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Drugs and Nutritional Supplements in the Therapy of Interstitial Pneumonia Complications in Post-COVID Fibrosis

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Abstract **Review Article**

Increased collagen synthesis is the cause of the disease fibrosis. Factors contributing to the development of fibrosis include chronic inflammation, infections, oxidative stress, autoimmune diseases, physical injuries, surgical procedures, long-term exposure to toxins, radiation therapy. Types of fibrosis are pulmonary, cardiac, renal, hepatic, intestinal, skin, skeletal muscle fibrosis. The aim of current study is the estimation of the potential beneficial effect of drugs and nutritional supplements in the therapy of Interstitial Pneumonia complicatioin in Post-COVID Fibrosis. The beneficial effect is shown of application of enzyme therapy using the product Fibrozim including the enzymes Serrazimes and Bromelain and antioxidant Quercetin ans Curcumin.

Keywords: Post-COVID Fibrosis, Interstitial Pneumonia, Serrazimes, Bromelain, Quercetin.

INTRODUCTION

I. Factors contributing to the development of fibrosis [1].

Fibrosis is a tissue degeneration, characterized with an excessive accumulation of connective tissue components in the extracellular matrix (ECM) area of tissues [1].

Factors contributing to the development of fibrosis include:

1. Chronic inflammation caused by conditions such as chronic liver inflammation (chronic hepatitis) or inflammatory bowel disease
2. Long-term infections such as tuberculosis
3. Oxidative stress [2]
4. Autoimmune diseases: rheumatoid arthritis or lupus are conditions in which the immune system mistakenly attacks its own tissues and fibrous tissue builds up.
5. Physical injuries
6. Surgical procedures
7. Long-term exposure to toxins, drugs or environmental pollutants – fibrosis of the lungs and liver.
8. Radiation therapy: can damage healthy tissues, causing fibrosis as a side effect.

II. Pathogenesis of fibrosis

The basic components of fibrotic tissue are collagen type I and III [1]. Disruption of collagen synthesis leads to disruption of the normal structure of tissues and organs. Collagen is the main structural protein in connective tissue, constituting 25% to 35% of the extracellular matrix. Collagen is composed of amino acids coiled together to form triple helices into elongated fibrils. It is found primarily in fibrous tissues such as tendons and skin. Common to all fibrotic diseases is the activation of myofibroblasts (a type of connective tissue cell) that produce extracellular matrix (the collection of substances surrounding cells in a given tissue type), which are key mediators of fibrous tissue remodeling [1].

The fibrosis process is associated with chronic inflammation, transforming growth factor-β1 (TGF-β1) signaling [3] and oxidative stress [2]. In the pathogenesis of fibrosis, oxidative stress plays a crucial role [4] by

promoting inflammation due to increasing the production of cytokines and growth factor TGF-β [5], and stimulation of myofibroblast differentiation and fibrogenesis. Pro-fibrotic factors and cytokines are among the mediators of fibrosis in lungs [6], heart [7], kidney [8] and liver [9].

III. Types of fibrosis

1. Pulmonary fibrosis

Pulmonary Fibrosis is connected with high levels of pro-inflammatory cytokines, such as interleukines [10].

2. Cardiac fibrosis

Cardiac fibrosis is caused by unsuitable fibroblast proliferation. Cardiac fibrosis affects the heart's ability to pump blood effectively. Angiotensin II stimulates collagen-secreting myofibroblasts via increasing fibroblast proliferation and differentiation. Transforming growth factor beta (TGF-β) mediates cardiac fibrosis [11] increasing the cardiac myofibroblasts production of fibronectin, and interstitial collagens [12].

3. Kidney fibrosis

Kidney fibrosis is a characteristic of the development of renal lesions and acute kidney injury contributes to renal fibrosis [8]. The renin-angiotensin-aldosterone system plays a potential role in epithelial-to-mesenchymal transition-induced renal abnormalities [13].

