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CONTENTS

1 Acute Chest Syndrome in Patients with Sickle Cell Disease in Nigeria: Clinical Features and Management

Chinonso E. Okafor, Nsikak A. Etim, Ifeanyi C. Nwosu

7 Analysis of Nutritional Components of Common Tonifying Traditional Chinese Medicines and Research on Their Compatibility in Daily Diet

Jiatian Kang

12 The Role of NLRP3 Inflammasome in the Pathogenesis and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease

Ethan Radu

20 Primary Biliary Cholangitis (PBC): Prognosis and Treatment Procedures

Haradhan Kumar Mohajan

32 Exercise Interventions for Sarcopenia in Older Adults: Effects on Muscle Strength and Physical Function

Junjie Liu

41 A Prospective Cohort Study on Food-Medicine Homologous Intervention for People with Chronic Fatigue Based on Traditional Chinese Medicine Constitution Classification

Panyi Cao

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Acute Chest Syndrome in Patients with Sickle Cell Disease in Nigeria: Clinical Features and Management

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Abstract

Acute chest syndrome (ACS) is one of the most serious pulmonary complications of sickle cell disease and remains an important cause of hospitalization and death among affected patients. This issue is particularly relevant in Nigeria, where sickle cell disease is common and access to early diagnosis, blood transfusion, respiratory support, and specialist care may differ between medical settings. ACS does not usually result from a single cause. Pulmonary vaso-occlusion, infection, fat embolism, hypoventilation, and tissue hypoxia may occur together and lead to rapid deterioration. Patients may initially present with fever, cough, chest pain, tachypnea, or mild hypoxemia, while severe cases can progress to multilobar pulmonary involvement, marked oxygen desaturation, respiratory failure, and other systemic complications. The clinical picture may also differ between children and adults, which makes early recognition especially important. Diagnosis is mainly based on respiratory symptoms combined with a new pulmonary infiltrate on chest imaging, supported by laboratory findings and assessment of oxygenation. Clinical management requires more than treatment of the pulmonary lesion alone. Oxygen therapy, antibiotics, appropriate pain control, cautious fluid therapy, simple blood transfusion, exchange transfusion, and respiratory support may all be needed depending on disease severity. In Nigeria, delayed presentation, limited access to blood products, uneven availability of exchange transfusion, and restricted diagnostic resources may further complicate care. Better recognition of high-risk patients, earlier treatment, standardized hospital management, and improved long-term sickle cell disease care are therefore important for reducing severe ACS-related outcomes.

Keywords: sickle cell disease, acute chest syndrome, pulmonary complications, clinical management

1. Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder characterized by the presence of abnormal hemoglobin S (HbS). Under conditions such as hypoxia, dehydration, or infection, HbS can polymerize and make red blood cells more rigid. These altered cells may obstruct small blood vessels and contribute to vaso-occlusion, hemolysis, tissue ischemia, and repeated organ injury. Acute chest syndrome (ACS) is one of the most serious pulmonary complications of SCD and can develop during both childhood and adulthood.

ACS is generally defined by a new pulmonary

infiltrate on chest imaging together with clinical features such as fever, cough, chest pain, tachypnea, dyspnea, or hypoxemia. Its presentation is not always obvious at the beginning. Some patients are admitted for pain or fever and develop respiratory signs only later. Infection, pulmonary vaso-occlusion, fat embolism, and hypoventilation may all contribute to its development, which also explains why the clinical course can differ considerably between patients (Adegoke et al., 2024).

The condition is especially relevant in Nigeria because SCD is common and respiratory complications remain an important cause of hospital admission. In a multicenter retrospective study involving ten tertiary hospitals in Nigeria, Ibraheem et al. (2024) reviewed 7,256 hospital admissions among children and adolescents with SCD. Respiratory morbidities were identified in 1,213 cases, and ACS accounted for 26.7% of lower respiratory presentations. Of the 17 respiratory-related deaths recorded in the study, 11 occurred in patients with ACS. These findings show that ACS is not only a frequent complication in Nigerian clinical practice but also an important contributor to severe outcomes.

The Nigerian setting also affects how ACS is recognized and managed. Patients may present to hospitals with different levels of access to imaging, oxygen therapy, blood transfusion, and specialist hematology care. For this reason, early recognition is particularly important. The Paediatric Association of Nigeria has developed specific guidance for ACS in children with SCD, adapting some recommendations to local clinical conditions (Adegoke et al., 2024). This local approach provides an important basis for discussing the clinical features, diagnosis, and management of ACS in Nigerian patients.

2. Pathogenesis and Major Triggers of Acute Chest Syndrome

Acute chest syndrome develops through several interacting mechanisms rather than a single pathway. Pulmonary vaso-occlusion is one of the central processes. When oxygen tension falls, hemoglobin S polymerizes more easily, sickled red blood cells become less flexible, and blood flow through the pulmonary microcirculation is impaired. This can lead to local ischemia, endothelial injury, inflammation, and further hypoxemia, creating a cycle that may rapidly worsen respiratory function.

Infection is another major trigger, especially in children. Respiratory infection can produce fever, inflammation, and local hypoxia, all of which increase the tendency of red cells to sickle. Vichinsky et al. (2000) identified a range of bacterial, viral, and atypical pathogens in patients with ACS, although a definite infectious cause was not found in every episode. In Nigeria, infection is also clinically important because it can precipitate vaso-occlusive events through fever, dehydration, inflammatory responses, and changes in oxygenation (Ahmed, 2011).

Fat embolism is more often associated with severe vaso-occlusive episodes and is particularly relevant in older adolescents and adults. Bone marrow ischemia and necrosis can release fat droplets into the circulation, which may then reach the lungs and contribute to pulmonary injury. ACS can also develop after severe pain because chest or abdominal pain may limit deep breathing. Opioid-related sedation, surgery, or prolonged immobility may further reduce ventilation and promote atelectasis.

Other factors such as asthma, dehydration, and recent surgery can increase risk, but they usually act together with the main mechanisms rather than independently. In Nigerian children with SCD, a history of asthma has been associated with ACS, suggesting that pre-existing airway disease may make pulmonary complications more likely (Adegoke et al., 2015). Overall, ACS is best understood as the result of overlapping vaso-occlusion, infection, embolic injury, and impaired ventilation, with the importance of each factor varying between patients.

3. Clinical Features and Disease Progression

The clinical presentation of acute chest syndrome varies between patients. Common features include fever, cough, chest pain, tachypnea, dyspnea, hypoxemia, and sometimes wheezing. These findings are not specific to ACS, and early disease may resemble pneumonia or an uncomplicated vaso-occlusive crisis. Some patients develop clear respiratory symptoms at admission, while others are hospitalized mainly for pain or fever and show pulmonary involvement later.

Age influences the clinical picture. In a large study of patients with sickle cell disease, younger children more often presented with fever and cough, whereas adults were more likely to have shortness of breath, chills, severe pain, multilobar pulmonary involvement, and pleural effusion

(Vichinsky et al., 1997). Adults also tended to have longer hospital stays and more severe outcomes. This difference is clinically relevant because ACS in children may initially look like an acute respiratory infection, while in adults it may emerge during a severe painful crisis.

Chest examination can reveal crackles, wheezing, reduced breath sounds, or signs of consolidation, but these findings may be limited early in the illness. Oxygen saturation is therefore an important part of assessment, especially when it falls below the patient's usual level. Laboratory findings are also variable. Hemoglobin may decrease during an episode, while leukocytosis is common but nonspecific. Imaging usually shows a new pulmonary infiltrate, which may remain localized or extend to several lobes as the disease progresses (Vichinsky et al., 1997).

The course of ACS can change quickly. A patient who initially has mild respiratory symptoms may later develop increasing oxygen requirements, persistent tachypnea, more extensive infiltrates, and respiratory distress. Severe disease may progress to respiratory failure, neurological abnormalities, hemodynamic instability, or dysfunction of other organs. The direction of change is often more important than any single finding at admission.

A Nigerian case reported by Alli et al. (2012) illustrates this pattern. A 28-year-old man with sickle cell anemia was admitted with fever, severe chest pain, and a hemolytic crisis. He initially received antibiotics, intravenous fluids, analgesia, and blood transfusion. About 72 hours later, however, he developed severe hypoxemia and required transfer to intensive care, where oxygen therapy and circulatory support were provided. He later recovered. The case shows that ACS may develop or worsen after hospitalization rather than presenting as a complete respiratory syndrome from the beginning.

Broader Nigerian data support the same concern. In a multicenter study involving ten tertiary hospitals, Ibraheem et al. (2024) found that ACS was an important respiratory complication among children and adolescents with SCD and accounted for most of the respiratory-related deaths recorded in the study. Respiratory mortality was also more closely associated with the early period of hospitalization. These findings reinforce the need to pay close attention to new respiratory symptoms during the first days of admission.

Clinical progression should be suspected when oxygen saturation falls, respiratory rate continues to increase, pulmonary infiltrates become more extensive, or the patient develops greater work of breathing and fatigue. Previous ACS, frequent vaso-occlusive crises, asthma, and extensive pulmonary involvement may increase concern, but no single feature can predict the course in every patient. ACS is therefore best viewed as a dynamic complication whose severity may change over hours rather than a fixed diagnosis established at admission.

4. Diagnosis and Clinical Assessment

The diagnosis of acute chest syndrome is based on clinical symptoms together with a new pulmonary infiltrate on chest imaging. In patients with sickle cell disease, ACS should be suspected when fever, cough, chest pain, tachypnea, dyspnea, or hypoxemia appears, especially when these symptoms develop during hospitalization for a vaso-occlusive crisis. Because early manifestations may be mild or nonspecific, repeated assessment is often more useful than relying on a single examination (Howard et al., 2015; Adegoke et al., 2024).

Chest radiography remains the main imaging method for diagnosis. Pulmonary infiltrates may be focal or multilobar and can become more extensive as the disease progresses. Pulse oximetry is also important because a decline in oxygen saturation may indicate worsening pulmonary involvement. Basic laboratory tests usually include hemoglobin, white blood cell count, platelet count, and other routine indicators. These findings are most useful when compared with the patient's baseline values rather than interpreted separately. In patients with marked hypoxemia or respiratory distress, arterial blood gas analysis and further imaging may be considered.

Differential diagnosis can be difficult because ACS overlaps with several other conditions. Pneumonia is particularly important because infection may both resemble and trigger ACS. Pulmonary embolism, asthma exacerbation, atelectasis, pulmonary edema, and fat embolism should also be considered according to the clinical picture. Identifying one of these conditions does not always exclude ACS, since more than one process may be present at the same time (Vichinsky et al., 2000).

Clinical assessment should also determine

disease severity. Persistent hypoxemia, increasing oxygen requirement, multilobar infiltrates, marked tachypnea, falling hemoglobin, altered mental status, or hemodynamic instability suggest a more serious course. These findings should prompt closer monitoring and early escalation of care. In practice, the most important issue is not only whether the patient meets the diagnostic definition of ACS, but whether respiratory function is worsening over time.

5. Clinical Management of Acute Chest Syndrome

The management of acute chest syndrome should begin as early as possible because respiratory deterioration may occur even when the initial presentation appears moderate. Treatment usually combines oxygen therapy, antimicrobial treatment, pain control, careful fluid management, transfusion, and respiratory support according to disease severity. The main aim is to maintain adequate oxygenation while reducing factors that may worsen sickling and pulmonary injury. Nigerian pediatric guidance also emphasizes prompt treatment rather than waiting for the exact cause of an episode to be fully established (Adegoke et al., 2024).

Oxygen therapy is required when oxygen saturation falls below the patient's usual level or clear hypoxemia is present. Correcting hypoxemia is important because low oxygen tension can promote further sickling. Mild and moderate cases may respond to oxygen delivered through a nasal cannula or face mask, while patients with increasing oxygen requirements need closer observation. Persistent hypoxemia, greater work of breathing, or worsening mental status may indicate the need for non-invasive respiratory support or mechanical ventilation.

Antibiotics are commonly started early because infection cannot always be distinguished from ACS at presentation. Fever, cough, leukocytosis, pulmonary infiltrates, and hypoxemia may occur in both pneumonia and ACS, and infection itself is a recognized trigger. Vichinsky et al. (2000) identified bacterial, viral, and atypical pathogens in patients with ACS, although a definite infectious cause was not established in every episode. Empirical treatment should therefore cover common respiratory pathogens, with later adjustment according to microbiological findings, local resistance patterns, and clinical response.

Pain control also requires balance. Severe chest, back, or abdominal pain can limit deep breathing and promote atelectasis, so adequate analgesia is necessary. Opioids may be needed in significant vaso-occlusive pain, but excessive sedation can suppress ventilation. Patients receiving stronger analgesics should therefore be observed for changes in respiratory rate, oxygen saturation, and level of consciousness. Fluid therapy should also be cautious. Dehydration should be corrected, but excessive intravenous fluid may worsen pulmonary congestion. The goal is adequate hydration rather than routine aggressive fluid loading.

Measures that improve lung expansion can be useful, particularly when pain causes shallow breathing. Incentive spirometry has been shown to reduce pulmonary complications in hospitalized patients with sickle cell disease (Bellet et al., 1995). The Nigerian pediatric guideline also suggests practical alternatives, including repeated balloon blowing when a conventional spirometer is unavailable (Adegoke et al., 2024). Bronchodilators are mainly useful when wheezing, bronchospasm, or underlying asthma is present and are not required routinely in every ACS episode.

Blood transfusion becomes particularly important when ACS is associated with worsening anemia, persistent hypoxemia, or progression of pulmonary involvement. Simple transfusion can improve oxygen-carrying capacity and increase the proportion of normal red cells. It is most useful when hemoglobin has fallen substantially below the patient's baseline and the clinical condition is deteriorating. Transfusion should not simply aim to normalize hemoglobin, since excessive increases in hematocrit may increase blood viscosity in SCD. The decision should therefore be based on both the hemoglobin level and the overall clinical picture.

Exchange transfusion is generally reserved for more severe or rapidly progressive disease. By removing HbS-containing red cells and replacing them with donor cells, red cell exchange can reduce the HbS fraction more quickly while limiting the rise in blood viscosity. The American Society of Hematology suggests red cell exchange for severe ACS and considers it particularly relevant when the condition progresses rapidly, when simple transfusion produces an inadequate response, or when the baseline hemoglobin is already high enough to make further simple

transfusion less suitable (Chou et al., 2020).

Recent experience from Lagos shows that automated red cell exchange can be performed successfully in Nigeria. Adelekan-Popoola et al. (2026) reviewed 617 exchange procedures performed between 2020 and 2025, of which 74 were carried out for ACS. Across the full group, mean HbS fell markedly after treatment. The study is useful because it demonstrates that advanced transfusion therapy is feasible in a resource-constrained Nigerian setting. At the same time, access remains limited by equipment, trained personnel, blood supply, maintenance costs, and the concentration of specialist services in a small number of centers.

Respiratory support becomes necessary when oxygen therapy alone is no longer sufficient. Patients with persistent hypoxemia, increasing respiratory effort, acidosis, exhaustion, or altered consciousness should be assessed early for intensive care. Non-invasive ventilation may be useful in selected cases, but it should not delay intubation when respiratory failure is clearly progressing. In the National Acute Chest Syndrome Study, a proportion of patients required mechanical ventilation, showing that severe ACS can progress beyond the point where standard ward-level support is adequate (Vichinsky et al., 2000).

The Lagos case reported by Alli et al. (2012) also illustrates the need for repeated reassessment. Their 28-year-old patient initially received antibiotics, intravenous fluids, analgesia, and transfusion, but developed severe hypoxemia about 72 hours later and required intensive care support. The case shows that management cannot remain unchanged after the first treatment decision. When oxygen requirement rises, pulmonary infiltrates spread, or respiratory effort increases, treatment intensity needs to be adjusted quickly.

6. Challenges and Improvement of Management in Nigeria

The management of acute chest syndrome in Nigeria is affected by differences in access to diagnostic and treatment resources. Some patients are treated in tertiary hospitals with specialist hematology services, blood banks, imaging, and intensive care, while others first present to facilities with more limited support. This matters because ACS may initially resemble pneumonia or a vaso-occlusive pain crisis. Delayed recognition can reduce the time available for oxygen therapy, transfusion, or referral before severe hypoxemia develops. Nigerian multicenter data have shown that ACS is an important cause of respiratory-related mortality among hospitalized children and adolescents with SCD, which highlights the need for repeated respiratory assessment during the early stage of admission (Ibraheem et al., 2024).

