Review

Medicine

Pathogenesis and Nutritional Intervention of Chronic Obstructive Pulmonary Disease-Associated Frailty

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Frailty, as a type of geriatric condition, has been a major focus of geriatrics researchers in recent years. COPD is one of the major risk factors associated with frailty. Consequently, chronic obstructive pulmonary disease-related frailty has become the focal point of numerous investigations. However, the majority of studies focus on cross-sectional investigations of the incidence of frailty in COPD and their associations. The study of its pathophysiology and intervention methods is dispersed, and there is a paucity of literature reviews. Moreover, in-depth research into the pathophysiology of such patients and the implementation of efficient therapeutic strategies are crucial for enhancing the long-term quality of life of patients. The purpose of this article is to provide a reference for creating nutritional intervention programs for chronic obstructive pulmonary disease and a debilitated population by describing the etiology of these patients and summarizing potential nutritional therapies based on recent research.

Keywords: Lung Disease; Chronic Obstructive Pulmonary Disease; Frailty; Pathogenesis; Intervention

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CHRONIC obstructive pulmonary disease (COPD) is on track to overtake heart disease as the third most prevalent cause of death worldwide due to its rising morbidity and mortality (1). Since COPD has a protracted course of illness, recurrent acute attacks, and progressive development, it not only has a negative impact on patients' health and quality of life but also places a significant financial burden on them, their families, and society as a whole due to high medical costs (2). Frailty is a type of decline in the physiological reserve of the elderly that results in increased body vulnerability, decreased resistance to infection, and other health problems. Studies have found that COPD patients frequently suffer from frailty. Frailty can also promote the further deterioration of COPD. An independent risk factor for bad outcomes in COPD is the generalized state of stress reduction (3). In order to serve as a guide for developing nutritional intervention programs for COPD-related frailty patients, this paper covers the potential pathophysiology and the advancement of nutritional interventions.

The Pathogenesis of COPD-Related Frailty

A number of mechanisms, including gut microbial activity, the inflammatory response, the oxidative stress response, signaling

pathway regulation, and growth differentiation factor (GDF) modulation may contribute to the occurrence and progression of COPD-related frailty.

Gut Microbiota

Numerous bacteria that are essential for preserving the body's delicate balance between health and disease reside in the gut. The "viscera-muscle axis" theory, which states that the intestinal flora may cause sarcopenia and frailty through a variety of factors, is being supported by research results on the pathogenesis of frailty (4, 5). One of these factors may be related to the regulation of gut microbes on appetite: the metabolites of various gut microbes may act as endocrine regulators of appetite and affect the host's appetite through hunger and eating habits (6), which can result in undernutrition, sarcopenia, and physical weakness. Short-chain fatty acids (SCFA), a molecule produced by the microbiota, can also increase mitochondrial activity (7), which has a significant effect on how well skeletal muscle cells operate. Accordingly, increasing mitochondrial fatty acid oxidation can cause skeletal muscle to remodel into an oxidative phenotype (8), whereas decreasing SCFA production in aging microbiota can result in a reduction in mitochondrial fatty acid oxidation capacity and increased intramuscular fat deposition. Intramuscular fat buildup encourages insulin resistance in skeletal muscle (9), a condition that eventually results in sarcopenia and frailty due to decreasing muscle mass and strength.

Hypoxia during the acute stage of COPD may increase intestinal permeability, result in the translocation of intestinal flora, and promote intestinal dysfunction (10, 11), all of which will weaken you. The damaged intestinal mucosa may obstruct digestion and nutrient absorption, which can result in malnutrition and further development into weakness. Additionally, hypoxemia and sympathetic nervous system activation in the acute phase of COPD may cause changes in intestinal perfusion, enterocyte hypoxia, and an impaired intestinal barrier (12). Finally, the intestinal flora may enter the tissues of the body along with blood circulation at the damaged endothelium. As can be shown, hypoxemia and COPD can readily lead to intestinal environment imbalance and malfunction, which makes it simpler to induce weakness via the underlying visceral-muscle axis mechanism (13). As a result, it's critical to monitor and modify the gastrointestinal function of COPD patients. Unbalanced gut flora may offer a fresh approach to treating COPD patients' crippling condition.