4. Chronic liver fibrosis

Chronic liver fibrosis is caused by chronic liver diseases such as hepatitis and is connected with cytokine release such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α) [14].

5. Intestinal fibrosis [15]

6. Skeletal muscle fibrosis [16]

7. Skin fibrosis: it is observed in cases such as scledederma [17].

IV. Pulmonary fibrosis

Pulmonary fibrosis is the process of replacing normal lung tissue with fibrous (connective) tissue, which leads to impaired lung function. Fibrosis is a dynamic process that occurs in phases. The local focus of sclerosis, in which a defect or focal necrosis is replaced, is called a cicatrix. This makes it difficult to transport oxygen in the blood and can lead to severe respiratory problems. The process develops gradually, and at first there may be no pronounced symptoms, but as the disease progresses, the symptoms become more and more obvious. Oxidative stress is an important factor for the developmemt of pulmonary fibrosis [2].

V. Types of pulmonary fibrosis [14]

1. Idiopathic Pulmonary Fibrosis (IPF)

This is the most common type of pulmonary fibrosis, in which the cause of the disease is unknown. IPF develops slowly and can lead to serious lung damage. High levels of pro-inflammatory cytokines, such as interleukines IL-1, IL-8, and IL-18 are produsedin the development of the disease [10]. Fibroblast transforming growth factor-β binding protein-2 [6] regulates lung fibroblast-to-myofibroblast differentiation in pulmonary fibrosis [3].

2. Pulmonary fibrosis due to inhalation of harmful substances

Inhalation of toxic chemicals, dust, gases, or other harmful substances, such as asbestos, can cause the development of pulmonary fibrosis. This condition is common in people who work in hazardous industries [10].

3. Pulmonary fibrosis in chronic diseases

Some chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and sarcoidosis can cause pulmonary fibrosis as part of their complications [10].

4. Fibrosis after infection

Some lung infections, such as pneumonia, can lead to permanent tissue damage and the development of fibrosis [10].

VI. Treatment of pulmonary fibrosis [14]

Treatment of pulmonary fibrosis includes:

1. Drug treatment

2. Oxygen therapy

In advanced cases, patients may need oxygen therapy to assist breathing and improve blood oxygen levels.

3. Lung physiotherapy

Physiotherapy can help improve lung function and relieve symptoms of shortness of breath and cough.

4. Lung transplantation

When the disease is in an advanced stage and other treatment methods are not effective, a lung transplant may be necessary.

VII. Drug treatment of pulmonary fibrosis

Drug treatment of pulmonary fibrosis includes [18].

1. Corticosteroids

For fibrosis associated with inflammation, corticosteroids may be prescribed. They help to reduce the inflammation in the lungs and relieve symptoms such as cough and shortness of breath. [19].

2. Antifibrotic drugs

Pirafenidone and Nindedanib are approved for the treatment of Idiopathic Pulmonary Fibrosis and slow the progression of the disease by reducing the formation of scar tissue in the lungs.

3. Immunosuppressive drugs

For fibrosis caused by autoimmune diseases such as rheumatoid arthritis or sarcoidosis, immunosuppressive drugs may be used due to they suppress the activity of the immune system and help to prevent damage of lung tissue.

4. Antioxidants – Vitamin C and Vitamin E

Reactive oxygen species play role in developmeut of fibrosis [20]. Vitamin C is a powerful antioxidant that plays a role in cell repair processes and is important for maintaining healthy connective tissue, which is a concern in pulmonary fibrosis. Vitamin E has antioxidant properties and may help to reduce the oxidative stress [21].

5. Omega-3 fatty acids

Omega-3 fatty acids, which are found in fish oil, flaxseed, and chia, are known for their anti-inflammatory properties. They can be very beneficial for patients with pulmonary fibrosis, as inflammation is a major factor in the development of this disease.

6. Glutathione

Glutathione is an important antioxidant that is produced by the body and plays an important role in protecting cells from oxidative stress and toxins. Low levels of glutathione can accelerate the development of lung diseases such as fibrosis, as the organs cannot effectively protect themselves from damage [21].