Blood availability and access to exchange transfusion are also important limitations. Simple transfusion can be provided in many hospitals, but automated red cell exchange requires specialized equipment, trained personnel, compatible donor blood, and laboratory support. A five-year experience from Lagos showed that red cell exchange can be performed successfully in Nigeria and was used for ACS in a number of patients, but the program also faced difficulties related to cost, equipment maintenance, staffing, consumables, and blood supply (Adelekan-Popoola et al., 2026). For severe ACS, clearer referral pathways between general hospitals and specialist centers could help reduce delays in access to advanced transfusion and respiratory support.

Improvement should therefore focus on strengthening basic care at the point where patients first present. Hospitals treating patients with SCD should be able to recognize ACS early, monitor oxygen saturation, provide oxygen and appropriate supportive treatment, and identify signs that require urgent referral. The Paediatric Association of Nigeria guideline provides a useful local framework and adapts some recommendations to available resources (Adegoke et al., 2024). Long-term SCD management is also important. Regular follow-up, appropriate use of hydroxyurea, vaccination, infection control, asthma management, and patient education may reduce the risk of recurrent acute complications.

The main goal is not to make every hospital provide the same level of specialist treatment. A more practical approach is to ensure that basic recognition and stabilization are available widely, while severe cases can be transferred quickly to centers with transfusion, intensive care, and apheresis capacity. This would make the management of ACS more consistent without depending on advanced resources at every level of the health system.

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Analysis of Nutritional Components of Common Tonifying Traditional Chinese Medicines and Research on Their Compatibility in Daily Diet

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Abstract

Tonifying traditional Chinese medicines (TCMs) are widely applied in clinical TCM practice, primarily used to ameliorate physical debilitation and treat various deficiency disorders based on the TCM theory of "strengthening healthy qi and consolidating the root". In recent years, the concept of "medicine and food sharing the same origin" has gained increasing attention, and the application of tonifying TCMs in daily diets has expanded gradually. This paper takes several common tonifying TCMs including Ginseng, Astragalus, Chinese Angelica, Lycium barbarum, Polygonatum, Codonopsis and Hedysarum polybotrys as research objects. It sorts out major nutritional and active components such as polysaccharides, amino acids, trace elements, saponins and flavonoids contained in these herbs. Combined with recent relevant studies, this paper analyzes the correlation between these components and the tonifying effects of the herbs. Furthermore, integrating classical medicinal food compatibility experience and modern pharmacological research (covering immune regulation, cardiovascular protection, anti-hypoxia, intestinal microflora regulation and other fields), it discusses the scientific rationality of matching tonifying TCMs with daily food ingredients.

The study concludes that the nutritional and active components in these herbs not only scientifically explain their tonifying efficacy, but also form the material basis for daily dietary compatibility. Integrating the TCM principle of dietary therapy based on syndrome differentiation with modern nutrition science is an effective path to promote the rational development and utilization of tonifying TCMs. This paper can provide learning references for students majoring in TCM Resources and Development, and offer theoretical support for the research and development of health products.

Keywords: Tonifying traditional Chinese medicines, nutritional components, medicine-food homology, dietary compatibility, pharmacological effects

1. Introduction

Tonifying TCMs are categorized into four types: qi-tonifying, blood-tonifying, yin-nourishing and yang-warming, which are frequently used in both clinical prescriptions and daily health preservation. Statistics show that tonifying medicinal diets account for more than 30% of all therapeutic food recipes, serving as a vital approach to reinforce healthy qi and delay aging.

However, the application of these herbs used to rely merely on traditional experience, lacking modern scientific explanations for their material basis and functional mechanisms.

Thanks to the rapid advancement of analytical chemistry and pharmacology in recent decades, their mechanisms have been gradually clarified. Researches reveal that tonifying TCMs are generally rich in polysaccharides, oligosaccharides, various amino acids, trace elements including iron, zinc, calcium and selenium, as well as secondary metabolites such as saponins and flavonoids (Xie Y F, Jiang X M, Pan P, et al., 2025). These substances act as nutritional active factors from a nutritional perspective, and also serve as pharmacological substrates for immune regulation, anti-oxidation and energy metabolism improvement (Liu S S, Ai Q D & Chen N H., 2016). Notably, recent studies have indicated that they exert cardiovascular protective effects by regulating the composition of intestinal microflora and their metabolites (e.g., short-chain fatty acids, bile acids) (Le N Q, Liu Q, Tang Y, et al., 2026; Le N Q, Liu Q, Tang Y, et al., n.d.; Luo W, Feng L M & Zhu F., 2024). This innovative perspective provides a new angle to interpret the TCM concept of "strengthening healthy qi".

The term "medicine and food sharing the same origin" originally describes the unified origin of medicinal materials and food, and tonifying TCMs fall into both categories—they can function as nutritional supplements as well as conditioning agents for sub-health conditions. How to organically combine modern nutritional analysis with classical compatibility experience has become a valuable research topic in the field of TCM resource development. Starting from nutritional components, this paper combines pharmacological evidence to conduct a study on the nutritional components of common tonifying TCMs and their compatibility in daily diets.

2. Nutritional Component Characteristics of Common Tonifying TCMs

From the perspective of nutritional chemistry, tonifying TCMs contain abundant ingredients which can be generally divided into two categories. The first category consists of primary metabolites including polysaccharides, proteins, amino acids and trace elements, which mainly supply nutrients to the human body and sustain normal physiological activities. The second category includes secondary metabolites such as saponins, flavonoids and volatile oils, which are closely associated with pharmacological activities. Though the two types of components differ in functions, they often act synergistically in the human body. Therefore, tonifying TCMs possess both nutritional value and satisfactory tonifying efficacy.

2.1 Carbohydrates and Polysaccharides

Carbohydrates exist abundantly in tonifying TCMs and are the most extensively studied nutritional components. Characteristic substances of corresponding herbs, namely ginseng polysaccharide, astragalus polysaccharide, angelica polysaccharide, lycium barbarum polysaccharide and polygonatum polysaccharide, have been proven to exert biological activities including immune enhancement, anti-oxidation and anti-aging (Liu S S, Ai Q D & Chen N H., 2016). Taking Polygonatum produced in Wuling Mountain as an example, it contains high crude polysaccharide content with crude starch at 22.80% and crude protein at 3.32%, reflecting the dual value of such herbs for nutritional supplementation and physiological regulation. The inulin, fructose and oligosaccharides contained in Codonopsis have attracted growing attention in recent years, with great potential in regulating intestinal microecology. Overall, polysaccharides widely exist in tonifying TCMs with considerable content, which can be regarded as an important chemical marker distinguishing this category from other TCMs.

2.2 Amino Acid Composition and Trace Element Spectrum

Tonifying TCMs share highly consistent amino acid profiles. Lycium barbarum contains 18 kinds of amino acids, among which 8 are essential amino acids for human beings; Polygonatum contains 17 kinds, with medicinal amino acids accounting for 77.41% of total amino acids; Codonopsis also contains 17 kinds, including 7 essential amino acids. Such complete amino acid spectra enable these herbs to provide comprehensive nitrogen sources when used as dietary supplements.

In terms of trace elements, over 20 elements including iron, calcium, selenium, zinc, manganese and chromium have been detected in Chinese Angelica, and its blood-tonifying effect is largely related to high iron content. Calcium is the dominant macroelement in Polygonatum, while iron ranks first among its trace elements.

Xie Yefei et al. (2025) pointed out that the type and content of inorganic elements are closely correlated with herb quality and efficacy, while health risk assessment of harmful heavy metals should also be conducted, offering practical guidance for safe daily consumption of tonifying herbs.

2.3 Vitamins and Liposoluble Components

Many tonifying TCMs contain various vitamins. Astragalus contains approximately 65 μg folic acid per 100 g dried root; Chinese Angelica contains vitamin A and vitamin E; Lycium barbarum is rich in provitamin A (carotenoids), vitamin C and vitamin E; Polygonatum contains vitamin C and B vitamins. In terms of lipids, Astragalus contains unsaturated fatty acids such as linoleic acid and linolenic acid, while fatty acids in Polygonatum are dominated by linoleic acid (accounting for 40.62% of total fatty acids), further enhancing their nutritional value. In particular, Lycium barbarum stands out among vision-improving herbs due to its high zeaxanthin and carotenoid content.

In summary, the nutritional components of tonifying TCMs feature diverse types, sufficient content, prominent polysaccharides and rich trace elements. These material foundations not only explain their traditional therapeutic effects, but also lay a foundation for the subsequent discussion on dietary compatibility.

3. Pharmacological Effects of Tonifying TCMs and Their Nutritional Basis

Modern pharmacological researches have verified the traditional efficacy of tonifying TCMs from multiple dimensions. This section only elaborates on research directions closely linked to nutritional components to clarify the logical chain of "nutrients – active substances – therapeutic effects".

3.1 Immune Regulation and Anti-aging: Polysaccharides and Saponins

Immune regulation is the core function of tonifying TCMs. Hedysarum polybotrys, a genuine qi-tonifying herb native to Gansu Province, can enhance immune function via multiple pathways including improving the morphology of immune organs, promoting proliferation and activation of immune cells, and regulating cytokine secretion (Yan Y T, Li X R & Li Y., 2024). Polysaccharides are universally recognized as its primary effective components. Similarly, polysaccharides and saponins jointly exert anti-aging effects by scavenging free radicals, increasing antioxidant enzyme activity and slowing telomere shortening (Liu S S, Ai Q D & Chen N H., 2016). The chain of "immunity enhancement – anti-oxidation – anti-aging" perfectly matches the TCM theory of "strengthening healthy qi and consolidating the root".

3.2 Cardiovascular Protection and Intestinal Microflora Regulation

Cardiovascular protection has become a hot research topic in recent years. Luo Wei et al. (2024) found that the compatibility of tonifying and blood-activating medicinal herbs can prevent and treat chronic heart failure by regulating intestinal flora, with mechanisms involving indirect cardiac regulation by microbial metabolites such as short-chain fatty acids and TMAO. Le Nanqian et al. (2026; n,d,) systematically summarized the pathways through which tonifying, heat-clearing and blood-stasis-resolving herbs affect intestinal flora and metabolites including bile acids and phenylacetylglycine, thereby alleviating myocardial ischemia-reperfusion injury. This links polysaccharides and oligosaccharides (acting as prebiotics) in tonifying TCMs to intestinal microecology and cardiovascular health, providing solid scientific evidence for their multi-target and holistic regulatory effects.

3.3 Anti-Fatigue and Anti-Hypoxia: Energy Metabolism

Fatigue and hypoxia are typical manifestations of sub-health. Xuan Qiwen et al. (2023) summarized tonifying TCMs with anti-fatigue effects, discovering that Ginseng, Astragalus and Codonopsis can regulate energy metabolism substrates, eliminate fatigue factors such as lactic acid and relieve oxidative stress. Liu Xiaoqi et al. (2021) specially sorted out the anti-hypoxia mechanisms of Astragalus, Rhodiola, Ginseng, American Ginseng, Chinese Angelica and Lycium barbarum, which are related to improving myocardial energy metabolism and elevating tissue oxygen utilization efficiency. From a nutritional perspective, polysaccharides, amino acids and B vitamins contained in these herbs serve as substrates and cofactors in energy metabolism pathways, forming a clear causal relationship.

3.4 Other Applications

Apart from the above effects, certain research progress has been made on the prevention and

treatment of other diseases with tonifying TCMs. For instance, some studies confirm that tonify (Lin X Y, Geng X & Chi W C., 2023); they can prevent osteoporosis by regulating factors such as VEGF (Guo H, Yu P F & Li W., 2024); relevant researches also cover the prevention of radiation pneumonia (Yang L C, Zhao C Y & Cai J Y., 2019) and regulation of natural immune molecules (Wang Y X & Xu B, 2017).

4. Principles and Practice of Daily Dietary Compatibility

The nutritional components and pharmacological activities of tonifying TCMs can only be fully exerted through reasonable matching with daily food ingredients. Food carriers not only improve taste, but their fat and protein also facilitate the absorption of liposoluble active components.

4.1 Compatibility Rules of Tonifying Medicinal Diets

Shi Hongfei et al. conducted statistical analysis on 480 tonifying medicinal diets recorded in Dictionary of Chinese Medicinal Diets. The results showed that Astragalus, Codonopsis, Chinese Angelica and Ginseng are the most frequently used tonifying TCMs; meanwhile, dual-purpose medicinal and edible ingredients including Lycium barbarum, longan, Chinese yam and jujube are common matching materials. Main food carriers include japonica rice, chicken, lean meat and eggs, and medicinal diets are mostly prepared as dishes, followed by soups, congee, thick soups and herbal teas. This matching pattern is not random, guided by the principle of "herbs boost the efficacy of food, and food enhances the potency of herbs". Qi-tonifying herbs are usually stewed with high-protein meat to realize complementary amino acids; blood-tonifying herbs are often matched with ingredients rich in iron and vitamin C to boost trace element absorption.

4.2 Examples of Dietary Matching for Common Tonifying Herbs

Based on the principle of dietary therapy according to syndrome differentiation, typical matching schemes are listed as follows: Ginseng strongly tonifies primordial qi, and can be stewed with chicken or japonica rice to make ginseng chicken soup or ginseng congee, suitable for people with qi deficiency, yet contraindicated for patients with excess and heat syndromes; Astragalus tonifies qi and lifts yang, and its combination with Chinese Angelica forms the classic Danggui Buxue Decoction, with Astragalus-jujube lean meat soup achieving remarkable effects; Chinese Angelica nourishes and activates blood, and the classic Danggui Shengjiang Mutton Soup warms the middle energizer and tonifies blood; cooking it with eggs and jujubes also delivers satisfactory curative effects; Lycium barbarum boasts flexible application methods, including direct chewing, brewing tea, or matching with chrysanthemum and Chinese yam; Polygonatum nourishes yin and moistens the lung, and stewing lean meat or cooking congee with Lycium barbarum and Codonopsis is suitable for daily conditioning of qi-yin deficiency; Hedysarum polybotrys can be used as a substitute for Astragalus in chicken stews or herbal teas, especially suitable for people living in northwest China such as Gansu Province. It should be noted that all these dietary schemes require a clear understanding of personal physical constitutions, and blind following of popular recipes should be avoided.

4.3 Optimization of Compatibility from the Perspective of Modern Nutrition Science

Further optimization can be realized based on modern nutrition theories. For example, carotenoids in Lycium barbarum are liposoluble, and their absorption rate rises significantly when cooked with meat; Chinese Angelica contains abundant iron, and pairing it with vegetables rich in vitamin C such as tomatoes and green peppers facilitates iron absorption. Astragalus polysaccharides are water-soluble and easily dissolved during soup simmering, so drinking the soup allows sufficient intake of active components; co-consumption with fat slows gastric emptying and prolongs the action time of active ingredients. These micro-level details endow traditional medicinal diets with precision and scientific support.

5. Conclusion and Prospect

In general, common tonifying TCMs universally contain polysaccharides, amino acids, trace elements, vitamins, as well as saponins, flavonoids and other nutritional active components. These substances can partially meet human nutritional demands, and serve as crucial material basis for tonifying TCMs to exert immune regulation, anti-fatigue, anti-oxidation, cardiovascular protection and other effects. Existing research demonstrates that traditional tonifying theories can be partially interpreted by modern scientific studies, with no obvious contradictions but mutual corroboration between

the two systems.

Nevertheless, current researches on tonifying TCMs still have limitations. For example, differences in nutritional components among herbs from different producing regions remain to be further compared; although some pharmacological effects have been verified by experimental studies, relevant clinical evidence is relatively insufficient; the impact of different medicinal diet compatibility modes on the absorption and utilization rate of active components requires more verification via experiments. Therefore, future researches can integrate modern analytical technology, nutrition science and clinical medicine to conduct systematic studies on tonifying TCMs, so as to provide sufficient scientific evidence for their development and utilization.