Irritation

The complicated process of lung inflammation in COPD is mediated by a number of inflammatory cells and transmitters, and it is a common progressive airway, alveolar, and microvascular inflammatory illness (14, 15). The structural cells of the airway and lung parenchyma and the lung interact with inflammatory cells such as macrophages, neutrophils, and lymphocytes, as well as inflammatory mediators like cytokines, chemokines, growth factors, and reactive oxygen species. When local inflammatory substances enter the bloodstream, the blood's amount of these factors rises, and further triggers systemic inflammatory responses (16). This ongoing chronic inflammation is regarded as a sign of accelerated biological aging and is frequently linked to aging or age-related illnesses.

Inflammatory substances have negative effects on the musculoskeletal metabolism and endocrine system, which can directly or indirectly cause debilitation (17, 18). The disruption of endothelial cell reactivity and muscle perfusion, as well as interference with the uptake of long-branched chain amino acids, which are crucial for muscle energy and protein anabolism, are the mechanisms through which inflammation impacts skeletal muscle metabolism. In addition, inflammation is linked to decreased insulin-like growth factor 1 (IGF-1) synthesis and activity, a growth factor essential for muscle regeneration and maintaining muscle integrity. The frailty of COPD patients is a result of inflammation's numerous effects on skeletal muscle, which lead to muscle degeneration, decreased muscular strength and mass, poor lower extremity function, and decreased mobility (19, 20). It is clear that in COPD patients, the inflammatory response interferes with the skeletal muscle cells' normal metabolism, causing a loss of muscle mass and functional impairment that encourages weakening. Therefore, by reducing the inflammatory response, it may be feasible to delay the onset of weakening in COPD patients.

Oxidative Stress

Reactive oxygen species (ROS) can build up in the body as a result of oxidative stress, which is the breakdown of the equilibrium between oxidation and antioxidation. The accumulating ROS cause oxidative damage to macromolecules, which in turn results in the gradual loss of tissue and organ function, according to the free radical aging theory, also known as the oxidative stress aging theory (21). As a result, several age-related illnesses, including frailty, have been linked to oxidative stress. Given that oxidative stress contributes to an increase in intracellular calcium, which encourages proteasome activity, one theory for the mechanism by which oxidative stress results in weakness is that it affects the functionality and strength of skeletal muscle. Increased activity impacts skeletal muscle function and bodily activity, speeds up muscle deterioration, and makes you weaker (22, 23). In all phases of COPD, oxidants and antioxidant abnormalities are common. Some COPD patients have an increased burden of inhaled oxidants together with an increase in the quantity of ROS produced by airway inflammation, immunology, and epithelial cells, which worsens oxidative stress in these individuals (24). There is proof that COPD patients' blood and lungs contain an unbalanced amount of oxidants and antioxidants (25). Numerous antioxidant deficiencies have been seen in COPD patients, and some studies have demonstrated that oxidative stress indicators are abundantly prevalent in the alveolar epithelial cell secretion of COPD patients (26). As can be observed, COPD patients are more likely to produce debilitation due to the unique nature of the disease, where they are more likely to cause a stress condition due to an imbalance between oxidation and anti-oxidation. Patients with COPD may be able to control their crippling condition by reducing the harm that oxidative stress causes.

Mammalian Target of Rapamycin (mTOR) Signaling Pathway: Akt/PI3K/Phosphatidylinositol 3-Kinase (PI3K)

Patients with COPD frequently have weakened muscles. Oxidative stress, malnutrition, inflammation, and poor gas exchange are the key contributors to muscular dysfunction. In addition to the aforementioned elements, the muscle PI3K/Akt/mTOR signaling pathway also has a significant impact on skeletal muscle strength and volume (27). A serine/threonine protein kinase called mTOR plays a crucial regulatory function in the development, proliferation, and differentiation of cells (28). In order to trigger a sequence of anabolism and restrict catabolism by activating mTOR, which controls mTOR, PI3K and Akt are important signaling molecules upstream of mTOR (29). The PI3K/Akt/mTOR signaling pathway controls cell development in part by inhibiting catabolism, which includes the autophagy of macromolecular proteins and the degradation of mRNA. Autophagy's programmed cell apoptosis, which is caused by the activation of the PI3K/Akt/mTOR signaling pathway, may play a significant role in the deterioration of skeletal muscle volume and quality, which may finally lead to sarcopenia (30). Poor physical function and sarcopenia are strongly connected, and the former can account for many clinical signs of frailty (31). Consequently, the PI3K/Akt/mTOR by controlling cell autophagy, the TOR signaling pathway may indirectly influence the development of frailty in COPD patients.

