extracellular matrix deposition, epithelial-mesenchymal transition and other processes, as well as transforming growth factor-β1, endothelin-1, matrix metalloproteinases and other cytokines to regulate the proliferation, differentiation and apoptosis of airway parietal cells, and promote the occurrence of airway remodeling. Genetic factors may also cause the occurrence of COPD, mainly because of the lack of α-1 antitrypsin in the body. When the level of α-1 antitrypsin is insufficient, trypsin will attack and damage lung tissue, leading to the development of COPD.

The treatment of COPD is mainly divided into two aspects: non-drug therapy and drug therapy. Non-drug treatment includes psychological intervention, respiratory training, exercise training, diet regulation, long-term oxygen therapy, and non-invasive positive pressure ventilation. Non-drug therapy has the advantages of non-invasiveness, adjustability, comfort and easy care. Drug therapy mainly includes bronchodilators, antibiotics, expectorant drugs, and traditional Chinese medicine therapy. The most commonly used bronchodilator is the β2-adrenoceptor agonist, which enters the body and binds to and interacts with the β2-adrenergic receptor to relax the airway smooth muscle by activating the adenylate-activating enzyme. Anticholinergic drugs are also commonly used bronchodilators, which relieve airflow limitation by inhibiting the release of acetylcholine from cholinergic nerve endings. Antibiotics mainly inhibit or kill the bacteria that cause infection, such as Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, etc. Help the body clear the source of infection to reduce inflammation. Expectorant drugs mainly reduce the symptoms of dyspnea and cough by removing mucus in the respiratory tract to improve the patency of breathing. Traditional Chinese medicine treatment can regulate immunity, relieve spasm and asthma, and also has the advantages of protecting lung function and diuresis.

3. Recent research and clinical diagnosis

In ancient times, the existence of COPD has been recognized, but it was not until the late 19th century and early 20th century that people began to study the symptoms, etiology and treatment of COPD in depth. Early studies mainly focused on the clinical manifestations and pathophysiological characteristics of COPD, such as airflow limitation, airway inflammation and lung tissue destruction. With the progress of medical science, in the 1960 s and 1970 s, people began to study the pathogenesis of COPD more deeply. At this stage, it is recognized that COPD is a complex disease caused by a variety of factors, including genetic factors, environmental factors and smoking. At the same time, some biomarkers and genetic variations related to the pathogenesis of COPD were also found.

After entering the 21st century, the research on the pathogenesis of COPD has made more significant progress. With the development of molecular biology, genomics and proteomics technology, people began to study the pathogenesis of COPD from the molecular level. For example, studies have found that patients with COPD have pathophysiological processes such as oxidative stress in airway and lung tissue, protease-antiprotease imbalance, inflammatory cell infiltration, and apoptosis. In addition, some genes and signaling pathways related to the pathogenesis of COPD were found, such as inflammatory factors, growth factors and apoptosis-related genes [5]. In recent years, with the rise of precision medicine and individualized treatment concepts, the study of the pathogenesis of COPD has also paid more attention to the role of individual differences and genetic factors [6]. For example, through the study of genomics and phenomics, it has been found that there are significant genetic and phenotypic differences between different COPD patients, which provides new ideas and methods for the accurate diagnosis and treatment of COPD. In addition, the diagnostic techniques of COPD are also constantly innovating.

In recent years, with the continuous development of medical imaging technology, especially the wide application of high-resolution CT, it is now possible to detect the possible imaging manifestations of emphysema, gas trapping, airway wall thickening and fibrosis in the lungs before the abnormality of lung function. Pulmonary function test is also a commonly used diagnostic technique. During pulmonary function test, continuous airflow limitation occurs and FEV1/FVC<70% after inhalation of bronchodilators, which is a necessary condition for the diagnosis of COPD. The emergence of biomarker diagnosis can better reflect the disease activity and fluctuate with the disease state, which is closely related to the occurrence and development of the disease. This contributes to the early prevention and treatment of COPD, disease assessment and risk prediction. In terms of treatment strategies, in addition to traditional drug treatment, non-drug treatment methods, such as pulmonary rehabilitation and oxygen therapy, have been actively explored. In addition, the application of traditional Chinese medicine in the treatment of COPD has

also received extensive attention, showing unique advantages.