7. Curcumin

Curcumin, the main active ingredient in turmeric, is known for its anti-inflammatory and antioxidant properties [22]. It may also be extremely beneficial as an antioxidant for people with pulmonary fibrosis, as inflammation plays a key role in the development and progression of the disease [23].

8. Magnesium

Magnesium is an important mineral that plays a role in many physiological processes, including regulating muscle contractions, which is important for the proper function of the respiratory system. People with pulmonary fibrosis often experience muscle spasms and chest tightness, which can be relieved by magnesium supplements.

VIII. Post-COVID Fibrosis

Progressive pulmonary fibrosis is the final stage of damage caused by a heterogeneous group of chronic interstitial lung diseases, particularly Acute Interstitial Pneumonia (AIP) caused by the COVID virus. Pulmonary fibrosis is a condition characterized by the abnormal accumulation of connective (fibrous) tissue in the lungs. This process primarily affects the interstitium – the supporting fine connective tissue and the space between the alveoli and blood vessels in the lung.

1. Similarities between Post-COVID Fibrosis and Idiopathic Pulmonary Fibrosis (IPF)

The clinical and imaging features of Post-COVID Fibrosis are often similar to those of Idiopathic Pulmonary Fibrosis (IPF). Progressive dyspnea (shortness of breath) and nonproductive cough, which are hallmarks of IPF, may also be seen in patients after COVID-19. Computer tomography (CT) findings of reticular induration, consolidation, traction bronchiectasis, and even ”honey combing”. In both cases, there is deregulation of the repair processes after injury, leading to uncontrolled fibrosis.

2. Differences (the key) between Post-COVID Fibrosis and Idiopathic Pulmonary Fibrosis (IPF).

Post-COVID fibrosis requires a new diagnostic and therapeutic approach. The post-COVID-19 patient has a clear, identifiable cause (viral infection), while IPF is by definition idiopathic (of unknown cause). This may lead to a different response to therapy. Many patients with post-COVID fibrosis initially had organizing pneumonia (OP) or acute respiratory distress syndrome (ARDS), which is different from the gradual onset of IPF.

3. Potential for regression of Post-COVID Fibrosis.

There is evidence that in some Post-COVID Fibrosis, especially in the early stages, fibrotic changes may regress or stop progressing more effectively than in IPF. This necessitates a different therapeutic window.
COVID creates a new type of patient that is different from the classic IPF patient. In post-IPF fibrosis, the etiology is known.

Diagnosis is less about finding a cause and more about:

1. Assessing disease progression.
2. Excluding concomitant autoimmune diseases provoked by the virus.

4. Treatment of Post-COVID Fibrosis.

Treatment of Post-COVID Fibrosis include corticosteroids, antifibrotic drugs, enzyme therapy [18].

4.1. Corticosteroids.

Corticosteroids are used empirically in the subacute phase (up to 6 months) to control inflammation. Long-term use is dangerous and should be avoided. A rapid response is sought in the active phase, but they are stopped quickly to avoid the complications of prolonged immunosuppression. Respiratory diseases, such as chronic obstructive pulmonary disease, asthma, and pneumonia, are associated with significant morbidity and mortality. [24]. In patients with acute exacerbation of

idiopathic pulmonary fibrosis early corticosteroid treatnment is important [25].

Systemic corticosteroid drugs are common used in several respiratory diseases [26], such as COVID-19 [27] pneumonia, severe community-acquired pneumonia, ARDS acute respiratory distress syndrome: [28, 29], and asthma [30].

In patients with acute respiratory distress syndrome after application of corticosteroids, a decreased mortality has been observed [31].

Severe forms of COVID-19 are attributed to an inflammatory cytokine storm and corticosteroids use could have the potential to decrease upregulated inflammatory response [24]. The RECOVERY study has shown the role of corticosteroids: in severe COVID-19: in the group of 2104 patiemts treated with 6 mg orally or intravenously dexamethasone once daily for up to 10 days, a significantly lower mortality has been reported [32].