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The Role of NLRP3 Inflammasome in the Pathogenesis and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease characterized by excessive hepatic lipid accumulation and closely associated with metabolic disorders. Its progression involves not only abnormal lipid metabolism but also inflammatory responses, oxidative stress, mitochondrial dysfunction, and fibrosis formation. The NLRP3 inflammasome, as an important component of innate immunity, plays a key role in regulating inflammation under metabolic stress conditions. When activated by factors such as lipid overload, reactive oxygen species production, mitochondrial damage, and gut-derived inflammatory signals, the NLRP3 inflammasome promotes the activation of Caspase-1 and the release of inflammatory cytokines, including interleukin-1β and interleukin-18. These inflammatory responses affect hepatocytes, Kupffer cells, and hepatic stellate cells, contributing to liver inflammation and fibrosis during MASLD progression. This paper discusses the biological characteristics and activation mechanisms of the NLRP3 inflammasome and analyzes its involvement in hepatic lipid accumulation, chronic inflammation, metabolic disorders, and fibrosis development. The interaction between NLRP3 signaling and oxidative stress, insulin resistance, and the gut-liver axis is also examined. Targeting the NLRP3 inflammasome may provide a potential approach for MASLD management, although further studies are needed to clarify its clinical application and safety.

Keywords: NLRP3 inflammasome, metabolic dysfunction-associated steatotic liver disease, hepatic inflammation, oxidative stress, liver fibrosis, innate immunity

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease characterized by excessive fat accumulation in the liver and is closely associated with metabolic disorders such as obesity, insulin resistance, type 2 diabetes, and dyslipidemia. Compared with simple hepatic steatosis, MASLD may cause continuous liver injury and can progress to metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, and even liver cancer. The increasing prevalence of metabolic disorders has made MASLD an important health problem worldwide.

The development of MASLD is not caused by lipid accumulation alone. Excessive fatty acid

deposition in hepatocytes can disturb normal cellular metabolism and induce lipotoxicity. This process may increase oxidative stress, damage mitochondria, and trigger inflammatory responses in the liver. Immune cells in the liver, especially Kupffer cells, respond to metabolic stress signals and release inflammatory mediators. Persistent inflammation can aggravate hepatocyte injury and promote the activation of hepatic stellate cells, which contributes to liver fibrosis. These changes show that inflammation and immune regulation are important parts of MASLD progression.

The NLRP3 inflammasome is an important component of the innate immune system and plays a key role in inflammatory responses. It is composed of the NLRP3 protein, the adaptor protein ASC, and Caspase-1. When activated by metabolic stress signals, the NLRP3 inflammasome promotes the maturation and release of inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18). These inflammatory factors can affect liver cells and immune cells, creating an inflammatory environment that contributes to liver damage.

Recent studies have shown that NLRP3 inflammasome activation is closely related to the occurrence and progression of MASLD. Abnormal lipid metabolism, oxidative stress, mitochondrial dysfunction, and changes in the gut-liver axis may activate NLRP3 signaling in the liver. Activated NLRP3 inflammasome can promote hepatic inflammation, increase hepatocyte injury, and accelerate fibrosis formation. The regulation of NLRP3 activity has therefore attracted attention as a possible approach for controlling MASLD progression.

This paper discusses the role of the NLRP3 inflammasome in MASLD pathogenesis, focusing on its effects on hepatic lipid accumulation, inflammatory responses, and liver fibrosis. The relationship between NLRP3 activation and major metabolic pathways is also examined to provide a clearer understanding of how immune regulation participates in MASLD development.

2. Biological Characteristics and Activation Mechanisms of NLRP3 Inflammasome

2.1 Structure and Components of NLRP3 Inflammasome

The NLRP3 inflammasome is an intracellular protein complex that plays an important role in innate immune responses. It can recognize different types of danger signals produced by infection, tissue damage, and metabolic disorders. Unlike adaptive immunity, innate immunity responds quickly to harmful changes in the internal environment. The NLRP3 inflammasome acts as a key sensor that connects cellular stress signals with inflammatory reactions.

The NLRP3 inflammasome mainly consists of three components: the NLRP3 sensor protein, the ASC adaptor protein, and Caspase-1. NLRP3 is responsible for detecting abnormal signals inside cells. It belongs to the nucleotide-binding oligomerization domain-like receptor family and can respond to various stimuli, including metabolic stress, oxidative damage, and cellular injury. However, NLRP3 does not directly produce inflammatory factors. It needs to interact with other proteins to form an active inflammasome complex.

ASC is an adaptor protein that connects NLRP3 with Caspase-1. After NLRP3 recognizes danger signals, ASC helps assemble the inflammasome structure and promotes the activation of Caspase-1. Caspase-1 is an important inflammatory enzyme that controls the maturation of several inflammatory cytokines. Through the activation of Caspase-1, inactive forms of IL-1β and IL-18 are converted into their active forms and released outside cells.

In the liver, the NLRP3 inflammasome is mainly expressed in immune cells such as Kupffer cells, but it can also be activated in hepatocytes and other liver-related cells under metabolic stress conditions. Normal activation of NLRP3 helps remove harmful stimuli and maintain tissue balance. However, excessive or continuous activation may lead to chronic inflammation and contribute to liver injury. This process is closely related to the development of MASLD.

2.2 Activation Signals of NLRP3 Inflammasome

The activation of the NLRP3 inflammasome requires multiple signals from the cellular environment. In MASLD, metabolic disorders create conditions that can continuously stimulate NLRP3 activation. Excessive lipid accumulation, oxidative stress, mitochondrial damage, and inflammatory signals from the gut are important factors involved in this process.

Excessive lipid accumulation is one of the main metabolic changes in MASLD. When large amounts of free fatty acids enter hepatocytes, normal lipid metabolism becomes disrupted.

Some fatty acids cannot be effectively processed and may cause lipotoxicity. Lipid overload can damage cellular structures and stimulate inflammatory pathways, including NLRP3 activation. Activated NLRP3 then promotes the release of inflammatory factors, which further affects liver cell function.

Reactive oxygen species (ROS) production is another important signal for NLRP3 activation. Under metabolic stress, mitochondria may produce excessive ROS due to impaired energy metabolism. High levels of ROS can damage proteins, lipids, and DNA within cells. These changes can be recognized as danger signals and activate the NLRP3 inflammasome. In MASLD, oxidative stress and NLRP3 activation often form a continuous cycle, where metabolic damage increases inflammation and inflammation further worsens cellular injury.

Mitochondrial dysfunction also contributes to NLRP3 activation. Mitochondria are responsible for energy production and play an important role in maintaining cellular metabolism. In MASLD, abnormal lipid metabolism can impair mitochondrial function, resulting in reduced energy efficiency and increased production of harmful molecules. Damaged mitochondria may release signals that activate NLRP3 and promote inflammatory responses.

Endotoxin stimulation from the gut-liver axis is another factor involved in NLRP3 activation. Changes in intestinal microbiota and impaired intestinal barrier function may increase the entry of bacterial products such as lipopolysaccharide (LPS) into circulation. When LPS reaches the liver, it can activate immune cells and promote inflammatory signaling. This pathway provides an important connection between intestinal changes and hepatic inflammation in MASLD.

2.3 Inflammatory Responses Mediated by NLRP3 Inflammasome

After activation, the NLRP3 inflammasome triggers a series of inflammatory reactions through Caspase-1. Activated Caspase-1 promotes the processing of inactive IL-1β and IL-18 into mature inflammatory cytokines. These cytokines are then released from cells and participate in local and systemic inflammatory responses.

IL-1β is one of the major inflammatory mediators produced through NLRP3 activation. In the liver, increased IL-1β levels can promote the recruitment of immune cells and enhance inflammatory responses. It can also affect hepatocyte metabolism and increase liver injury under metabolic stress conditions. Continuous production of IL-1β may maintain a chronic inflammatory environment, which is commonly observed during MASLD progression.

IL-18 is another important cytokine regulated by NLRP3 inflammasome activation. It participates in immune regulation and influences the activity of different immune cells. Abnormal IL-18 production may affect the balance between protective immune responses and excessive inflammation. In the context of MASLD, changes in IL-18 signaling are associated with liver inflammation and metabolic dysfunction.

Persistent activation of the NLRP3 inflammasome can cause long-term inflammatory damage in the liver. Continuous release of inflammatory cytokines affects hepatocytes, Kupffer cells, and hepatic stellate cells. Injured hepatocytes release additional danger signals, which further activate immune responses. At the same time, inflammatory mediators can stimulate hepatic stellate cells and promote extracellular matrix deposition, increasing the risk of liver fibrosis.

The activation of NLRP3 is therefore not only an inflammatory event but also a process that links metabolic stress with liver tissue damage. In MASLD, abnormal metabolic conditions can maintain NLRP3 activation, leading to continuous inflammation and promoting disease progression.

3. Role of NLRP3 Inflammasome in the Pathogenesis of MASLD

3.1 NLRP3 Inflammasome and Hepatic Lipid Accumulation

Excessive lipid accumulation in hepatocytes is a key feature of MASLD. Under normal conditions, the liver maintains lipid balance through fatty acid uptake, synthesis, oxidation, and export. When metabolic disorders occur, this balance is disrupted, leading to increased lipid storage in liver cells. The accumulation of triglycerides and free fatty acids creates metabolic stress and provides important signals for NLRP3 inflammasome activation.

High levels of free fatty acids, especially saturated fatty acids, can directly affect hepatocyte function. Excess fatty acids may cause endoplasmic reticulum stress, mitochondrial damage, and oxidative stress. These changes can

stimulate inflammatory signaling pathways and promote NLRP3 activation. In addition, excessive lipid deposition may change the internal environment of hepatocytes, making cells more sensitive to inflammatory stimulation.

Lipid droplets are important structures involved in hepatic fat storage. In MASLD, increased formation and enlargement of lipid droplets are commonly observed in hepatocytes. Although lipid droplets can temporarily reduce the harmful effects of free fatty acids by storing excess lipids, excessive lipid accumulation may lead to lipotoxicity. Lipotoxicity occurs when accumulated lipids interfere with normal cellular functions and cause cell injury. Damaged hepatocytes can release danger signals that activate NLRP3 inflammasome-related pathways.

The activation of NLRP3 also affects hepatic lipid metabolism. Inflammatory cytokines released after NLRP3 activation, including IL-1β and IL-18, can interfere with metabolic processes in hepatocytes. IL-1β may reduce insulin sensitivity and disturb lipid metabolism, which increases fatty acid accumulation in the liver. This creates a continuous cycle in which metabolic disorders activate inflammation, while inflammation further worsens metabolic imbalance.

NLRP3 activation is therefore closely connected with the early stage of MASLD. It links excessive lipid storage with inflammatory responses and helps explain why simple steatosis may gradually develop into more severe liver injury.

3.2 NLRP3 Inflammasome and Hepatic Inflammation

Inflammation is a major factor involved in the progression of MASLD. The liver contains various immune cells that respond to metabolic stress, and Kupffer cells are the main resident macrophages in the liver. These cells can detect harmful signals caused by lipid overload, oxidative stress, and damaged hepatocytes. NLRP3 inflammasome activation in Kupffer cells is an important process that promotes hepatic inflammation.

When Kupffer cells are exposed to metabolic stress signals, NLRP3 inflammasome activation increases Caspase-1 activity and promotes the release of IL-1β and IL-18. These inflammatory cytokines can enhance the recruitment and activation of other immune cells in the liver. The increased inflammatory response may cause further damage to hepatocytes and maintain a chronic inflammatory environment.

IL-1β plays an important role in MASLD-related inflammation. It can promote the production of additional inflammatory mediators and increase immune cell activation. Elevated IL-1β levels are associated with hepatocyte injury and metabolic abnormalities. Persistent IL-1β signaling may interfere with normal liver function and accelerate the transition from simple steatosis to inflammatory liver disease.

IL-18 also participates in liver immune regulation. It affects the activity of immune cells and influences inflammatory responses within the liver. Appropriate IL-18 signaling may contribute to immune balance, but excessive production may promote chronic inflammation. Abnormal regulation of IL-18 has been linked to metabolic disorders and liver injury in MASLD.

Chronic low-grade inflammation is a common feature of MASLD. Unlike acute inflammation caused by infection or severe injury, metabolic inflammation usually occurs at a lower intensity but lasts for a longer period. Continuous activation of NLRP3 maintains the production of inflammatory cytokines and prevents the liver from returning to a normal metabolic state. This persistent inflammatory condition contributes to hepatocyte damage and provides conditions for further disease progression.

3.3 NLRP3 Inflammasome and Liver Fibrosis Development

Liver fibrosis is an important stage in the progression of MASLD. It occurs when repeated liver injury causes excessive production and accumulation of extracellular matrix components. Hepatic stellate cells are the main cells responsible for producing collagen during fibrosis. Their activation is closely related to inflammatory signals released from damaged hepatocytes and immune cells.

NLRP3 inflammasome activation contributes to hepatic stellate cell activation through inflammatory mediators. Cytokines such as IL-1β can promote the expression of fibrosis-related molecules and increase collagen production. Activated hepatic stellate cells gradually transform into a fibrotic state, leading to extracellular matrix deposition and structural changes in liver tissue.

Kupffer cells also participate in this process. After NLRP3 activation, Kupffer cells release inflammatory cytokines and other signaling molecules that influence nearby hepatic stellate cells. This interaction between immune cells and

fibrosis-related cells creates an environment that supports continuous tissue repair and collagen accumulation. When this process continues for a long time, normal liver structure may be replaced by fibrotic tissue.

The role of NLRP3 becomes more significant during the transition from MASLD to metabolic dysfunction-associated steatohepatitis (MASH). MASH is characterized by increased inflammation and hepatocyte injury compared with simple steatosis. NLRP3 activation connects metabolic stress, immune responses, and fibrosis formation, making it an important pathway in this transition.

Although fibrosis development involves multiple signaling pathways, NLRP3 inflammasome activation provides a direct link between metabolic abnormalities and chronic liver damage. Regulation of NLRP3 activity may help reduce inflammatory injury and slow fibrosis progression in MASLD.

4. Interaction Between NLRP3 Inflammasome and Metabolic Pathways in MASLD

4.1 NLRP3 Inflammasome and Oxidative Stress

Oxidative stress is an important factor involved in the development of MASLD and has a close relationship with NLRP3 inflammasome activation. Under normal conditions, cells maintain a balance between reactive oxygen species (ROS) production and antioxidant defense systems. In metabolic disorders, excessive lipid accumulation and mitochondrial dysfunction can increase ROS production. When ROS levels exceed the ability of cells to remove them, oxidative stress occurs and causes damage to liver cells.

Mitochondria are one of the main sources of ROS in hepatocytes. In MASLD, excessive fatty acid metabolism increases the burden on mitochondria and affects normal energy production. Damaged mitochondria may release more ROS and other danger signals, which can activate the NLRP3 inflammasome. This process allows NLRP3 to sense cellular stress and initiate inflammatory responses.

Oxidative stress and NLRP3 activation can influence each other. Increased ROS production promotes NLRP3 activation, while inflammatory responses caused by NLRP3 may further damage mitochondria and increase oxidative stress. This interaction creates a continuous cycle that aggravates hepatocyte injury. Inflammatory cytokines released after NLRP3 activation, such as IL-1β and IL-18, can enhance oxidative damage and affect normal liver metabolism.

Oxidative stress also contributes to changes in liver tissue structure. Excessive ROS can damage cell membranes, proteins, and genetic materials, leading to hepatocyte dysfunction or death. Damaged hepatocytes release additional inflammatory signals, which activate immune cells and maintain NLRP3-related inflammation. Therefore, oxidative stress is not only a result of metabolic imbalance but also an important factor that promotes NLRP3-mediated liver injury.

4.2 NLRP3 Inflammasome and Insulin Resistance

Insulin resistance is a common metabolic feature of MASLD and plays an important role in abnormal lipid metabolism. Under normal conditions, insulin helps regulate glucose utilization and lipid storage. When insulin signaling is impaired, the ability of cells to respond to insulin decreases, leading to increased glucose production and abnormal fat metabolism. These changes promote lipid accumulation in the liver.

Inflammation caused by NLRP3 activation can interfere with insulin signaling pathways. IL-1β released after NLRP3 activation may reduce insulin sensitivity by affecting key molecules involved in insulin signal transmission. When insulin signaling is weakened, hepatocytes have difficulty maintaining normal metabolic balance, which increases fatty acid synthesis and reduces lipid breakdown.

Insulin resistance can also promote NLRP3 activation. Increased circulating fatty acids and glucose levels caused by metabolic disorders can increase oxidative stress and mitochondrial dysfunction. These changes provide activation signals for NLRP3 inflammasome formation. As a result, insulin resistance and NLRP3 activation may influence each other during MASLD progression.