4. Mechanism of COPD

4.1. Inflammatory mechanism

COPD is a chronic airway inflammatory disease, which mainly affects the airway, lung parenchyma and pulmonary vessels. Airway inflammation is the main cause and main pathological changes of COPD. Inflammation can damage airway epithelial cells, make airway submucosal gland hypertrophy, goblet cell hyperplasia and ciliary dysfunction, lead to mucus accumulation and airway obstruction [7]. In COPD, airway inflammation is primarily mediated by a diverse array of inflammatory cells, including neutrophils, macrophages, Tlymphocytes, and others. A significant number of neutrophils are accumulated in the airway of COPD patients under oxidative stress, which can secrete serine proteases, including matrix metalloproteinase (MMP) and neutrophil elastase (NE) [8]. MMP is significantly elevated in patients with emphysema and traverses the extracellular matrix of the lung, which has been degraded by serine proteases. This results in airway remodelling and a heightened susceptibility to infection in neutrophils. When patients with chronic obstructive pulmonary disease are stimulated by infection, neutrophils leave the circulation and gather in the lungs, protecting cells and surrounding tissues by engulfing infectious factors, forming proteases and bactericidal proteins, and producing ROS. T This is a vital mechanism for the body to protect itself from the damaging effects of free radicals and an inducer of oxidative stress. Furthermore, the efficacy of neutrophil migration and aggregation is contingent upon an individual's level of physical fitness. Consequently, COPD is more prevalent in the elderly population, which is correlated with the expression of phosphatidylinositol 3-kinase (PI3K). Inhibition of type PI3K-δ or PI3K-γ can improve the accuracy of neutrophil migration. The activation of macrophages plays a pivotal role in regulating the onset and resolution of various inflammatory processes. In patients with COPD, the binding of interferon-γ (IFN-γ) secreted by Th1, CD8 + cells and B cells to IFN-γ receptors triggers a series of signalling cascades, resulting in the activation and differentiation of M1 macrophages. This, in turn, leads to the production of a large number of cytokines, including TNF-α, IL-1β and interleukin-6 (IL-6), according to the specific tissue site. Conversely, M2 macrophages are stimulated by a multitude of cytokines, including interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13), and facilitate airway remodelling through the remodelling and repair of damaged tissues. The inflammatory factor IL-6 produced by neutrophils and macrophages can induce the production of elastase and oxygen free radicals, increase pulmonary vascular permeability, and aggravate the destruction of lung tissue. Furthermore, TNF-α is capable of regulating endothelial adhesion molecules, accumulating polymorphonuclear leukocytes, and releasing a substantial quantity of elastase and ROS-damaged alveolar epithelium. In the progression of COPD, TNF-α [9] will induce an inflammatory cascade reaction in conjunction with IL-1β. In patients with COPD, macrophages and neutrophils infiltrate the airway, upregulate chemokines such as monocyte chemoattractant protein (MCP-1, CCL-2), and release a substantial number of inflammatory factors, thereby indicating their potential role in the pathogenesis of COPD.

Airway inflammation plays a key role in the pathogenesis and development of COPD. It can lead to airway mucosal congestion, edema, increased secretions, and airway smooth muscle contraction and other pathophysiological changes. These changes make the airway narrow and airflow limited, resulting in typical symptoms such as cough, expectoration and asthma. Airway inflammation also destroys the normal structure of the airway and lung tissue, leading to emphysema and other lesions. With the progress of the disease, airway inflammation will further aggravate, forming a vicious circle, making the patient 's lung function gradually decline.