The GDF's Regulatory Impact

The characteristic frailty symptoms of weariness, lethargy, and decreased activity are more prevalent in COPD patients, and this decline in function is brought on by a reduction in muscle mass and muscle oxidative capacity, in which GDF plays a crucial regulatory role (32). The systemic characteristics of COPD, such as increased inflammatory signaling, oxidative stress, and hypoxia, can all cause an increase in the expression of GDF15, which is a stress-responsive growth regulator (33). GDF15 can lead to muscle wasting in patients with COPD and is related to muscle mass in those individuals (34). A study suggested that similar rodent studies have produced consistent outcomes because it was conducted on mice that expressed GDF15 in the front tibia. Following analysis of muscle fiber size, it was discovered that the expression of GDF15 dramatically decreased fiber diameter and moved the distribution of fibers to the left, suggesting that this protein either induced muscular atrophy or impeded muscle regeneration (35). One of the main causes of frailty is sarcopenia, which is brought on by muscular loss. Therefore, a significant contributor to frailty in COPD patients is the overexpression of GDF15. Along with GDF15, the absence of GDF11 may possibly be a significant contributor to frailty. GDF11 is abundantly expressed in skeletal muscle and has actions that are anti-aging, rejuvenating, and supportive of muscle regeneration. Lack of exercise is associated with a decrease in GDF11 in COPD patients (36). It is clear that the regulation of GDF may play a significant role in the development of COPD-related weakness and controlling GDF in the body may represent a future research focus for the prevention of COPD-related weakness.

Potential Use of Dietary Interventions in Reducing COPD Patients' Frailty

There are few intervention studies specifically focusing on frailty in COPD patients, so nutritional intervention may be the future target for COPD-related interventions. With an increase in nutritional intervention research on frail patients in recent years, the mechanism of nutritional intervention on frailty has gradually been revealed.

Improvement of Microbial Composition of the Gastrointestinal Tract

Inulin and fructooligosaccharides, two prebiotic components, have been linked in studies to an increase in the number of good bacteria in the gut, and selective fermentation of prebiotics has been shown to alter the composition of the intestinal flora, composition and activities of communities, potentially improving personal health (37, 38). Following a prebiotic diet can significantly lower and even improve one's level of frailty (39). The benefits of the Mediterranean diet on the human flora have also been confirmed, in addition to the prebiotic component's positive regulatory effect on the flora. Ghosh et al. conducted years of Mediterranean diet intervention, and the analysis of the flora before and after the intervention concluded that adherence to the Mediterranean diet was associated with changes in specific flora, and the changes in flora were positively correlated with the reduction of interleukin-17 and C-reactive protein, two inflammatory indicators, in an antagonistic relationship (40). It is hypothesized that altering one's diet and eating habits, such as consuming prebiotics over an extended period of time or adopting a Mediterranean diet high in protein and vitamins with a variety of vegetables, fruits, fish, different beans, grains, and olive oil, may be able to significantly improve the intestinal microbial environment of COPD patients, thereby reducing their crippling symptoms. Therefore, improving the food composition may be a useful strategy to reduce COPD-related debility.

Lessening of the Production of Inflammatory Chemicals

Frailty is strongly linked to the amount of inflammatory markers in the blood, and nutritional intervention can control the body's level of inflammation, which influences how frailty develops. The active ingredient, n-3 polyunsaturated fatty acid (n-3 PUFA), comes from deep-sea fish (41). Some scientists think that n-3PUFA helps prevent systemic chronic inflammation brought on by COPD because it is an anti-inflammatory drug (42). n-3PUFA in the diet can be processed by homologous enzymes that compete with n-6PUFA, decreasing the n-6PUFA metabolites' ability to cause inflammation (43), which has a significant regulatory impact on suppressing inflammatory responses. The aforementioned viewpoint was also supported by a survey of 274 COPD patients undertaken by de Batlle et al. and discovered a link between systemic inflammation in COPD patients and dietary intake of n-3 PUFAs, with higher intake being associated with systemic inflammation (44). In COPD patients, n-3PUFA can lower the level of tumor necrosis factor (TNF), one of the serum inflammatory markers (45). Additionally, n-3PUFA can successfully improve muscular motor performance and lower the incidence of frailty (46).