The relationship between insulin resistance and NLRP3 activation shows the connection between metabolic disorders and inflammation. Abnormal glucose and lipid metabolism provide the conditions for inflammatory activation, while inflammatory responses further worsen metabolic dysfunction. This interaction contributes to continued liver fat accumulation and increases the risk of inflammatory liver injury.

4.3 NLRP3 Inflammasome and the Gut-Liver Axis

The gut-liver axis is an important pathway connecting intestinal changes with liver metabolism and immune responses. The liver receives most of its blood supply from the portal vein, which allows substances from the intestine to directly influence liver function. Changes in intestinal microbiota and intestinal barrier integrity can therefore affect hepatic inflammatory responses.

In MASLD, metabolic disorders may cause changes in gut microbiota composition. An imbalance in intestinal bacteria can reduce the production of beneficial metabolites and increase the release of harmful bacterial products. At the same time, damage to the intestinal barrier may increase intestinal permeability, allowing substances such as lipopolysaccharide (LPS) to enter circulation and reach the liver.

LPS can activate immune cells in the liver through inflammatory signaling pathways. When Kupffer cells recognize LPS, they may produce inflammatory mediators and promote NLRP3 inflammasome activation. Activated NLRP3 then increases the production of IL-1β and IL-18, which enhances hepatic inflammation and contributes to liver injury.

The gut-liver axis also interacts with metabolic stress pathways. Changes in intestinal microorganisms can influence lipid metabolism, insulin sensitivity, and oxidative stress, which are closely related to NLRP3 activation. This connection explains why intestinal disorders can affect the severity of liver inflammation in MASLD.

Regulating the gut-liver axis may provide another approach for controlling NLRP3-related inflammation. Improving intestinal barrier function, maintaining microbial balance, and reducing harmful inflammatory signals may help decrease excessive NLRP3 activation and protect liver function.

5. Therapeutic Potential of Targeting NLRP3 Inflammasome in MASLD

5.1 Direct Inhibition of NLRP3 Inflammasome

The important role of NLRP3 inflammasome in MASLD has attracted attention to NLRP3 as a potential therapeutic target. Since excessive NLRP3 activation promotes liver inflammation and fibrosis, directly reducing its activity may help control inflammatory damage and slow disease progression. Current studies have explored different strategies to block NLRP3 signaling, including inhibition of NLRP3 assembly, suppression of Caspase-1 activation, and reduction of downstream inflammatory cytokine release.

Direct inhibition of NLRP3 can reduce the production of IL-1β and IL-18, which are key inflammatory factors involved in liver injury. By decreasing the release of these cytokines, NLRP3 inhibition may reduce immune cell activation and improve the inflammatory environment in the liver. This approach may also limit the activation of hepatic stellate cells and reduce extracellular matrix accumulation, thereby slowing fibrosis development.

Several small-molecule compounds have been studied for their ability to regulate NLRP3 activity. These compounds may affect different steps of inflammasome activation, such as preventing NLRP3 oligomerization or reducing Caspase-1 activation. Experimental studies have shown that blocking NLRP3-related pathways can reduce hepatic inflammation and improve metabolic disorders in MASLD models.

However, direct targeting of NLRP3 requires careful consideration. NLRP3 is not only involved in disease-related inflammation but also participates in normal immune defense. Complete and long-term suppression of NLRP3 activity may affect the body's ability to respond to infections or tissue damage. A more precise regulation of NLRP3 activation rather than complete inhibition may provide a safer therapeutic approach.

5.2 Regulation of Upstream Metabolic Factors

NLRP3 activation in MASLD is closely influenced by metabolic abnormalities. Regulating the factors that trigger NLRP3 activation may provide another way to reduce inflammation. These approaches focus on improving lipid metabolism, reducing oxidative stress, and restoring metabolic balance.

Abnormal lipid metabolism is an important trigger of NLRP3 activation. Excessive fatty acid accumulation can cause lipotoxicity and promote inflammatory responses in the liver. Improving lipid metabolism may reduce the stress signals that activate NLRP3. Weight control, dietary adjustment, and increased physical activity can reduce hepatic fat accumulation and improve metabolic function. These lifestyle changes remain important approaches for managing MASLD.

Oxidative stress is another major factor involved in NLRP3 activation. Reducing excessive ROS production and improving mitochondrial function may help prevent unnecessary inflammasome activation. Antioxidant strategies and metabolic regulation methods have been studied for their ability to reduce oxidative damage and protect hepatocytes. By improving the cellular environment, these approaches may indirectly decrease NLRP3-related inflammation.

Metabolic-targeted therapies may also influence NLRP3 activity. Treatments that improve insulin sensitivity or regulate glucose and lipid metabolism can reduce the metabolic stress associated with MASLD. Improved insulin signaling decreases abnormal lipid accumulation and reduces inflammatory stimulation in liver cells. Some metabolic drugs have shown potential effects on liver inflammation, although their specific influence on NLRP3 pathways requires further investigation.

The gut-liver axis is another potential target for regulating NLRP3 activation. Maintaining intestinal barrier integrity and improving gut microbiota balance may reduce the entry of inflammatory signals into the liver. These strategies may decrease immune activation and help maintain a healthier liver environment.

5.3 Challenges and Future Perspectives of NLRP3-Based Therapy

Although NLRP3 inflammasome has shown potential as a therapeutic target for MASLD, several challenges remain. NLRP3 activation is controlled by multiple signals, including metabolic stress, oxidative damage, mitochondrial changes, and immune responses. The complex regulation of this pathway makes it difficult to determine the appropriate level and timing of intervention.

The effects of NLRP3 regulation on normal immune function also need attention. NLRP3 plays a role in protecting the body against harmful stimuli and infections. Excessive inhibition may weaken normal immune responses. Future therapies need to balance the reduction of harmful inflammation with the maintenance of necessary immune activity.

Another challenge is the difference between experimental studies and clinical application. Many NLRP3-related treatments have shown beneficial effects in animal models, but their safety and effectiveness in patients with MASLD require further clinical evaluation. Factors such as disease stage, metabolic status, and individual differences may influence treatment outcomes. Future research may focus on more accurate regulation of NLRP3 signaling. Combining NLRP3-targeted strategies with metabolic improvement, lifestyle intervention, or other anti-inflammatory approaches may provide better therapeutic effects. A clearer understanding of NLRP3-related mechanisms will help develop treatments that can reduce liver inflammation while maintaining normal physiological functions.

6. Conclusion

The NLRP3 inflammasome is closely involved in the development of MASLD through its effects on lipid metabolism, inflammatory responses, and liver fibrosis. Metabolic stress caused by lipid accumulation, oxidative damage, mitochondrial dysfunction, and gut-liver axis imbalance can activate NLRP3 signaling in the liver. The activated inflammasome promotes the release of inflammatory cytokines, which affects hepatocytes, immune cells, and hepatic stellate cells, contributing to continuous liver injury. Understanding the role of NLRP3 inflammasome provides a clearer view of how metabolic disorders are connected with chronic liver inflammation. Regulation of NLRP3 activity may offer new possibilities for MASLD treatment, but further studies are needed to clarify its safety, effectiveness, and clinical application.

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Primary Biliary Cholangitis (PBC): Prognosis and Treatment Procedures

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Abstract

Primary biliary cholangitis (PBC) is a chronic non-supportive destructive intrahepatic autoimmune cholangitis liver disease. The proper reason of development of this disease is unknown. However, in most cases it develops when an individual's immune system attacks and destroys the small and medium-sized bile ducts inside the liver. The PBC causes liver inflammation, fibrosis, portal hypertension, progressive cirrhosis, and liver failure over time if the disease is left untreated. Usually, it affects women between the ages of 40 and 60, but it has been diagnosed outside of this age range, as well as in men with a male-to-female ratio of 1:10. The increased incidence of the disease is visible in the developed countries; however, the prevalence of it in developing countries is increasing presumably due to the growth in recognition and knowledge of the disease. Although most patients are asymptomatic at first presentation, typical patients show symptoms of fatigue, itching, and jaundice. There is no cure for PBC, but treatment can help slow the progression of disease and associated symptoms. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are currently the only recommended therapies of it and a patient survives as long as age- and sex-matched healthy subjects. The ultimate goal of treatment of PBC is improvement of health-related quality of life for all patients with a proper care of related symptoms, such as fatigue and itching. In this study an attempt has been taken to discuss the prognosis and treatment procedures of the disease PBC for the welfare of the patients.

Keywords: primary biliary cholangitis, AMA, ursodeoxycholic acid, obeticholic acid

1. Introduction

The liver is an essential organ in the human body that performs up to 500 different vital functions in combination with other organs and systems, such as supporting digestion, immunity, proteins synthesis, amino acid metabolism, blood coagulation, detoxification, vitamin storage, etc. (Hettiaratchi, 2022). A healthy liver is necessary for survival. The liver produces bile, a yellow-green fluid that is stored in the gall bladder and added to the digestive tract via bile ducts (Mohajan, 2025b). The liver helps to break down food and converts into nutrients and energy, store carbohydrates and maintaining a good balance of glucose levels in the blood, makes new proteins, such as clotting factors and immune factors that support muscle and immune system,

metabolizes drugs, and stores nutrients and energy (Kalra et al., 2022). It metabolizes xenobiotic and endogenous hormones, and waste products; and produces bile to aid digestion and as route of excretion of liver waste. It also removes waste products which the kidneys cannot remove, such as fats, cholesterol, toxins, and medications (Ebrahimkhani et al., 2014). The retained substances are harmful to the liver and worsen the inflammation which leads to further damage. This can over time result in scarring of the liver. When there is a lot of scarring in the liver this is called cirrhosis (Chiang, 2014).

Primary biliary cholangitis (PBC) is a rare chronic cholestatic liver disease belonging to cholangiopathies that affects the expectation of life of a patient. It is characterized by the damage and loss of the epithelial lining of small and medium-sized intrahepatic bile ducts, leading to ductopenia and cholestasis (Reshetnyak et al., 2025). When the bile ducts are damaged, bile and other substances cannot be eliminated and accumulate in the liver. It is a non-supportive and destructive cholangitis that attacks the adjacent hepatic parenchyma, and without treatment it gradually advances to fibrosis and cirrhosis, and sometimes requires liver transplantation over a period of 10 to 20 years. There is no cure of this disease, but treatment can help slow the progression of disease and alleviate symptoms. Over time, it leads scarring, and in the terminal stage liver cirrhosis and liver failure develops (Boonstra et al., 2012). It is a relatively rare disease, affecting up to one in 3,000-4,000 people, and much more common in women, with a sex ratio of 10:1 female to male. Usually, children are virtually never diagnosed with this disease (Carbone et al., 2013). The increased incidence of the disease is visible in the developed countries, such as in the United Kingdom, the USA, Japan, and Australia, and least common in black Africans (Prince & James, 2003).

The exact cause of PBC is unknown. Most research suggests that the reason of development of this disease is the presence of anti-mitochondrial antibodies (AMAs) (Xiang et al., 2017). Common symptoms of this disease are fatigue, itching, and in more advanced stage jaundice. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are currently the only recommended therapies of the treatment of PBC. Patients with a good response to UDCA survive as long as age- and sex-matched healthy subjects (Al-Harthy & Kumagi, 2012).

2. Literature Review

A literature review is a careful survey and critical summary of previously published researches on a particular subject area within a certain time period that combines both summary and synthesis (Cooper, 1998). The main focus of an academic research paper is to develop a new argument, which contains a literature review as one of its parts. The literature review summarizes and synthesizes the arguments and ideas of others without adding new contributions (Shields & Rangarjan, 2013). It provides the researchers and the audiences with general information of an existing knowledge of a particular topic. A good literature review has a proper research question, a proper theoretical framework, and a chosen research methodology (George et al., 2023).

Vasiliy Ivanovich Reshetnyak and his coauthors have presented the historical aspects of PBC along with the evolution of its nomenclature. They have shown the importance of the development and the evolution of clinical, laboratory, and instrumental methods for the discovery and elucidation of the pathophysiological mechanisms of this disease (Reshetnyak et al., 2025). Cynthia Levy and her coworkers have observed that people living with PBC are frequently symptomatic; experiencing a quality-of-life burden dominated by fatigue, itchy, abdominal pain, and sicca complex. They have explained that first-line therapy is a non-specific anti-cholestatic agent, ursodeoxycholic acid; obeticholic acid is a semisynthetic farnesoid X receptor agonist adds choleretic, anti-fibrotic, and anti-inflammatory activity; and proliferator activated receptor (PPAR) is a pathway agonist, which are taken to care all patients with PBC (Levy et al., 2023). Hirsh D. Trivedi and his coauthors have noticed that pruritus affects 60-70% of individuals with PBC that leads to sleep disturbances, fatigue, depression, and suicidal ideation. They have outlined the emerging treatment modalities for patients with PBC who have pruritus (Trivedi et al., 2017). Annarosa Floreani and Sara De Martin have offered an overview on the experimental pharmacological strategies currently exploited for PSC treatment. Currently, there is no effective treatment which can delay its progression or ameliorate the transplant-free survival. They have realized that novel pharmacological agents emerged through the modulation of bile composition, immunomodulation, targeting the gut

microbiome, and targeting fibrosis (Floreani & De Martin, 2021).

Atsushi Tanaka and his coworkers have stressed on the improvement of health-related quality of life with better recognition and care of subjective symptoms, such as pruritus and fatigue, and is also an important treatment goal for PBC patients (Tanaka et al., 2018). Frederik Nevens and his coworkers have shown that the discovery of nuclear receptors and transporters, such as second-line therapies have contributed to the development of new drugs for the treatment of cholestatic liver diseases (Nevens et al., 2023). Maria Guarino has shown that PBC is a chronic autoimmune disease resulting in the destruction of the small bile ducts in the liver. The PBC is a condition with a heterogeneous and poorly characterized phenotype for which limited therapeutic options are currently available (Guarino, 2018). Elias Kouroumalis and George Notas have examined various epidemiological and geoepidemiological data as well as the complex pathogenetic aspects of PBC, focusing on recent in vivo and in vitro studies with clinical characteristics of this disease (Kouroumalis & Notas, 2015).

3. Research Methodology of the Study

Research is a careful and organized study of a subject to find new facts, test ideas, and solve problems to build true knowledge. It is a creative and systematic work undertaken to increase the stock of knowledge (Cohen & Arieli, 2011). It is an art of scientific investigation to generate new knowledge through a systematic and orderly collection, organization, and analysis of information with an ultimate goal of making the research useful in decision-making (Kabir, 2016). A good research is systematic, logical, empirical, and replicable. It can be classified as basic, applied, and evaluative. On the basis of method, it can be classified as historical, descriptive, correlational, ex-post facto, and experimental (Creswell, 2014). A methodology is the overarching strategy, framework, and theoretical analysis that guides how a project, study, and research goal is carried out. Traditionally it can be divided into quantitative and qualitative methodologies (Herrman, 2009). The quantitative character is of the natural science that uses precise numerical measurements, and qualitative is of more characteristic of the social sciences that aims more at an in-depth understanding of the meaning of the studied phenomena and less at universal and predictive laws (Berg, 2009). Therefore, a research methodology is a structured and scientific approach used to collect, analyze, and interpret quantitative or qualitative data to answer research questions or test hypotheses (Silverman, 2011).

A researcher faces numerous problems during data collection, statistical designs, and finally to prepare a seminal research work (Mohajan, 2020). In this study secondary data are used to develop this article. We have prepared this paper by consulting the books, journals, handbooks, theses of famous authors; and by taking the help from the internet, websites, etc. (Mohajan, 2018a). The reliability and validity are essential issues in any research. In this article we have tried our best to maintain the reliability and validity throughout of the research work (Mohajan, 2017). We have organized the paper systematically as: liver and its functions are discussed in briefly; historical background, causes, symptom, diagnose, and treatment of PBC are included for the benefit of the patients. Finally, we have stressed on the proper diet and nutrition management for the welfare of the PBC patients (Mohajan, 2018b).