4.1.1 Oxidative stress mechanism

Oxidative stress is involved in the development of a variety of inflammation, which is an important pathogenic factor of COPD. The stimulation of soot to patients can cause lung cell damage. Excessive mucus secretion and neutrophil accumulation produce a large amount of reactive oxygen species (ROS). Oxidative inactivation of anti-protease is lost due to ROS, and the structure of lung tissue is destroyed. The accumulation of neutrophils also leads to the activation of a large number of inflammatory factors, which produces more ROS and aggravates oxidative stress. The oxidative system is involved in the secretion of airway epithelial mucus. When stimulated by toxic gases such as cigarettes, oxidative stress is produced, leading to a large accumulation of ROS and regulating related mucus genes such as Muc5b [10] and mu5ac [11].In addition, epidermal growth factor [12] is also involved in mucus production. The 3ignalling pathway of these factors often exists in the activation of airway cells by oxidants, which is involved in the occurrence of COPD. In the destruction of lung tissue structure caused by protease-anti-protease imbalance, α-1-antitrypsin is the most active one, and its inactivation is the most critical factor. A large number of oxidants released by harmful gases, oxidative stress also inactivates anti-protease, and eventually protease-anti-protease imbalance occurs. Oxidative stress also enhances lung inflammation by regulating oxidative sensitive transcription factors such as nuclear factor NF-κB (NF-κB) and activator protein 1 (AP-1), releasing a large number of cytokines such as IL-1β and tumor necrosis factor-α (TNF-α). In addition, the accumulation of ROS reduces the activity of histone deacetylase (HADC) and increases the activity of histone acetyltransferase, which may lead to further aggregation of inflammatory cells, especially neutrophils. Therefore, in the pathological sections of chronic obstructive pulmonary disease, we often observed a large number of neutrophil infiltration. If COPD worsens, excessive

oxidative stress can cause inflammatory cells to accumulate and produce a large amount of ROS and then the systemic response occurs. Nuclear factor E2 (Nrf2) regulates antioxidant genes. In the oxidative stress response, Nrf2 dissociates. It is then transported to the nucleus to activate the transcription of antioxidant genes. Due to the decrease of Nrf2 level, the self-protection mechanism of COPD patients is weakened, resulting in a decrease in the production of endogenous antioxidants [13].

4.1.2 Mechanism of airway remodeling

Airway remodeling is an important mechanism of COPD, especially small airway remodeling (diameter less than 2mm) is the main cause of persistent airflow limitation in COPD.Currently, it is believed that airway remodeling in COPD is inseparable from inflammatory response, extracellular matrix deposition, epithelial-mesenchymal transition and other major aspects. Harmful substances such as cigarette smoke stimulate airway epithelial cells and produce a large number of inflammatory cells to infiltrate the airway, causing repeated damage and repair of airway wall tissue, resulting in airway remodeling [14]. Chronic inflammation of COPD due to neutrophils, macrophages and other continuous aggregation, release of TNF-α, IL-8 and other inflammatory factors, the destruction of lung structure. Phosphorylation of NF-κB can promote the expression of inflammatory mediators, thereby activating the inflammatory response of airway and lung parenchyma, and causing airway wall damage [15]. Extracellular matrix (ECM) is mainly composed of collagen, elastin, proteoglycan and fibronectin. It mainly maintains tissue stability and elasticity, participates in cell migration and control behavior. The high expression of MMP-9, MMP-12 and other proteases can also cause the degradation of pathological matrix proteins [16]. Metalloproteinase tissue inhibitors promote collagen synthesis and fibroblast proliferation [17]. The imbalance of MMPs/TIMPs leads to the destruction of extracellular matrix function, resulting in the imbalance of collagen and fibrin, and eventually develops into airway remodeling [18]. Harmful substances stimulate airway inflammation and oxidative stress, induce airway epithelial cell dysfunction and epithelial-mesenchymal transition (EMT). It is characterized by changes in tissue, cell and molecular components, which affect airway smooth muscle, epithelial-mesenchymal transition, blood vessels and extracellular matrix. [19] Transforming growth factor-β (TGF-β) induces the transformation of fibroblast muscle fiber cells, aggravates the process of epithelial fibrosis, and increases the deposition of ECM. The adhesion between epithelial cells decreased, and the cytoskeletal protein changed. As the cell migration ability increased, the related signaling pathways were activated, ECM was over-deposited, epithelial cells were fibrotic, and the damage of the small airway parenchymal structure of COPD was aggravated, thereby aggravating airway remodeling.