4.2. Antifibrotic drugs

The lungs are the primary target of infection. Coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome-virus 2 (SARS-CoV-2). Antifibrotic drugs are not routine treatment for all post-COVID patients, but are reserved for those whose condition worsens after 1 year of diagnosis [33]. Antifibrotics in pulmonary fibrosis [34] in post-COVID-19-induced severe pneumonia [35] are Nintedanib [35, 36] and Pirfenidone [35, 37]. Antifibrotics Pirfenidone and Nintedanib are used only in cases of proven progression and lack of regression after a thorough assessment of functional abnormalities. Nintedanib in the treatment of idiopathic pulmonary fibrosis blocks profibrotic signaling [36].

Pirfenidone is an anti-fibrotic drug approved for the treatment of patients with Idiopathic Pulmonary Fibrosis, the mechanism of action is based on the suppression of pro-fibrotic and pro-inflammatory signalling pathways as inhibition of TNF-α, TGF-β1, platelet-derived growth factor and collagen deposition [38]. Due to antiinflammatory and antifibrotic properties Pirfenidone can be effective against COVID-19 infection [39, 40].

4.3. Enzyme therapy with Serrazimes and Bromelain

In treatment of post-COVID fibrosis are applied natural components, such as enzymes (Serrazime, Bromelain) and antioxidants as Quercetin and Curcumin. Proteolytic enzymes are biologically active substances that participate in the breakdown of unnecessary or damaged protein structures in the body. One of the particularly effective representatives of this class is Serrazime I – a proteolytic enzyme, with fibrinolytic and anti-inflammatory effects. Like serrapeptase, Serrazime I supports the breakdown of fibrin – a protein involved in the formation of inflammatory plaques, adhesions and edema. Unlike serrapeptase, which is extracted from bacteria in the silkworm, Serazime I is isolated by fermentation from edible mushrooms *Aspergillus oryzae* and *Aspergillus melleus*, which makes it suitable for vegetarians and people with sensitivity to animal products [41].

Bromelain is a plant-based natural proteolytic enzyme, extracted mainly from pineapple (*Ananas comosus*). [42]. Bromelain is a cysteine protease [43], which breaks down fibrin and improves normal blood and lymph flow. has powerful anti-inflammatory and analgesic properties, is used to reduce swelling and muscle pain, supports immunity and has antioxidant activity [44].

Bromelain inhibits cyclooxygenase and modulates prostaglandins and thromboxane [45]. Bromelain alone [46]. Kumar and in combination with curcumin [47]. Kritis, can be used in the prevention of severe COVID-19, due to Curcumin exerts antioxidant activity [48].

Quercetin is a natural plant pigment (flavonoid) found in many fruits, vegetables, and grains (onions, apples, citrus, blueberries), known for its powerful antioxidant properties. Quercetin, as an anti-inflammatory compound is a potential treatment for severe inflammation in patients with COVID-19 [49]. From the experimental investigation a beneficial effect was reported when applying enzyme therapy using the product Fibrozime including the enzymes Serrazimes and Bromelain) and antioxidant Quercetin. Against COVID-19 positive effect exerts combination of bromelain, quercetin and vitamin C [50].

CONCLUSION

Post-COVID fibrosis is a clinically significant and distinct group. It is characterized by younger patients and, most importantly, by the potential for partial regression. An individualized and multidisciplinary approach is needed. Therapeutic decisions should be based on the dynamics of the process (progression vs. regression), not on a static diagnosis

Abbreviations

AIP	Acute Interstitial Pneumonia
ARDS	acute respiratory distress syndrome
CT	computer tomography
CTGF	connective tissue growth factor
ECM	extracellular matrix
IL	interleukines
IPF	Idiopathic Pulmonary Fibrosis
OP	organizing pneumonia
PDGF	platelet-derived growth factor
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study

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