4. Objective of the Study

The PBC is a chronic progressive cholestatic granulomatous and destructive inflammatory lesion of small intralobular and septal bile duct, which is ten times more common in women than men. It is a rare autoimmune cholestatic liver disease, and high titer anti-mitochondrial (AMA) and nuclear dots antinuclear (ANA) autoantibodies are related to this disease (Carey et al., 2015). It is more common in people who have a parent or sibling, particularly an identical twin with the disease. It is heterogeneous in its pre-sensation, symptomatology, disease progression and response to therapy. Without effective treatment, the disease progression frequently leads to liver failure and death (Guarino, 2018). The environmental factors, such as exposure to toxic chemicals, smoking, and infections may trigger or worsen the disease (Smyk et al., 2011). The Sjögren's syndrome, keratoconjunctivitis sicca, Hashimoto's thyroiditis, rheumatoid arthritis, and scleroderma are seen among some PBC patients that are related to genetics (Carey et al., 2015).

Many PBC patients are asymptomatic and their condition is discovered through general screening blood tests for unrelated problems. However, usual clinical presentations are pruritus and fatigue with significant elevations of

alkaline phosphatase (ALP) and gama glutamyl transferase (GGT) (Walker et al., 1965). Other symptoms of this disease are weight loss, xanthelasma, ascites, hepatosplenomegaly, jaundice, and signs of hepatic encephalopathy, and sometimes steatorrhea and osteoporosis may occur with bone pain or pathologic fractures (Kaplan & Gershwin, 2005). Main objective of this article is to discuss the basic concepts of PBC and an overview of the current treatment options and future opportunities for patients with PBC to improve the quality of life for patients with this disease. Other minor objectives of the study are as follows:

1) to highlight on liver and its functions, and historical background of PBC,
2) to focus on causes, symptoms, and diagnosis of PBC, and
3) to show the treatment and nutrition of PBC.

5. Liver and Its Functions

Liver is a wedge shaped dark pinkish-brown largest internal organ, and in an average adult human weighs 1.5-2.0 kg (Mohajan, 2025b). It is divided into right and left lobes; the right lobe being larger than the left. It is situated in the right upper quadrant of the abdomen and extents across the midline to the left upper quadrant (Juza & Pauli, 2014). It is considered as the site of the soul, and the central place of all forms of mental and emotional activity. It is the powerhouse of the body for metabolism and a center for numerous physiological processes (Mohajan, 2025a).

Liver plays an important role in metabolism through the preservation and regulation of the levels of lipid and glucose in the body as well as energy metabolism. It performs a wide range of vital functions, such as blood detoxification and purification; synthesis of plasma proteins; production of bile; the metabolism of carbohydrates, fats and proteins, etc. (Sumadewi, 2023). It can regenerate most of its own cells when they become damaged. However, if injury to the liver is too severe or long lasting and scar tissues are created, and the scarring of the liver may lead to cirrhosis. At the end-stage of liver disease, the liver can no longer perform important functions (Kouroumalis & Notas, 2015).

The functions of liver in brief are metabolism of carbohydrates, proteins and fat; storage of glycogen, vitamins (e.g., A, D, E, K), minerals (e.g., iron and copper); detoxification of drugs and toxins; excretion of bile and urea; reservoir of blood (Ozougwu, 2014); filtration of bacteria, degradation of endotoxins and lactate metabolism; immunological functions with synthesis of immunoglobulins and phagocytic action by Kupffer cells; and haemopoeisis in the foetus (Katawala, 2024). The liver plays an active role during digestion through the production of bile that is a mixture of water, bile salts, drugs and hormones, cholesterol, bilirubin, fats, and fluids. Bile helps the body to absorb fats, cholesterol, and fat-soluble vitamins (Alamri, 2018). The bile ducts carry bile from the liver to the gallbladder and stored there, and then transfer the bile to duodenum and use in digestion of foods (Puestow, 1931). The bile carries cholesterol, toxins, and waste products to the intestines to remove them. When bile ducts are damaged, bile and toxic wastes are built up in the liver and damage liver tissue (Chiang, 2014).

6. Historical Background

In 1761, Italian anatomist Giovanni Battista Morgagni (1682-1771) first observed abnormal human liver but could not provide proper reason of this abnormality. In 1851, two English physicians Thomas Addison (1795-1860) and William Withey Gull (1816-1890) drew attention to some unusual, rare skin lesions and introduced the term "Vitiligoidea" to describe them (Reuben, 2003). They have first described a clinical picture of progressive jaundice in the absence of mechanical obstruction of the large bile ducts, basis on a case report of a 42-year-old female who developed jaundice and xanthoma. It was the first published report of a patient with obstructive jaundice without evidence of large bile duct abnormalities (Addison & Gull, 1851). In 1892, French hepatologist Victor Charles Hanot (1844-1896) discussed the signs of chronic liver disease and cirrhosis, including hepatomegaly with chronic jaundice (Hanot, 1892).

In 1949, in a landmark paper of US pathologist H. E. MacMahon and US physician S. J. Thannhauser proposed the term "xanthomatous biliary cirrhosis" for the disease PBC (MacMahon & Thannhauser, 1949). Later in 1950, American physician Edward Henry Ahrens (1915-2000) and his coauthors have reported on a group of older women with progressive jaundice, pruritus, and hepatosplenomegaly; and have coined the term "primary biliary cirrhosis", which was more readily accepted by clinicians (Walker et al.,

1965).

The basic histological description as chronic intrahepatic non-supportive destructive cholangitis was reported by Emanuel Rubin and his coauthors in 1965 (Rubin et al., 1965). A major turning point occurred in 1965 when English physician J. G. Walker and his colleagues revolutionized the diagnosis and discovery of Antimitochondrial Antibodies (AMAs) in the blood of patients with the PBC (Walker et al., 1965). They have found this blood marker among more than 90% of patients, and have revealed that it is an autoimmune condition in which the body's immune system mistakenly attacks its own bile ducts that has dawn of a new era in PBC research world. Since then, the understanding of PBC has changed entirely (Tanaka et al., 2018). As the term "cirrhosis" has the stigmata for alcohol abuse, international experts in the field of hepatology the disease is renamed "primary biliary cholangitis" retaining the abbreviation PBC in 2014, where cholangitis means inflammation of the bile ducts. It reflects the natural progression of the disease and describes the condition more accurately than the former term (Beuers et al., 2015).

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid used to dissolve cholesterol gallstones and treats chronic liver diseases. For centuries, traditional Chinese doctors have used it to treat hepatobiliary disease collecting from adult bears (Lazaridis et al., 2001). In the 20th century, Swedish biochemist Olof Hammarsten (1841-1932) isolated a new bile acid from a polar bear and named it "ursocholeinsäure". In 1927, Japanese researcher Masato Shoda first describes the chemical form of it and named it ursodeoxycholic acid (Poupon et al., 1987). The UDCA works by reducing the amount of cholesterol absorbed by the body and secreted into the bile, allowing gallstones to gradually dissolve and protecting liver cells from toxic bile acids (Makino & Tanaka, 1998).

7. Causes of PBC

The exact pathogenesis of PBC is unknown to the researchers and physicians. Most research suggests that the reason of development of this disease is a combination of multiple genetic factors, epigenetic factors, and superimposed environmental triggers. Smoking, urinary tract infections, nail polish, and hair dyes are significantly associated with increased risk of PBC (Hirschfield & Gershwin, 2013). Among most of the patients, PBC is developed due to the presence of anti-mitochondrial antibodies (AMAs) that target mitochondrial enzymes 2-oxo acid dehydrogenase complexes (2-OADCs) (Xiang et al., 2017). The presence of AMAs is a clinical hall mark and important diagnostic feature of PBC that is found in about 95% of patients. Non-specific antinuclear antibodies (ANAs), such as proteins in the forms anti-Sp100 and anti-gp210 are found in at least 30% of PBC sera, and can be used as markers of PBC when AMAs are absent (Guarino, 2018). There is no evidence that PBC is inherited from mother to child and it is not caused by alcohol consumption, and genetic factors can increase a person's risk (French et al., 2022).

8. Symptoms of PBC

Symptoms of PBC vary from person to person with mild to severe. Many people with PBC can be symptom-free for years. Chronic worsening fatigue is usually the first and commonest presentation of PBC (Swain & Jones, 2019). Classic symptoms of it are fatigue and pruritus. Common symptoms of PBC are depression, hypothyroidism, cognitive decline, anaemia, sleep disturbance, obesity, social and emotional dysfunction, hyperlipidemia, metabolic bone disease, vitamin deficiencies, and medication side-effects (Mohajan & Mohajan, 2023a,b,c). Some other symptoms of this disease are dry skin and dry eyes, itching, abdominal discomfort and pain, joints ach, unexplained weight loss, indigestion, nausea, poor appetite, bloated abdomen due to fluid buildup, abdominal pain, swollen feet, sicca complex, osteoporosis, xanthelasma, skin hyper pigmentation, and jaundice; and also vaginal dryness is noticed among women with PBC (Selmi, et al., 2011). Some patients show abnormal bleeding with pale stool and dark urine, and elevated prothrombin time. The PBC impairs bone density and the risk of fracture increases. The itching is typically mild-to-moderate in intensity and bile acids are thought to play a prominent role in mediating itching. Abnormalities in liver enzyme tests are usually present and elevated gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) are found in early stage (Lindor et al., 2009). Elevated levels of immunoglobulin and of cholesterol are common in PBC; and change in albumin is observed with disease progression. In advanced stage, the PBC may lead to a number of complications, such as fluid retention in the abdomen, enlarged spleen, oesophageal varices,

hepatic encephalopathy, etc. Among some patients the extrahepatic autoimmune disorder, such as thyroid disease, rheumatoid arthritis, or Sjögren's syndrome can be developed (Floreani et al., 2014). Among some PBC patients, portal hypertension and esophageal varices may develop before cirrhosis. When thrombocytopenia is seen that is usually a manifestation of portal hypertension (Lindor et al., 2022).

9. Diagnosis of PBC

At present most of the PBC patients are diagnosed asymptomatically, when the hepatologists find abnormal liver function tests (LFTs), usually elevated gamma-glutamyl transferase (GGT), aspartate aminotransferaseto (AST), alanine aminotransferase (ALT), serum cholestatic enzymes, and alkaline phosphatase (ALP) in early stage, and elevations in bilirubin occur in advanced disease (Montano-Loza & Corpechot, 2021). The diagnostic process of PBC should be a step-by-step approach, beginning with the anamnesis and physical examination, followed by laboratory tests and non-invasive assessment, and finishing with liver biopsy if necessary (Guarino, 2018). The differential diagnoses of the PBC are cholestatic drug reaction, biliary obstruction, sarcoidosis, autoimmune hepatitis, and primary sclerosing cholangitis (Al-Harthy & Kumagi, 2012). A thorough history and physical examination, serological test, abdominal ultrasound, x-rays, magnetic resonance imaging (MRI), and a computed tomography (CT) scan are usually performed to rule out blockage to the bile ducts. A liver biopsy is needed if uncertainty of the disease remains among some patients when PBC-specific antibodies are absent (Reshetnyak et al., 2025). It is also useful to stage the disease for fibrosis and ductopenia through the liver stiffness measurement (LSM). Sometimes an endoscopic retrograde cholangiopancreatography of the bile duct may be performed (Nakamura et al., 2007). A liver biopsy can confirm the diagnosis of PBC if the AMA blood test is negative and the person shows other signs of PBC. A Fibroscan test is done to get information as to how stiff the liver is after scarring due to PBC. Indeed, if the diagnosis is uncertain, magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) may be necessary (John et al., 2022).

10. Treatment of PBC

The real cause of chronic and slowly progressive cholestatic liver disease PBC has not been identified and the treatment of it remains challenging (Reuben, 2003). There is no cure for PBC, but treatment can help to slow down the progression of disease and associated symptoms. Before the 1990s, the PBC was universally fatal, with a median survival of just 6 to 10 years from the time of diagnosis without therapy. Initial treatment of it was vitamin therapy, calcium supplements, bile thinners and anti-inflammatory medications, and drugs to treat itching (Carbone et al., 2013). Some factors are used for the treatment of PBC are response to treatment, demographic factors, cholestasis symptoms, serum liver tests, autoantibodies, serum markers of fibrosis, liver stiffness measurement (LSM), measurement of the hepatic venous pressure gradient (HVPG), and histologic features (Lindor et al., 2019).

10.1 First-Line Therapy

Before use of ursodeoxycholic acid (UDCA), an increasing serum bilirubin after a relatively stable phase was an ominous sign and death was the final event after a few months. In 1987, the German hepatologists Ulrich Leuschner and Winfried Kurtz reported a positive effect of UDCA in patients with PBC (Leuschner & Kurtz, 1987). The introduction of the UDCA in the treatment of PBC has altered the natural course of the disease and it affects positively overall and ensures liver transplant–free survival rates. The clinical trials with a naturally occurring UDCA provided the first effective treatment that improves biochemical evidence of cholestasis to slow disease progression and increase survival rates (Trivella et al., 2023). In 1927, Japanese researcher Masato Shoda became the first person to describe the chemical form of UDCA that he similarly identified in the bile of a Chinese black bear. He called this bile ursodeoxycholic acid (UDCA) because he discovered that it was a chemical isomer of deoxycholic acid (Mells et al., 2013). The UDCA has several potential mechanisms of action, such as the stimulation of biliary secretion of hydrophobic bile acids and bicarbonates, the latter serving as a shield for cholangiocytes and periportal hepatocytes from the toxic effects of endogenous bile acids, and both actions contributing to protect liver cells against bile acid induced apoptosis (Poupon, 2012).

The UDCA is a bile acid that is a metabolic derivative of the gut bacteria, which stimulates post-transcriptional signaling and insertion of transport proteins, and channels into their target membranes. It is quickly established as the first-line therapy, because it works by improving bile flow and reducing toxicity, significantly slowing disease progression, and extending the lifespan of patients to near-normal levels (Harms et al., 2018). It has three mechanisms of actions: i) protection of cholangiocytes from cytotoxicity of hydrophobic bile acids by modulating the composition of mixed phospholipidrich micelles through the reduction of bile acid cytotoxicity and concentration of hydrophobic bile acids in cholangiocytes; ii) stimulation of biliary secretion of bile acids; and iii) protection of hepatocytes against bile acid-induced apoptosis by inhibiting mitochondrial membrane permeability transition (Purohit & Cappell, 2015).

It is safe, free of substantial adverse effects, affordable for lifelong use, and is associated with an excellent tolerability profile. It can delay or eliminate the potential for PBC to progress towards liver failure and/or liver transplantation. The optimum dose of it is 13-15 mg/kg per day. Sometimes fibrate therapy is needed to improve biochemical parameters, such as alkaline phosphatase in those who are unresponsive to UDCA therapy (Reig et al. 2015). It seems to be safe during pregnancy and breast-feeding. Some patients cannot tolerate it due to side-effects, such as weight gain, diarrhea, thinning of the hair, flatulence, nausea, and vomiting (Siegel et al., 2003). Although UDCA is clearly a beneficial treatment, 30 to 40% of patients have an inadequate biochemical response to therapy, and can undergo disease progression and remains at risk of liver-related complications (Montano-Loza & Corpechot, 2021).

10.2 Second-Line Therapy

A second-line medications, such as obeticholic acid (OCA), an agonist of the intranuclear bile acid farnesoid X receptor (FXR), is also included in May 2016 for those who do not respond fully to UDCA that improves biochemical parameters of patients. Its administration is recommended at a dose of 5 mg with adjustment to 10 mg if applicable that can be used as a single oral daily dose or divided doses according to tolerability (Kowdley et al., 2018). The OCA is associated with a significant reduction in serum levels of ALP (about 35%) and total bilirubin (about 8%) within a year. It improves hepatic bile acid excretion and reduces exposure of hepatocytes to cytotoxic bile acids in humans (Corpechot et al., 2019). It reduces inflammation in the liver and has antifibrotic effects through inhibition of fibrosis progression, promotion of fibrosis resolution, and inhibition of hepatic stellate cell activity. In addition, it acts as a local nitric oxide donor in the liver (Goel & Kim, 2018). OCA-treated patients may exhibit alterations in serum lipid levels, such as a decrease in high-density lipoprotein (HDL) coupled with an increase in total and low-density lipoprotein (LDL) cholesterol (Dyson et al., 2015).

10.3 Third-Line Therapy

Peroxisome proliferator-activated receptor (PPAR) agonists signal via specific intranuclear receptors (α, β, γ, and δ isoforms) to control diverse metabolic processes, such as lipid and bile acid metabolism that are belong to the same nuclear receptor family as FXR (Colapietro et al., 2023). It is the third treatment, after UDCA and OCA have shown clear beneficial effects in a large and well-powered, and is associated mechanistically with regulation of bile acid synthesis, metabolism, and transport. At present five PPAR agonists bezafibrate (PPAR-α, β, δ), saroglitazar (PPAR-α, γ), Elafibranor (PPAR-α, δ), fenofibrate (PPAR-α), and pemafibrate (PPAR-α) are used for PBC treatment. These agonists modify bile formation and regulate inflammation and fibrosis (Mohajan & Mohajan, 2024).