4.1.3 Genetic factors

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease that can be caused by a variety of factors, including genetic susceptibility. One of the genetic factors is α-1 antitrypsin deficiency (AATD), which has been identified as an important factor in the development of COPD. In addition, there are other genetic variants with less impact, which can be combined with AATD or alone to increase the risk of COPD. AATD is a genetic disease characterized by a lack of α-1 antitrypsin, a protein that helps to protect the lungs from damage caused by enzymes released during inflammation. When α-1 antitrypsin levels are insufficient, trypsin attacks and damages lung tissue, leading to the development of chronic obstructive pulmonary disease, even in people who never smoke. It is worth noting that not all AATD patients develop COPD because other environmental and lifestyle factors also play a role. However, compared with the general population, the risk of AATD patients is much higher. AATD-related COPD usually occurs at an earlier age, usually between 30 and 40 years old, and is characterized by a faster progression of pulmonary function decline. AAT is an important anti-inflammatory protein, and its genetic variation may lead to decreased AAT levels or weakened function, thereby increasing the susceptibility to COPD. There may be an interaction between genetic factors and environmental factors, which together affect the incidence of COPD. For example, smoking is one of the major risk factors for COPD, and some genetic variants may increase the degree of lung damage caused by smoking, thereby increasing the risk of COPD. In general, there is a correlation between COPD and genetics, and genetic factors play an important role in the pathogenesis of COPD. However, COPD is a multifactorial disease that requires a combination of multiple factors to assess risk and develop preventive measures.

5. Treatment and mechanism of COPD

5.1. Non-drug therapy

5.1.1 Psychological Intervention

Patients with chronic obstructive pulmonary disease are more likely to have bad psychology such as worry and anxiety due to the disease. At this time, they should pay attention to the psychological changes of patients at any time, communicate with patients, and inform patients about the pathological knowledge of the disease in detail, so as to make them correctly understand, clarify the importance of psychological adjustment to their treatment, increase the compliance of treatment, and help to establish good interpersonal relationships, which will be more beneficial to the recovery of the disease. For some patients with anxiety and irritability, relaxation training can be appropriately carried out, and patients can also be shown movies to help patients relieve anxiety, divert attention and maintain optimism. In addition, health education should be carried out to guide patients to actively

participate in the process of pulmonary rehabilitation, and to understand the basic knowledge of COPD, drugs and instruments. At the same time, it can also set up small lectures, telephone interviews, and other educational methods to improve knowledge mastery.

5.1.2 Breathing training

Muscle strength training and endurance training are common ways of breathing training. (1) Muscle strength training: Exhaled muscle exercise and inspiratory muscle exercise were achieved by special instruments. The inspiratory muscle training commonly used in clinical practice includes CO2 hyperventilation and resistance breathing, which can increase the inspiratory muscle strength of patients and improve the symptoms of dyspnea. (2) Endurance training: how to assist patients in the use of respiratory muscles when breathing, reduce respiratory work, through the endurance training of respiratory muscles. If you persist in training for a long time, the patient 's diaphragmatic activity will increase, and the symptoms of dyspnea will also be improved. Abdominal breathing is a commonly used breathing method in clinic. Abdominal breathing method: to guide the patient in the abdomen at the same time, the left and right hands were placed in the abdomen and chest position, with the nose deep inspiratory, exhaled by the mouth of the abdomen, repeated training with hand pressure, each 10~20 min/times, 2~3 times/d. Long-term adherence to abdominal breathing training has a significant alleviating effect on pulmonary dysfunction and dyspnea, and has a promoting effect on health. Breathing: take supine, upright or semi-supine position, whistling lips when exhaling, gently blow out the gas in the lungs, exhale for 4~6 s/time, inhale with the nose, 5~10 min/time, 1 time/d.

5.1.3 Sports Training

Common clinical rehabilitation exercises include weightlifting, throwing balls and dumbbell exercises. Lower limb training includes jogging, swimming, treadmill exercise, running, etc. The patient 's exercise tolerance and immunity are improved through exercise training, and then improve the quality of life. The American Heart and Lung Rehabilitation Association recommends that exercise programs should be 8~12 weeks, 2~5 times/week, and 20~30 minutes/time. If respiratory failure occurs, it is recommended to inhale low-flow oxygen for a long time. According to the actual situation of the patient, the exercise cycle should be adjusted reasonably, and the exercise intensity should be paid attention to. The intensity and method of exercise directly affect the rehabilitation effect of the lungs. Intermittent exercise, the former uses exercise-rest-exercise multiple times in a short period of time, which is easy for patients to accept. The latter refers to those patients with better physical fitness, after reaching the target heart rate, will exercise for a specified time to improve their exercise endurance.