The motor performance of COPD patients can be greatly improved by the n-3PUFA dietary supplement, which contains 340 mg, 700 mg of eicosatetraenoic acid, 1,200 mg of linolenic

acid, 760 mg of linolenic acid, and 400 mg of stearic acid (47). Therefore, patients with frailty related to COPD may want to think about including n-3 PUFA dietary supplements. In addition to unsaturated fatty acids, vitamin D has been shown to reduce systemic inflammation (48). The use of vitamin D in anti-inflammatory intervention studies is already widespread, but the consistency of vitamin D's ability to reduce inflammation across groups and its potential role in the prevention and treatment of COPD patients with severe symptoms are yet unknown. Accordingly, vitamin D should only be taken as a supplement when there is a deficiency rather than on a regular basis to fend off weakness (49). Therefore, further studies on vitamin D's effectiveness for patients with COPD-related frailty are required.

Mitigation of the Harm Brought on by Oxidative Stress

The mechanism by which diet controls aging is currently the subject of comparatively little research, and the internal interactions between the two remain rife with uncertainty. However, it is certain that nutrition can control the body's degree of oxidative stress, which in turn affects how quickly people age (50, 51). Whey protein has antioxidant benefits primarily because it can increase the availability of reduced glutathione and the activity of endogenous antioxidant enzyme systems (52). Early nutritional intervention can significantly lower the levels of advanced oxidation protein products (AOPP) and erythrocyte malondialdehyde (MDA) in COPD patients (53). It demonstrates the value of early nutritional support, such as whey protein, in enhancing antioxidant function, minimizing oxidative stress-related damage to the body, and delaying the onset of debilitation. Additionally, because COPD is a hypermetabolic disease, patients still need a lot of energy while at rest, and dietary supplements are sometimes insufficient to meet this need (54). This can easily result in malnutrition. Therefore, it is crucial for COPD sufferers to consume enough protein. Older people with chronic illnesses or malnutrition should consume 1.2-1.5 g of protein per kg of body weight every day (55). Therefore, the recommended protein intake for COPD patients can still be studied, and additional interventional studies will be required in the future to confirm it.

Effective Nutritional Fatigue Management

Fatigue is a key indicator of aging frailty in the elderly. There is not enough knowledge on the pathophysiological mechanisms behind fatigue, and there is no accepted method for measuring fatigue in clinical practice. Study has revealed that dietary inadequacies play a significant role in weariness (56). The body will catabolize stored energy to supply energy when protein and energy intake are insufficient to meet individual demands. This process consumes body fat and muscle and is followed by symptoms like weariness (57). However, this does not imply that consuming more nutrients is always beneficial. Excessive nutrient intake can have negative effects and consuming too many foods that promote obesity may also be a contributing reason for weariness (58). Cholecystokinin (CCK), a short-term satiety hormone released after consuming fat, rises in the blood after eating and may contribute to weariness by influencing the pattern of sleep (59). People with COPD-related weakness may not be able to consume foods high in calories, such as those high in fat and sugar. It may be helpful to draw ideas from some population studies on sleep disorders when determining which diets are appropriate for fragile COPD patients. According to certain research, there is a link between low-protein diets and insomnia, meaning that when the diet's protein content is less than 16% of the total calories, it will have a negative impact on the quality of one's sleep (60). On the other hand, consuming foods like fish, milk, and high-quality protein-rich fruits and vegetables can encourage sleep (61). Therefore, consuming these meals may help COPD patients feel less tired and better control their condition.

Conclusion

Because of the unique nature of the disease, COPD is vulnerable to debilitation. Gut microbiota, inflammatory response, oxidative stress response, signaling system, GDF regulation, and other factors may all play a role in the etiology of this disease. Nutritional therapy can alleviate patient fatigue, lessen inflammation, lessen oxidative stress damage, and alter the microbial community in the patient's gastrointestinal system. It might be a novel concept to lessen and prevent COPD patients' crippling frailty. It is therefore necessary to conduct more in-depth and more focused nutritional intervention research on COPD-related frailty patients in the future because the research on nutritional interventions for patients with COPD-related frailty is still relatively lacking and there are not many efficient intervention strategies for these patients.■

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