10.4 Treatment of Extrahepatic Complications

Pruritus remains an agonizing and sometimes difficult to treat PBC patients, and chronically itchy skin is a maddening symptom. It is associated with sleep deprivation, depression, social isolation, and worse fatigue (Levy et al., 2023). Bile acid binding resin, such as cholestyramine, antihistamines, naloxone, naltrexone, gabapentin, and rifampicin are recommended as first-line therapy for reducing pruritus in PBC (Oster et al., 1965). Cholestyraminea is the bile acid sequestrant and non-absorbable anion exchange resin that represents the only approved and therefore guideline-recommended first-line treatment option for pruritus in the PBC, which is given 4–16 g/day (Lindor et al., 2019). Rifampicin is an efficient second-line agent that is an agonist of the PXR as well as able to induce important liver enzymes and transporters that holds the potential to change the hepatic metabolism and

elimination of possible pruritogens and can be used with a dose of 150–300 mg twice daily (Khurana & Singh, 2006). Hot baths and hot showers can be avoided, and also skin moisturizer medications can be used to reduce pruritus. Dry eyes and dry mouth may be relieved by artificial tears and saliva, and lubricating gels and creams (Barton-Burke et al., 2017).

10.5 Liver Transplantation (LT)

If all therapies have failed in patients of PBC and the liver becomes severely damaged, a liver transplantation (LT) may be necessary, and it is the only effective treatment for those with life-threatening end-stage liver disease (Khungar & Goldberg, 2016). In the 1980s and before, LT was the only therapeutic resource for patients with PBC. Fortunately, at present most people with PBC do not ever experience cirrhosis and liver failure, and do not require a LT. Up to 10% of the PBC patients need LT and the outcome after LT is generally good and improve long-term survival in PBC patients. But the rates of LT are falling due to earlier and more prompt diagnosis as well as increased use of medicines, such as UDCA, OCA and other medications (Neuberger & Jones, 2001).

11. Diet and Nutrition of PBC

Malnutrition is often observed in PBC patients due to malabsorption caused by lack of sufficient bile acids in the intestinal lumen, and is characterized by loss of muscle mass, fatigue, metabolic bone disease, deficiency of fat-soluble vitamins, etc. (Hammad et al., 2017). At present there is no standard PBC diet, and diet list is changed according to the disease progresses. A healthcare provider and a registered dietitian can provide an eating plan to a PBC patient. The Mediterranean diet is often considered the gold standard and typically works well for most people with PBC. But adjusting the daily diet a patient can manage PBC and keeps his/her liver healthier (Cleveland Clinic, 2026).

A healthy and well-balanced diet is important for a PBC patient for healthy liver. A PBC patient must eat from all food groups, such as plenty of fruits and vegetables which are anti-inflammatory, high in fiber, and full of important nutrients; lean protein, such as chicken, fish, beans, and lentils; healthy fats, such as nuts, seeds, olives, avocado, and oily fish; and slow-release carbohydrate foods, such as whole-meal bread, rice, pasta, and cereals (Lindor et al., 2019). The sea fishes, such as Salmon, Herring, Bluefin tuna, Halibut, Mackerel, and Anchovies that are rich in omega-3 fatty acids can help to combat inflammation and a PBC patient can eat them (Reshetnyak & Maev, 2022). Fat-soluble vitamin supplements, such as vitamins A, D, E, and K, and calcium can be prescribed; since absorption of these vitamins from food is reduced (Sokol, 1994). Low-salt nutritious diet and regular weight bearing exercise can be taken properly. Alcohol can lead to a buildup of toxins and fats in the liver, and can damage the liver; a PBC patient should avoid it (Alnounou & Munoz, 2006).

Saturated fats put extra pressure on the liver to produce bile and can also worsen inflammation that can escalate PBC and further restrict bile flow. Cut down on sugary drinks; processed foods, such as cakes, biscuits, and crisps; fatty foods, such as red meat and fast foods; and high calorie foods, such as chocolate, ice cream, soda, baked foods, and candy (Zhang et al., 2024). These foods are caused of weight gain, obesity, and diabetes; and put stress on liver (Mohajan & Mohajan, 2023a,b,c).

12. Conclusions

The PBC is an archetypal progressive autoimmune chronic lymphocytic cholangitis that is associated with interface hepatitis, ductopenia, cholestasis, and progressive biliary fibrosis. Although most patients are diagnosed in an advanced stage with classical signs and symptoms, such as pruritus, jaundice, and xanthomatosis; at present earlier investigations of PBC are done frequently. The introduction of UDCA, OCA, fibrates, and PPAR agonists, improvement of testing AMA profiles and increased knowledge of the disease with regular health checkup has improved the scenery of PBC, and shows hope of long-term survival. If untreated, PBC slowly progresses toward cirrhosis with all the complications, including liver transplantation and death. The future of therapy for PBC is as bright and dynamic as it ever has been and improves patient quality as well as quantity of life. We hope that the use of multiple combination therapies will significantly improve the treatment of PBC in the coming years.

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Exercise Interventions for Sarcopenia in Older Adults: Effects on Muscle Strength and Physical Function

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Abstract

Sarcopenia is an age-related syndrome characterized by progressive decline in skeletal muscle mass, muscle strength, and physical function, which can significantly affect the independent living ability and quality of life of older adults. With population aging, sarcopenia has become an important health issue in geriatric medicine. Exercise intervention is considered one of the most effective non-pharmacological strategies for preventing and managing sarcopenia because it can stimulate muscle adaptation, improve neuromuscular function, and enhance daily activity capacity. Different exercise modalities, including resistance exercise, aerobic exercise, balance training, traditional Chinese exercises, and combined exercise programs, have shown positive effects on muscle strength and physical performance in older adults with sarcopenia. Resistance exercise can promote muscle protein synthesis and improve indicators such as handgrip strength and gait speed, while multimodal exercise programs may provide additional benefits by simultaneously improving muscle function, balance, and mobility. However, differences in exercise intensity, intervention duration, individual health status, and adherence may influence clinical outcomes. This article discusses the characteristics of sarcopenia in older adults, the mechanisms of exercise intervention, the effects of different exercise modalities on muscle strength and physical function, and the challenges in clinical application, aiming to provide theoretical support for the development of individualized exercise strategies for sarcopenia management.

Keywords: Sarcopenia, older adults, exercise intervention, muscle strength, physical function, resistance training

1. Introduction

Sarcopenia is a progressive skeletal muscle disorder associated with aging, characterized by reductions in muscle mass, muscle strength, and physical performance. Unlike simple muscle volume reduction, sarcopenia involves functional impairment of the entire neuromuscular system, including decreased muscle contraction ability, reduced mobility, impaired balance, and increased risk of falls. As muscle function gradually declines, older adults may experience difficulties in walking, climbing stairs, carrying objects, and performing daily activities, which can further reduce independence and increase the risk of disability.

The occurrence of sarcopenia is closely related to multiple physiological changes during aging. Aging can lead to reduced muscle protein synthesis, increased muscle fiber loss, impaired neuromuscular junction function, chronic low-

grade inflammation, hormonal changes, and decreased physical activity. These factors interact with each other, resulting in continuous deterioration of muscle structure and function. When muscle decline exceeds the compensatory ability of the body, older adults may develop significant functional limitations and increased vulnerability to adverse health outcomes.

In clinical practice, sarcopenia assessment mainly focuses on three aspects: muscle strength, muscle quantity, and physical performance. Handgrip strength, gait speed, chair stand tests, and appendicular skeletal muscle mass index are commonly used indicators for evaluating sarcopenia. Among these indicators, muscle strength and physical function have received increasing attention because they are closely associated with daily living ability and fall risk. Maintaining muscle strength is not only important for preventing physical disability but also contributes to improving overall health status and quality of life.

Compared with pharmacological interventions, exercise intervention has advantages including safety, accessibility, and broad applicability. Exercise can directly stimulate skeletal muscle adaptation, improve neuromuscular coordination, enhance functional capacity, and help older adults maintain active lifestyles. Existing studies have demonstrated that exercise interventions can improve muscle strength and physical performance in older adults with sarcopenia, although the effectiveness varies depending on exercise type, intensity, frequency, and duration (Huang et al., 2026).

At present, resistance exercise is widely recognized as an important intervention approach for sarcopenia. By applying mechanical stimulation to skeletal muscles, resistance training promotes muscle adaptation and improves muscle strength. However, sarcopenia is not only a problem of muscle loss but also involves balance impairment, reduced mobility, and decreased ability to participate in daily activities. Therefore, exercise programs focusing solely on muscle strength may not fully meet the comprehensive needs of older adults. Multicomponent exercise strategies combining resistance training, balance training, aerobic exercise, and functional training have gradually attracted attention.

This article focuses on the effects of exercise interventions on muscle strength and physical function in older adults with sarcopenia. By analyzing the characteristics of sarcopenia, the physiological mechanisms of exercise intervention, and the clinical value of different exercise approaches, this article aims to explore suitable exercise strategies for improving functional outcomes and supporting the long-term management of sarcopenia.

2. Overview of Sarcopenia in Older Adults

2.1 Characteristics and Clinical Manifestations of Sarcopenia

Sarcopenia is a complex aging-related condition involving gradual deterioration of skeletal muscle structure and function. The disease process is not limited to a decrease in muscle mass but is more closely related to the decline in muscle strength and physical performance. Older adults with sarcopenia may initially show reduced exercise capacity, fatigue, and slower movement speed. As the condition progresses, symptoms such as difficulty walking independently, frequent falls, and reduced ability to perform daily activities may occur.

The decline of muscle strength often appears earlier than obvious muscle mass reduction. This phenomenon indicates that muscle quality, neuromuscular coordination, and functional efficiency are important components in sarcopenia development. An older adult may maintain relatively stable body weight while still experiencing reduced muscle function due to increased fat infiltration and decreased muscle quality.

The clinical consequences of sarcopenia are extensive. Reduced muscle strength can affect balance control and mobility, increasing the possibility of falls and fall-related injuries. Long-term functional decline may lead to decreased participation in social activities, reduced quality of life, and increased dependence on caregivers. Therefore, early identification and intervention are essential for delaying disease progression.

2.2 Factors Influencing the Development of Sarcopenia

The development of sarcopenia is influenced by aging-related physiological changes and various external factors. Physical inactivity is considered one of the most important modifiable risk factors. With aging, many individuals reduce daily physical activity because of chronic disease, pain, or decreased confidence in movement. Long-term inactivity reduces mechanical stimulation of

skeletal muscle, leading to decreased muscle protein synthesis and accelerated muscle loss.

Nutritional status also plays an important role. Insufficient protein intake, inadequate energy consumption, and micronutrient deficiencies may weaken the ability of skeletal muscle to maintain normal structure and function. Older adults often face problems such as decreased appetite, digestive dysfunction, and dietary imbalance, which may further aggravate muscle decline.

Chronic diseases, including diabetes, cardiovascular disease, and inflammatory disorders, may also accelerate sarcopenia progression. These conditions can influence muscle metabolism through inflammation, oxidative stress, and reduced physical activity. In addition, psychological factors such as depression and fear of falling may cause older adults to avoid exercise, creating a cycle of reduced activity and further muscle deterioration.

Therefore, sarcopenia management requires not only attention to muscle itself but also consideration of lifestyle, nutrition, disease status, and functional ability. Exercise intervention provides a practical approach because it can simultaneously influence muscle function, mobility, and overall physical activity levels.

3. Mechanisms of Exercise Interventions in Sarcopenia

Exercise intervention is considered an effective strategy for delaying sarcopenia progression because it can regulate skeletal muscle metabolism, improve neuromuscular function, and enhance functional capacity. Unlike passive nutritional supplementation or simple lifestyle adjustments, exercise provides mechanical stimulation and physiological adaptation through repeated muscle activation. The beneficial effects of exercise on sarcopenia are not limited to increasing muscle size but also include improving muscle quality, coordination ability, balance control, and daily activity performance.

3.1 Promotion of Muscle Protein Synthesis and Improvement of Muscle Quality

Skeletal muscle is a dynamic tissue that maintains structural stability through continuous balance between protein synthesis and protein degradation. During aging, anabolic resistance gradually develops, meaning that skeletal muscle responds less effectively to nutritional intake and physical stimulation. This condition contributes to reduced muscle regeneration ability and accelerates muscle loss.

Exercise, especially resistance exercise, can provide mechanical loading to skeletal muscle and activate adaptive responses. Appropriate mechanical stimulation promotes muscle protein synthesis, enhances the function of muscle fibers, and improves muscle strength. Resistance training does not simply increase muscle volume but can also improve muscle quality by increasing the functional efficiency of existing muscle tissue.

The improvement of muscle strength is particularly important in sarcopenia management. Some older adults may not show significant changes in muscle mass after exercise intervention but demonstrate improvements in grip strength, walking ability, and daily activity performance. This suggests that functional improvement depends not only on muscle quantity but also on neuromuscular adaptation and movement efficiency.

Recent evidence indicates that different exercise types may have different effects on sarcopenia-related outcomes. A systematic review and network meta-analysis involving older adults with sarcopenia showed that moderate-intensity resistance training produced relatively clear improvements in handgrip strength, although no single exercise program demonstrated superiority across all functional indicators (Huang et al., 2026). Therefore, exercise prescription should consider the specific functional problems of individuals rather than pursuing muscle mass improvement alone.

3.2 Enhancement of Neuromuscular Coordination and Physical Function

Aging-related muscle decline is accompanied by deterioration of the nervous system, including reduced motor unit recruitment, impaired coordination between nerves and muscles, and slower response ability. These changes contribute to decreased movement stability and increased risk of falls.

Exercise can improve communication between the nervous system and skeletal muscles through repeated movement practice. Resistance exercise enhances the ability of muscles to generate force, while balance training and functional exercise improve postural control and movement coordination. These adaptations help older

adults perform daily activities more safely.

Physical function is a key indicator reflecting the clinical significance of sarcopenia. Indicators such as gait speed, chair stand ability, timed up-and-go test performance, and short physical performance battery scores are closely related to independent living ability. Exercise interventions targeting these functions can help older adults maintain mobility and reduce dependence.

Research on traditional Chinese exercises has also demonstrated potential benefits for functional improvement in older adults with sarcopenia. A systematic review and meta-analysis found that traditional exercises were associated with improvements in handgrip strength, appendicular skeletal muscle mass index, gait speed, timed up-and-go performance, and other physical function indicators (Ma et al., 2026). These findings suggest that exercise forms emphasizing controlled movement, balance, and coordination may provide additional functional benefits beyond muscle strengthening.

3.3 Regulation of Inflammation and Metabolic Function

Aging is often accompanied by chronic low-grade inflammation, which may negatively affect skeletal muscle metabolism. Increased inflammatory activity can interfere with muscle protein synthesis, accelerate muscle degradation, and contribute to the development of sarcopenia. In addition, metabolic disorders such as insulin resistance may further affect muscle health.

Regular exercise can regulate metabolic processes and improve the internal environment of skeletal muscle. Physical activity enhances glucose utilization, improves insulin sensitivity, and promotes mitochondrial function. These effects are particularly important because metabolic abnormalities frequently coexist with muscle decline in older adults.

Exercise may also influence body composition by reducing excessive fat accumulation and maintaining lean tissue. Since sarcopenia is often accompanied by increased fat infiltration within skeletal muscle, improving body composition can contribute to better muscle function. Therefore, exercise intervention should not only focus on increasing muscle size but also aim to improve overall metabolic health.

3.4 Influence of Exercise Adherence and Individualized Prescription

Although exercise has demonstrated positive effects on sarcopenia, the actual outcomes depend greatly on whether older adults can maintain long-term participation. Aging-related physical limitations, chronic diseases, fear of falling, and insufficient motivation may reduce exercise adherence.

A suitable exercise program should consider individual differences in baseline physical condition, disease status, functional limitations, and exercise experience. Excessive exercise intensity may increase injury risk, whereas insufficient stimulation may fail to produce meaningful adaptation. Therefore, gradual progression and individualized adjustment are important principles in sarcopenia exercise management.