5.1.4 Diet regulation

Patients should pay attention to control the amount of oil eaten, eat more food that is beneficial to moistening the intestines, eat more vegetables and fruits that promote gastrointestinal motility, so as to avoid the occurrence of constipation. At the same time, eat more easily digestible food, eat more eggs, milk and vegetables, etc., eat less talk, adhere to a small number of meals, reasonable control of the diet. Advise patients to pay attention to control the consumption of more oil food, eat more food conducive to bowel defecation, eat more vegetables and fruits, promote the peristalsis of the gastrointestinal tract, avoid constipation. At the same time, eat more digestible food, eat more eggs, milk and vegetables, eat less talk, adhere to a small number of meals, reasonable control of diet.

5.1.5 Long-term oxygen therapy

Long-term oxygen therapy is an important method in pulmonary rehabilitation. Long-term oxygen therapy can significantly alleviate the patient 's hypoxia syndrome, and ultimately improve the patient 's respiratory muscle fatigue. Exercise, smoking cessation and oxygen therapy are common rehabilitation training methods for patients with COPD. The oxygen source of general oxygen therapy is a home oxygen generator, oxygen bag or compressed oxygen cylinder with oxygen flow of 0.5 ~ 2.5L / min and daily oxygen inhalation time > 12h through bilateral nasal catheters. Studies have shown that oxygen therapy is proportional to the clinical efficacy of oxygen time. However, due to the low compliance of most patients with oxygen therapy, it is difficult to achieve effective clinical efficacy. Therefore, we should strengthen the health education of oxygen therapy for patients, so that they have a full understanding of the importance of oxygen therapy.

5.1.6 Noninvasive positive pressure ventilation

For patients with severe chronic obstructive pulmonary disease and their unsatisfactory motor response, non-invasive positive pressure ventilation can be used to reduce the respiratory muscle load and the decline of ventilation function and lung function, so as to improve the symptoms of dyspnea. The clinical non-invasive positive pressure ventilation modes of pulmonary rehabilitation include pressure support ventilation, continuous positive airway pressure ventilation, and bi-level positive pressure ventilation. Among them, bi-level positive pressure ventilation is a common rehabilitation treatment mode, which can effectively improve the respiratory function of patients and improve the quality of life of patients.

5.2. Drug therapy

5.2.1 Single bronchodilator

The pathological mechanism of airflow limitation in COPD includes the decrease of elastic retraction force caused by the destruction of pulmonary emphysema and

the remodeling / destruction of small airways or the combination of the two. Among them, emphysema reduces elastic retraction force and small airway attachment point damage can cause small airway expiratory phase collapse; small airway remodeling is characterized by abnormal epithelial cell growth, smooth muscle hypertrophy and mucosal metaplasia. The increase of mucus secretion can lead to bronchial lumen obstruction and epithelial thickening. The change of airway surface tension makes it more inclined to collapse in the expiratory phase, which eventually leads to airflow obstruction. Studies have shown that when lung function has not yet been abnormal, small airway lumen stenosis and number reduction have occurred. It can be seen that small airway lumen stenosis and loss are early features of COPD patients. Therefore, relaxing the bronchus and preventing airway collapse is the main treatment principle of COPD. At present, inhaled bronchodilators are mostly used in the clinical treatment of COPD, among which long-acting bronchodilators are the best drugs. Long-acting β2 receptor agonists (LABA) and cholinergic receptor antagonists (LAMA) are effective vasodilators for patients with COPD. LABA/LAMA mainly acts on airway smooth muscle cells and postganglionic parasympathetic nerve cells, which can synergistically promote bronchodilation. In 2020, GOLD pointed out that for patients with chronic obstructive pulmonary disease, long-acting bronchodilators should be used for maintenance treatment as soon as possible before discharge from hospital after acute exacerbation. In the treatment of COPD patients, long-acting muscarinic receptor antagonists can not only block the muscarinic acetylcholine receptor expressed on tracheal smooth muscle to regulate the contraction function and airway hyperresponsiveness of the trachea, but also regulate the hyperresponsiveness and contraction function of the trachea through anti-inflammatory mechanisms. researchers used tiotropium bromide to treat COPD. The results showed that after treatment, the lung function of the patients was effectively improved, the level of inflammatory factors in the body was significantly reduced, the immune function was significantly enhanced, and there was no obvious adverse reaction. It has high safety, indicating that in the treatment of COPD, tiotropium bromide can be combined with smooth muscle cells to produce cholinergic receptors, which is conducive to improving nerve tension, effectively avoiding bronchial smooth muscle contraction, promoting airway relaxation, and expanding the bronchus. Long-term and effective treatment helps to improve the patient 's lung function, reduce the residual volume in the lung, strengthen the patient 's exercise endurance, and improve the quality of life.