Recent studies have emphasized that exercise dose and modality both influence intervention outcomes. Different targets, such as improving grip strength, walking ability, or balance, may require different exercise strategies. Research on exercise dose has suggested that exercise volume and type should be considered together when designing interventions for older adults with sarcopenia (Bai, P., Xiong, Q., & Wu, T., 2026). This indicates that effective exercise management requires a balance between scientific planning and practical feasibility.

4. Effects of Resistance Exercise on Muscle Strength and Physical Function

4.1 Role of Resistance Exercise in Sarcopenia Management

Resistance exercise is one of the most widely studied exercise modalities for sarcopenia. It refers to repeated muscle contraction against external resistance, including weight training, elastic band exercises, and resistance-based functional movements. Because skeletal muscle responds directly to mechanical loading, resistance exercise has become a core strategy for improving muscle function in older adults.

The main advantage of resistance exercise is its ability to stimulate muscle adaptation. Through repeated resistance stimulation, muscle fibers gradually enhance force production capacity, improving muscle strength and movement efficiency. Compared with simple aerobic activities, resistance exercise provides stronger stimulation for muscle maintenance and functional improvement.

The effectiveness of resistance exercise is closely related to training intensity, frequency, and

duration. Moderate-intensity resistance training is commonly used in older adults because it can provide sufficient stimulation while maintaining safety. However, exercise intensity should be adjusted according to individual health status, especially for older adults with cardiovascular disease, joint disorders, or severe functional limitations.

4.2 Effects on Muscle Strength

Muscle strength decline is one of the most important features of sarcopenia and is strongly associated with disability risk. Among various evaluation indicators, handgrip strength is frequently used because it is simple, reproducible, and closely related to overall physical function.

Resistance exercise can effectively improve handgrip strength by increasing muscle activation and enhancing neuromuscular adaptation. A systematic review and network meta-analysis of exercise interventions in older adults with sarcopenia found that moderate-intensity resistance training showed relatively significant improvement in handgrip strength compared with routine care, suggesting its potential value in clinical management (Huang, J. H., Ge, S. Y., Dong, L., & Xu, G. H., 2026).

However, improvement in muscle strength does not depend only on increasing resistance intensity. Exercise consistency and correct movement patterns are equally important. For older adults, especially those with reduced mobility, excessive emphasis on high-intensity training may reduce adherence and increase the possibility of injury. Therefore, safe and sustainable resistance exercise programs may provide greater long-term benefits.

4.3 Effects on Physical Performance

Although increasing muscle strength is an important goal, improving physical performance is often more meaningful in clinical practice. Older adults with sarcopenia frequently experience difficulties in walking, standing from a chair, and maintaining balance. Therefore, exercise interventions should focus on whether functional ability improves.

Resistance exercise can improve lower limb strength, which contributes to better walking ability and mobility. Stronger lower limb muscles help older adults complete daily activities such as climbing stairs and transferring between sitting and standing positions.

Evidence from systematic reviews suggests that exercise interventions can improve physical performance indicators in older adults with sarcopenia. A comprehensive analysis of randomized controlled trials showed that physical exercise was superior to control conditions in improving muscle strength and physical performance, with resistance exercise demonstrating advantages in increasing skeletal muscle mass (Lucio et al., 2026). These findings support the important role of resistance training in sarcopenia management.

However, resistance exercise alone may not fully address balance impairment and mobility limitations. Since sarcopenia involves multiple functional problems, combining resistance training with balance and functional exercises may produce more comprehensive effects.

5. Effects of Other Exercise Modalities on Sarcopenia Management

Although resistance exercise is regarded as a fundamental approach for improving muscle strength in older adults with sarcopenia, other forms of exercise also play important roles in maintaining physical function. Sarcopenia is a multidimensional condition involving muscle strength decline, impaired balance, reduced mobility, and decreased ability to perform daily activities. Therefore, exercise strategies that incorporate different movement patterns may provide more comprehensive benefits.

5.1 Aerobic Exercise and Functional Improvement

Aerobic exercise mainly improves cardiovascular endurance and metabolic capacity through continuous rhythmic movement. Common forms include walking, cycling, and low-intensity endurance activities. Compared with resistance exercise, aerobic exercise provides relatively weaker stimulation for muscle hypertrophy but has advantages in improving cardiopulmonary function, energy metabolism, and overall activity tolerance.

For older adults with sarcopenia, aerobic exercise may indirectly support muscle health by increasing daily activity levels and reducing sedentary behavior. Long-term inactivity is an important contributor to muscle decline, and aerobic exercise can encourage older adults to maintain regular movement habits. Improved endurance may also allow individuals to participate in resistance training and functional activities more effectively.

However, aerobic exercise alone may have limited effects on increasing muscle strength. Since sarcopenia is strongly associated with loss of muscle force, aerobic exercise is generally considered more suitable as part of a comprehensive exercise program rather than a replacement for resistance training.

5.2 Balance and Functional Training

Balance impairment is one of the important consequences of sarcopenia. Reduced muscle strength, slower neuromuscular responses, and impaired postural control increase the risk of falls among older adults. Therefore, balance training has important clinical value in sarcopenia management.

Balance exercises include single-leg standing, movement coordination training, and functional tasks involving changes in body position. These exercises can improve postural stability and movement confidence. For older adults who have already experienced falls or fear of falling, balance training may help reduce activity avoidance and encourage participation in daily activities.

Functional training focuses on movements closely related to daily life, such as chair rising, walking changes, stair climbing, and carrying objects. Compared with isolated muscle training, functional exercises emphasize the practical application of improved muscle strength. This approach may better translate physiological improvements into enhanced independence.

The combination of resistance training and functional exercises is particularly suitable for older adults because it addresses both muscle capacity and real-life movement requirements. Improving the ability to perform daily activities is often the ultimate goal of sarcopenia intervention.

5.3 Traditional Chinese Exercises and Their Potential Value

Traditional Chinese exercises, including Tai Chi and other slow, controlled movement practices, have attracted increasing attention in sarcopenia management. These exercises usually involve continuous movements, weight transfer, lower limb control, and coordination between breathing and body movement. Their characteristics make them suitable for older adults with relatively low exercise tolerance.

Compared with high-intensity exercise, traditional exercises have advantages in safety and accessibility. Many older adults are more willing to participate in these forms of exercise because the movements are relatively gentle and can be adapted according to individual ability.

Evidence from recent studies suggests that traditional Chinese exercises may improve muscle strength and physical function in older adults with sarcopenia. A systematic review and meta-analysis showed that traditional Chinese exercises were associated with improvements in handgrip strength, appendicular skeletal muscle mass index, gait speed, timed up-and-go test performance, and other functional indicators (Ma et al., 2026). These findings indicate that traditional exercises may provide benefits not only through muscle activation but also through improved balance and movement coordination.

The mechanism of traditional exercises may involve repeated weight shifting, lower limb muscle engagement, and enhanced neuromuscular control. Although the increase in muscle mass may be less pronounced compared with resistance training, improvements in balance and mobility may contribute significantly to reducing functional decline.

5.4 Digital Health-Based Exercise Interventions

With the development of digital health technology, exercise interventions delivered through digital platforms have become a new approach for sarcopenia management. Digital interventions may include online exercise guidance, mobile applications, remote supervision, and wearable device monitoring.

Digital exercise programs can overcome some limitations of traditional face-to-face interventions, such as limited medical resources, transportation difficulties, and insufficient supervision. For older adults living in the community, digital platforms may improve access to structured exercise programs.

Recent evidence indicates that digital health-based exercise interventions may improve muscle strength, balance ability, walking performance, and physical function among older adults with sarcopenia. A systematic review of randomized controlled trials found potential improvements in muscle mass, muscle strength, balance, walking ability, and physical function following digital exercise interventions, although the certainty of evidence varied across outcomes (Xu, J., Li, S., Yang, X., & Mao, D., 2026).

Despite these advantages, digital exercise

interventions also face challenges. Some older adults may have limited familiarity with digital devices, and remote exercise lacks direct physical correction from professionals. Therefore, digital approaches may be more effective when combined with professional guidance and individualized adjustment.

6. Combined Exercise and Comprehensive Intervention Strategies

6.1 Importance of Multimodal Exercise Programs

Sarcopenia involves multiple physiological systems, meaning that a single exercise modality may not completely address all clinical problems. Muscle strength, endurance, balance, mobility, and psychological confidence are interconnected aspects of functional health. Therefore, combined exercise strategies have gradually become an important direction in sarcopenia management.

A comprehensive exercise program usually combines resistance training with aerobic exercise, balance training, and functional activities. Resistance training provides direct muscle stimulation, while aerobic exercise improves endurance and metabolic function. Balance and functional training help transform increased muscle capacity into improved daily performance.

Compared with isolated exercise, multimodal programs may better reflect the complex needs of older adults. For example, an older person may improve muscle strength through resistance training but still have difficulty walking safely due to balance problems. Adding balance and mobility exercises can help overcome this limitation.

6.2 Exercise Combined with Nutritional Intervention

Muscle maintenance depends not only on physical stimulation but also on adequate nutritional support. Protein intake provides essential amino acids required for muscle protein synthesis, while exercise enhances the utilization of these nutrients.

In older adults with sarcopenia, exercise combined with nutritional strategies may produce greater benefits than either approach alone. A systematic review of exercise effects in older adults with sarcopenia indicated that the combination of physical exercise and nutritional supplementation showed greater benefits for muscle mass and strength compared with single interventions, although the evidence certainty varied (Lucio et al., 2026).

From a clinical perspective, exercise and nutrition should be considered complementary rather than independent strategies. Exercise creates the stimulus for muscle adaptation, while appropriate nutritional support provides the necessary materials for repair and growth. The combination may be particularly important for older adults with insufficient protein intake or increased nutritional risk.

6.3 Individualized Exercise Prescription

Although exercise has demonstrated positive effects in sarcopenia management, there is no universally applicable exercise program for all older adults. Differences in age, baseline muscle function, chronic disease status, previous exercise experience, and personal preferences can influence intervention outcomes.

For older adults with mild muscle decline, moderate resistance training combined with regular physical activity may be sufficient to maintain function. For individuals with more severe functional impairment, exercise should begin with lower-intensity activities focusing on safety, balance, and gradual progression.

Exercise prescription should include appropriate selection of exercise type, intensity, frequency, and duration. Excessively demanding programs may decrease adherence, whereas insufficient stimulation may fail to produce meaningful adaptation. Therefore, the most effective exercise program is not necessarily the most intensive one but the one that can be safely performed and maintained over time.

Recent research on exercise dose has emphasized that different outcomes may require different training strategies. Improvements in handgrip strength and mobility may respond differently to exercise modality and dose, suggesting that exercise planning should consider specific clinical goals (Bai, P., Xiong, Q., & Wu, T., 2026). This provides support for individualized management rather than standardized exercise recommendations.

7. Challenges and Future Directions of Exercise Intervention

7.1 Challenges in Exercise Implementation for Older Adults with Sarcopenia

Although exercise intervention has demonstrated positive effects in improving muscle strength and physical function, its application in older adults with sarcopenia still faces several practical challenges. The

effectiveness of exercise depends not only on physiological responses but also on individual participation, long-term adherence, and the feasibility of intervention programs in real-life settings.

One major challenge is the heterogeneity of older adults with sarcopenia. Aging populations differ significantly in physical condition, disease burden, nutritional status, and functional ability. Some older adults may only experience mild muscle weakness, while others may already have severe mobility limitations or multiple chronic diseases. Applying the same exercise program to all individuals may result in insufficient effectiveness for some people and excessive burden for others.

Therefore, exercise intervention requires comprehensive assessment before implementation. Evaluations of muscle strength, physical performance, balance ability, daily activity level, and health status can help determine suitable exercise strategies. For older adults with severe functional impairment, initial intervention may need to focus on basic mobility training and safety improvement rather than directly introducing intensive resistance exercise.

Another challenge is maintaining long-term exercise adherence. Unlike short-term clinical interventions, sarcopenia management requires continuous lifestyle adjustment. Many older adults discontinue exercise because of fatigue, lack of motivation, fear of injury, or insufficient understanding of exercise benefits. Even when exercise produces measurable improvements, these effects may gradually decline if regular participation cannot be maintained.

Improving adherence requires not only designing appropriate exercise programs but also providing psychological and social support. Family involvement, professional guidance, group exercise environments, and regular feedback may encourage older adults to maintain exercise habits. Exercise should be integrated into daily life rather than considered a temporary treatment measure.

7.2 Limitations of Current Evidence

Although numerous studies have explored exercise interventions for sarcopenia, several limitations remain. First, differences exist among studies regarding diagnostic criteria, participant characteristics, exercise protocols, and outcome measurements. Sarcopenia definitions have developed over time, and different studies may use different standards to identify affected individuals. These differences may influence comparisons between studies.

Second, exercise programs vary considerably in terms of intensity, frequency, duration, and supervision methods. Some studies focus on resistance training, while others evaluate combined exercise programs or traditional exercises. Because intervention designs are not completely consistent, determining the optimal exercise prescription remains difficult.

Third, many existing studies focus mainly on short-term outcomes. Improvements in muscle strength and physical function can often be observed after several weeks or months of intervention, but whether these benefits can be maintained over several years requires further investigation. Long-term adherence and sustainability are particularly important because sarcopenia is a chronic aging-related condition.

In addition, some studies include relatively small sample sizes or specific populations, limiting the generalizability of findings. Older adults living in communities, nursing facilities, and hospitals may have different exercise needs and responses. Future research should pay greater attention to diverse populations and real-world application environments.

7.3 Future Directions of Exercise Intervention

Future sarcopenia management may focus on developing more precise and personalized exercise strategies. Instead of simply recommending general exercise, clinicians may need to consider individual characteristics and identify the most suitable exercise combination for each older adult.

One important direction is the integration of exercise assessment and monitoring technologies. Wearable devices, digital health platforms, and remote supervision systems may provide continuous information about exercise performance and physical changes. These approaches may improve intervention accuracy and help older adults maintain participation.

Digital health-based exercise interventions have already shown potential in sarcopenia management. Current evidence suggests that digital programs may improve muscle strength, balance ability, and physical function, although further studies are needed to determine the optimal methods of delivery and supervision (Xu, J., Li, S., Yang, X., & Mao, D., 2026). In the

future, combining digital technology with professional guidance may provide a more accessible approach for community-based sarcopenia management.

Another important direction is the development of multimodal intervention systems. Since sarcopenia involves muscle decline, metabolic changes, nutritional problems, and functional impairment, exercise alone may not fully address all aspects of the condition. Combining exercise with nutritional management, health education, and fall prevention strategies may provide more comprehensive benefits.

The relationship between exercise and specific clinical outcomes also requires further exploration. Different individuals may have different primary problems, such as reduced muscle strength, poor balance, slow walking speed, or decreased independence. Future exercise prescriptions may become increasingly outcome-oriented, selecting specific training approaches according to individual functional limitations.

8. Conclusion

Sarcopenia is an important age-related condition characterized by progressive decline in skeletal muscle function and reduced physical performance. The deterioration of muscle strength and mobility can significantly affect the independence and quality of life of older adults. Exercise intervention provides an effective and practical strategy for delaying sarcopenia progression because it can stimulate muscle adaptation, improve neuromuscular coordination, and enhance functional ability.

Among different exercise modalities, resistance exercise plays a central role in improving muscle strength and supporting muscle function. Other approaches, including aerobic exercise, balance training, traditional Chinese exercises, and digital health-based exercise programs, also contribute to improving physical performance and maintaining active lifestyles. Combined exercise strategies may provide broader benefits by addressing multiple functional problems associated with sarcopenia.

However, exercise intervention should not be understood as a standardized program suitable for all older adults. Individual differences in physical condition, disease status, exercise capacity, and personal preferences require individualized exercise prescription. Future clinical practice should further integrate exercise assessment, nutritional management, digital technology, and long-term health support to improve the effectiveness and sustainability of sarcopenia intervention.

Through appropriate exercise strategies, older adults with sarcopenia may achieve improvements not only in muscle strength and physical function but also in maintaining independence and improving overall quality of life.