5.2.2 Double bronchodilators

At present, the dual therapy mainly includes the combination of inhaled glucocorticoids and bronchiectasis, in which the bronchodilator is still an important cornerstone for preventing the progressive exacerbation of COPD patients. The combination of the two drugs can effectively reduce the risk of acute exacerbation of COPD, and play an anti-inflammatory role by blocking the muscarinic receptor M3 pathway. At the same time, the bronchodilator can also activate the β2 receptor, strengthen the anti-inflammatory effect, and better relax the airway smooth muscle. Xuan Wang Ning et al used budesonide formoterol combined with tiotropium bromide to treat asthma-COPD overlap (ACO). Budesonide formoterol is a compound preparation of glucocorticoid + long-acting β2 receptor agonist. The drug can play a complementary and synergistic role. After atomization inhalation, the patient can play a dual role of anti-asthma and anti-inflammatory, and has both quick and long-term advantages. However, patients with extensive use of hormone therapy can produce certain drug resistance. Tiotropium bromide is a highly selective new M choline receptor blocker, which can bind to M1 and M3 receptors on bronchial smooth muscle, thereby blocking the type transfer of M receptors and exerting relaxation of bronchial smooth muscle. Therefore, the combination of the two drugs has a significant effect on reducing the level of inflammation in patients, improving lung function and enhancing cellular immune function.

5.2.3 Antibiotics

Due to the increase of bacterial load in respiratory tract, the bacterial load of COPD patients increases with the aggravation of the disease. Compared with healthy people, COPD patients have more pathogenic bacteria colonized in the lungs. Respiratory system infection is an important cause of exacerbation of COPD patients, and Moraxella catarrhalis, Streptococcus pneumoniae, haemophilus influenzae, Mycoplasma pneumoniae infection are common susceptible pathogens [20]. Antibiotics have become the main drugs for the treatment of COPD. Macrolide antibiotics are secondary metabolites of a variety of actinomycetes. They not only have good antibacterial effects, but also inhibit mucus secretion, anti-inflammatory and immunomodulatory effects. They have a negative regulatory effect on the biofilm and help prevent the occurrence of increased infection in severe COPD patients with lower respiratory tract bacterial colonization. However, long-term use of an antibiotic treatment can easily increase the body 's drug resistance, which greatly affects the treatment effect. Zhang Yuanyuan et al. treated stable COPD by oral administration of low-dose azithromycin for different courses of treatment. The results showed that the lung function and quality of life of patients were effectively improved after treatment, but 6 months was the best course of treatment. Azithromycin, as a widely used macrolide drug in clinic, not only has antibacterial effect, but also has strong immune regulation function. It has a significant therapeutic effect on chronic inflammatory respiratory diseases, which is helpful to improve the immune level of the body and enhance the resistance to external pathogenic microorganisms.

5.2.4 Expectorant drugs

The expectorant drugs can stimulate the secretion of serous glands and mucous glands in the respiratory tract mucosa, and increase the amount of fluid in the respiratory tract. This helps dilute the sputum and make it easier to cough up. Antiphlegm drugs can reduce the viscosity of sputum, reduce the mucopolysaccharide components in sputum, and make sputum easier to flow and cough out. This helps relieve cough and dyspnea in COPD patients caused by thick sputum. Antiphlegm drugs can stimulate the cilia movement on the respiratory tract mucosa and accelerate the clearance of sputum by cilia. The movement of cilia helps push the sputum to the throat, making it easier to cough up. Some expectorants also have anti-inflammatory effects, which can reduce the inflammatory response of respiratory mucosa and reduce the release of inflammatory mediators. This helps to reduce respiratory inflammation in COPD patients and relieve symptoms such as cough and expectoration. By diluting sputum and promoting sputum excretion, expectorants can reduce airway obstruction and improve ventilation function. This helps to alleviate the symptoms of dyspnea in patients with COPD and improve the quality of life.

5.2.5 Chinese medicine therapy

There is no name of COPD in traditional Chinese medicine. According to the symptoms of the disease, it is attributed to the categories of ' lung distension ', ' cough ' and ' asthma syndrome '.It is believed that the occurrence and development of the disease are closely related to the factors such as the disorder of the lungs of the patients, which leads to the accumulation of phlegm turbidity caused by the weakness of internal qi and the unconsolidation of the lung. When phlegm accumulates into blood stasis, it can cause the patients to have loose striae and obstruction of nasal orifices. The coexistence of various internal unfavorable factors can further lead to the deficiency of the viscera of the patients. When the wind evil and cold evil are encountered again, it can cause the evil to invade the nasal orifices and the lung qi is not declared. Peng Junjie et al. used Guben Pingchuan Decoction combined with symptomatic treatment of stable COPD. After treatment, the TCM syndrome scores of the patients were significantly decreased, the lung function indexes were effectively improved, and the dyspnea grading was significantly improved. Guben Pingchuan Decoction contains traditional Chinese medicine such as roasted ephedra, astragalus and white mustard seed. The combination of various drugs has the effect of tonifying qi, relieving cough and asthma. Guben Pingchuan Decoction can regulate immunity, relieve spasm and asthma, and also protect lung function and diuresis.

6. Current problems

(1) Oral administration of drugs is the first-line treatment for COPD. Clinically, it is mainly symptomatic treatment such as anti-infection, bronchiectasis, and dilution of sputum. Bronchodilators, anticholinergic drugs, and theophylline drugs are widely used. Antibiotics and hormones are indispensable for alleviating acute bronchial-airway inflammation and oxidative stress in patients with COPD. However, with the progress of the disease, the patients' lung function gradually decrease, the treatment compliance decrease, and the adverse effects of hormones and other drugs are large. Long-term use will lead to many complications such as osteoporosis, pulmonary heart disease or respiratory failure, resulting in psychological pressure and economic burden. The treatment effect is not ideal. Moreover, the global drug therapy for COPD lacks drug therapy that can reverse the potential characteristics of airway remodeling, emphysema and vascular abnormalities. Although some new drug clinical trials are underway, only one new drug category has been approved for COPD treatment in the past 30 years. In addition, the availability of COPD drugs in low-and middle-income countries is also in urgent need of improvement, and many patients cannot afford the cost of COPD drug treatment. (2) Inhalation is the core of COPD treatment, but about 2/3 of COPD patients around the world can not use the inhalation device correctly. At the same time, patients ' compliance with inhalation therapy is also low due to mild symptoms, inconspicuous effects or concerns about side effects. These factors may affect the effect of inhalation therapy. (3) In terms of non-pharmacological interventions, access to advanced treatments such as endobronchial valves, lung volume reduction surgery, and lung transplantation will also be limited in some high-income countries, but almost impossible in low-and middle-income countries. This makes many COPD patients unable to obtain the best treatment options. (4) The level of early diagnosis and standardized diagnosis and treatment is insufficient, the incidence of COPD is hidden, the early respiratory symptoms are not obvious, and the rate of missed diagnosis is high; when there are obvious symptoms of airflow limitation (such as shortness of breath after activity, dyspnea), the decline of lung function and airway hyperresponsiveness are irreversible, and the prognosis is general. Although COPD has become a global health problem, its early diagnosis and standardized diagnosis and treatment are still low. Many patients fail to be diagnosed and treated in time, leading to disease progression and deterioration. (5) COPD is a chronic disease that requires long-term management, but many patients lack sufficient knowledge and skills to effectively manage their own diseases. This may lead to poor disease control, frequent acute exacerbations and decreased quality of life. In order to solve these problems, more research is needed to explore new pathophysiological mechanisms and intervention targets, and to develop more effective drug and non-drug treatment methods. At the same time, it is also necessary to strengthen patient education and self-management support, improve the ability of primary health care institutions to prevent and treat COPD, and promote health policy reform and resource allocation optimization worldwide.

7. Summary

COPD is a complex and heterogeneous disease with complex pathogenesis. If it is not treated in time and effectively after the onset, it will seriously endanger human health and even life safety. Therefore, early identification of the mechanism and treatment of COPD plays an important role in the condition and prognosis. In recent years, with the rapid development and progress of scientific research, there has been a more accurate and detailed study on the mechanism and treatment of COPD, so as to formulate a standardized and scientific rehabilitation treatment plan according to the actual situation of patients, which can not only improve the clinical symptoms of patients, but also reduce the burden of family and society, so that patients can recover at an early date.

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