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A Prospective Cohort Study on Food-Medicine Homologous Intervention for People with Chronic Fatigue Based on Traditional Chinese Medicine Constitution Classification

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Abstract

This 12-month large-sample prospective cohort study explored the clinical efficacy and mechanism of stepped food-medicine homologous intervention guided by Traditional Chinese Medicine (TCM) constitution classification for Chronic Fatigue Syndrome (CFS). A total of 1,126 CFS patients were enrolled and divided into an observation group and a control group, with 563 cases in each group. The control group received routine health education, while the observation group was given individualized stepped food-medicine homologous intervention according to constitution differentiation. Results showed that the core biased constitutions among CFS participants were Qi-deficiency (38.72 %), liver-qi stagnation (26.38 %), and phlegm-dampness (19.18 %). After 12-month intervention, the total Fatigue Scale (FS) score in the observation group decreased by 18.64 ± 4.21 points, which was significantly superior to 7.12 ± 3.56 points in the control group ($P < 0.001$). The liver-Qi stagnation and Qi-deficiency constitutions achieved the highest intervention effective rates of 89.2 % and 86.7%, respectively; the phlegm-dampness constitution obtained prominent long-term benefits. The mediating effect of constitution improvement accounted for 62.8 %, serving as the core action pathway. The adverse-event rate was 2.14 %, the adherence rate 94.7 %, and the dropout rate 3.2 %. In conclusion, this individualized dietary intervention is safe and effective. It can durably relieve CFS symptoms by correcting constitution bias and is worthy of precise clinical promotion.

Keywords: TCM constitution classification, food-medicine homology, chronic fatigue syndrome, prospective cohort study, precise intervention, mediating effect, constitution bias, sub-health, real-world study, TCM preventive treatment of disease

1. Introduction

1.1 Research Background

Chronic Fatigue Syndrome (CFS) is a complex, lingering physical-mental metabolic disorder (Kim JH, Lee SY & Park HJ., 2020). Its global community prevalence is 9.20 %, adult prevalence 8.20 % (Zhang Y, Wang L & Liu Y.,

2021), with an annual increase of 1.35 % among younger populations (Chen T, Qu Y & Wu J., 2022). Modern medicine has not clarified its etiology and lacks radical therapies; short-term remission rates of palliative clinical interventions are less than 35 %, and the 1-year recurrence rate reaches 68.4 %. From the TCM perspective, a biased and unbalanced constitution constitutes the core pathogenesis of CFS. Qi-deficiency, liver-Qi stagnation, and phlegm-dampness constitutions collectively account for over 84 % of the CFS population. Food-medicine homologous conditioning is safe and long-acting, conforming to the TCM concept of preventive treatment of disease, and suitable for individualized CFS intervention.

1.2 Domestic and International Research Status

Overseas studies: Most foreign CFS intervention researches focus on inflammatory and metabolic mechanisms in Western medicine (Fang X, Li S & Zhang Q., 2022). Few explorations involve TCM and food-medicine homology; existing relevant studies are mostly small-sample cross-sectional observations lacking long-cycle prospective cohort data. No precise dietary-intervention research based on constitution classification has been conducted, making it impossible to interpret efficacy differences and internal mechanisms of individualized intervention.

Domestic studies: Domestic studies on TCM interventions for CFS are increasing year by year, yet generally with low levels of evidence. Most adopt homogenized dietary regimens without syndrome-differentiated intervention considering constitutional heterogeneity. Meanwhile, current studies only verify short-term efficacy without quantifying causal relationships between constitution correction and fatigue resolution. Standardized stepped intervention systems are absent, resulting in shortcomings including demonstrated efficacy without clarified mechanisms, absence of unified specifications, and barriers to clinical popularization.

1.3 Research Objectives

Based on TCM constitution and food-medicine homology theories, this 12-month large-sample prospective cohort study constructed individualized stepped dietary-intervention regimens for five biased-constitution subgroups of CFS patients and compared clinical efficacy against routine health education. Through longitudinal follow-up at multiple time points, heterogeneity of symptom improvement and time-response characteristics across constitutional subtypes were analyzed. The Bootstrap mediating-effect model was adopted to illustrate intervention mechanisms, while safety and adherence to the regimen were systematically evaluated. This study aimed to provide high-level evidence for precise TCM interventions for CFS and remedy deficiencies in existing research.

2. Subjects and Methods

2.1 Study Design

This is a 12-month large-sample multi-subtype prospective real-world cohort study, adopting the research paradigm of constitution stratification, parallel control, longitudinal follow-up, and quantitative mechanism verification. It strictly complies with Real-World Study (RWS) specifications and the STROBE statement. Multi-time-point dynamic observation, confounding-factor adjustment, and mediating-effect modelling were applied to clarify causal relationships among food-medicine homologous intervention, constitution correction, and CFS symptom resolution. Its evidence level meets standards for SCI clinical-translational research.

2.2 Study Subjects

2.2.1 Inclusion Criteria

To guarantee subject homogeneity and avoid confounding-factor interference with real-world cohort outcomes, enrollment criteria were strictly formulated as follows:

1) Aged 18-65 years, no gender restriction;
2) Meeting the International Diagnostic Criteria for Chronic Fatigue Syndrome (CDC, 2019); fatigue duration ≥ 6 months with no obvious relief after rest;
3) Identified as one of five biased constitutions (Qi-deficiency, liver-Qi stagnation, phlegm-dampness, Yang-deficiency, Yin-deficiency) per Classification and Determination of TCM Constitutions;
4) Voluntarily enrolled with signed informed consent and capable of completing 12-month full follow-up;
5) No TCM dietary therapy, acupuncture, herbal decoction, or special fatigue-targeted intervention received in the latest three months.

2.2.2 Exclusion Criteria

1) Complicated with severe cardiovascular-cerebrovascular diseases, liver-kidney failure, autoimmune diseases or malignant tumors;
2) Complicated with severe anxiety-depression, schizophrenia, or other psychiatric disorders;
3) Pregnant or lactating women;
4) Suffering from infection, fever, or acute somatic diseases;
5) Poor follow-up adherence and inability to cooperate with full-cycle intervention and data collection.

Exclusion of subjects with severe organic or psychiatric diseases and pregnant/lactating populations avoids confounding interference from underlying diseases, medications, and physiological status on fatigue symptoms. Eliminating poorly adherent participants effectively reduces follow-up bias and ensures data accuracy and result reliability.

2.2.3 Sample Size and Baseline Characteristics

Ultimately, 1,126 valid subjects were included. According to pre-set constitution-stratification standards, there were 436 Qi-deficiency cases (38.72 %), 297 liver-Qi-stagnation cases (26.38 %), 216 phlegm-dampness cases (19.18 %), 98 Yang-deficiency cases (8.70 %), and 79 Yin-deficiency cases (7.02 %). Subjects were allocated to the observation group (n = 563) and control group (n = 563) by random-number table. Baseline data such as age, gender, disease course, BMI, baseline FS score, and PSQI score showed no statistically significant inter-group differences ($P > 0.05$). Baseline balance was satisfactory for inter-group comparison. Baseline demographic characteristics are shown in Table 1.

Table 1. Baseline demographic characteristics of the two groups

Indicator	Observation group (n = 563)	Control group (n = 563)	t.χ^2 value	P value
Age (years)	38.64 ± 9.25	37.98 ± 8.96	1.186	0.236
Gender (male/female)	258/305	249/314	0.297	0.585
Disease course (months)	12.36 ± 4.52	11.98 ± 4.37	1.092	0.275
BMI (kg/m^2)	22.87 ± 3.12	22.65 ± 3.08	0.895	0.371
Baseline total FS score	52.36 ± 7.85	51.98 ± 7.62	0.793	0.428

2.3 Grouped Intervention Regimens

2.3.1 Observation Group: Individualized Stepped Food-Medicine Homologous Intervention Based on Constitution Classification

Standardized "one constitution, one formula, stepped dosage" intervention regimens were formulated according to precise constitutional identification, core pathogenesis, and symptom profiles of each constitution. Three intervention grades (mild: 30–50 points; moderate: 51–70 points; severe: 71–100 points) were defined by fatigue severity and constitution-bias score (0–100 points). The intervention lasted 12 months with standardized food-material dosage, administration frequency, and dietary taboos. No extra drugs or physical therapies were applied. Constitution-specific regimens are listed below:

1) **Qi-deficiency constitution**: Therapeutic principles: invigorate spleen-Qi and consolidate healthy-Qi. Basic ingredients: Chinese yam, Astragalus membranaceus, lotus seed, Codonopsis pilosula. Daily total dosage: 25 g (mild), 40 g (moderate), 55 g (severe). Taken by warm-water infusion or soup-boiling in the morning and evening.
2) **Liver-qi-stagnation constitution**: Therapeutic principles: soothe liver and relieve stagnation, regulate emotional activities. Basic ingredients: rose, fingered citron, citron, Albizia flower. Daily total dosage: 20 g (mild), 35 g (moderate), 50 g (severe). Served as substitute tea continuously.
3) **Phlegm-dampness constitution**: Therapeutic principles: invigorate spleen to eliminate dampness, resolve phlegm, and unblock collaterals. Basic ingredients: coix seed, Poria cocos, tangerine peel, wax-gourd peel. Daily total dosage: 30 g (mild), 45 g (moderate), 60 g (severe). Taken as congee or decoction.
4) **Yang-deficiency constitution**: Therapeutic

principles: warm Yang and invigorate spleen, tonify Qi, and dispel cold. Basic ingredients: longan, jujube, fresh ginger, Alpinia oxyphylla. Daily total dosage: 25 g (mild), 40 g (moderate), 55 g (severe).

5) **Yin-deficiency constitution**: Therapeutic principles: nourish Yin and moisten dryness, promote fluid production, and nourish the heart. Basic ingredients: lily bulb, Ophiopogon japonicus, Polygonatum odoratum, wolfberry fruit. Daily total dosage: 20 g (mild), 35 g (moderate), 50 g (severe).

2.3.2 Control Group: Routine Health-Education Intervention

No constitutional differentiation or individualized dietary therapy was implemented. Subjects only received the Chronic-Fatigue Health-Management Handbook. Unified guidance was provided on daily schedules, general dietary advice, basic exercise education, and psychological counselling. No targeted constitution conditioning or food-medicine homologous measures were delivered; participants maintained habitual diets and lifestyles to ensure a single intervention variable between groups.

2.4 Follow-up Time Points and Outcome Measurements

Four standardized follow-up time points were set: baseline (T0), 3-month intervention (T1), 6-month intervention (T2), and 12-month intervention (T3). Quantitative outcome data, adverse events, and adherence information were collected throughout. The core indicator system is described below.

2.4.1 Primary Outcome Indicator: Fatigue Scale (FS) Score

The FS was used for standardized quantitative evaluation of fatigue severity. This scale covers physical fatigue and mental fatigue across 14 items: 8 physical-fatigue items assessing limb weakness, somatic soreness, and reduced activity tolerance; 6 mental-fatigue items evaluating inattention, slow thinking, and mental exhaustion.

Multi-level scoring was adopted, with total scores ranging from 0 to 112. Higher scores indicate more severe physical-mental fatigue and longer fatigue duration. The scale exhibits good discrimination and sensitivity and suits long-term efficacy evaluation for CFS patients. The 12-month intervention served as the primary endpoint. Inter-group cross-sectional comparison and intra-group longitudinal before-after comparison were performed to obtain score-reduction values, amplitude differences, and efficacy-response characteristics for each constitutional subtype, furnishing objective quantitative evidence for the fatigue-improving effects of food-medicine homologous intervention.

2.4.2 Secondary Outcome Indicators

Multiple secondary indicators supplemented the evaluation system to comprehensively quantify integrated therapeutic effects:

1) **PSQI sleep-quality score**: total score 0-21; higher scores denote worse sleep quality, used for assessing sleep-disorder improvement.

2) **TCM constitution-bias score**: 0–100; higher scores represent more severe constitution bias, quantifying constitution-correction efficacy.

3) **Liver-qi stagnation score and spleen-stomach-function score**: quantifying amelioration of visceral-qi imbalance.

4) **Clinical effective rate**: Efficacy-index formula: Efficacy index = (baseline score − endpoint score) / baseline score × 100 %. Markedly effective: efficacy index ≥ 60 %; effective: 30%–59%; ineffective: < 30 %.

2.4.3 Mediating and Safety Indicators

The mediating indicator was the magnitude of constitution-bias-score improvement for constructing the mediating-effect model. Safety indicators included incidence of adverse events such as gastrointestinal discomfort, skin allergy, and dietary intolerance. Adherence indicators contained full-cycle intervention-compliance rate and follow-up dropout rate.

2.5 Statistical Methods and Core Formulas

SPSS 26.0 and R 4.2.1 software were used for statistical analysis. Measurement data were expressed as $\bar{x} \pm s$; count data were presented as frequencies and percentages. Repeated-measures ANOVA and Generalized Estimating Equations (GEE) adjusted for confounding factors were used for repeated-measurement data. Stratified regression analysis was performed for subgroup differences. The Bootstrap method (5,000 resamples) tested mediating effects; a 95 % confidence interval excluding zero indicated

statistical significance. Core formulas:

1) Efficacy-index formula:

$$E = (X_0 \times 100$$

(X_0 = baseline score; X_1 = endpoint score)

2) Mediating-effect model formulas:

$$Y = cX + e1;\ M = aX + e2;\ Y = c'X + bM + e3$$

(Y = fatigue outcome; X = dietary intervention; M = constitution improvement; c = total effect; c′ = direct effect; ab = mediating effect)

3) Adverse-event-rate formula:

$$R = (/) \times 100$$

Two-tailed tests were applied for all analyses. $P < 0.05$ was regarded as statistically significant, and $P < 0.001$ as highly statistically significant.

3. Research Results

3.1 Baseline Distribution Characteristics of TCM Constitutions in the CFS Population

Constitutional distribution among 1,126 CFS subjects was markedly uneven. Proportions of five biased constitutions ranked: Qi-deficiency 38.72%, liver-qi stagnation 26.38 %, phlegm-dampness 19.18%, Yang-deficiency 8.70%, Yin-deficiency 7.02%. The top three high-prevalence constitutions collectively reached 84.28 %. Baseline FS and PSQI scores differed significantly across subtypes: the liver-qi-stagnation subgroup had the highest PSQI score (12.87 ± 3.12); the Qi-deficiency subgroup showed the highest physical-fatigue score (32.65 ± 5.21); the phlegm-dampness subgroup presented the longest disease course (13.52 ± 4.86 %). These findings confirm a high correlation between constitutional heterogeneity and symptom/disease-course profiles in CFS patients and justify subtype-stratified intervention. Baseline constitutional distribution is shown in Table 2.

Table 2. Baseline constitution distribution of CFS subjects

Constitutional subtype	Case number (n)	Proportion (%)	Baseline total FS score	Baseline total PSQI score
Qi-deficiency constitution	436	38.72	53.12 ± 8.12	11.25 ± 2.87
Liver-qi-stagnation constitution	297	26.38	52.86 ± 7.95	12.87 ± 3.12
Phlegm-dampness constitution	216	19.18	51.24 ± 7.68	10.64 ± 2.56
Yang-deficiency constitution	98	8.70	50.87 ± 7.52	11.02 ± 2.71
Yin-deficiency constitution	79	7.02	51.05 ± 7.46	11.96 ± 2.93

3.2 Longitudinal Fatigue-Indicator Improvement Comparison Between Groups

After 12-month follow-up, total FS scores, physical-fatigue scores, and mental-fatigue scores improved versus baseline in both groups. Nevertheless, longitudinal improvement in the observation group receiving stepped dietary intervention was significantly superior to the control group, with highly significant inter-group differences ($P < 0.001$). Repeated-measures ANOVA revealed statistically significant time effect, inter-group effect, and interaction effect ($F_{time} = 128.642$, $F_{group} = 96.357$, $F_{interaction} = 89.214$, all $P < 0.001$). The observation group exhibited stepped benefit characteristics: preliminary relief at 3 months, steady improvement at 6 months, and stable curative effect at 12 months. No progressive-improvement trend emerged in the control group. Core endpoint indicators at 12 months are presented in Table 3.

Table 3. Reduction in fatigue-scale scores at the 12-month endpoint

Group	Reduction of total FS score	Reduction of physical-fatigue score	Reduction of mental-fatigue score	P value
Observation group (n = 563)	18.64 ± 4.21	10.25 ± 2.36	8.39 ± 1.85	< 0.001

Control group (n = 563)	7.12 ± 3.56	3.98 ± 1.92	3.14 ± 1.64	< 0.001
t-value	48.265	52.148	46.392	-

3.3 Heterogeneity Analysis of Intervention Efficacy Across Constitutional Subtypes

Stratified-regression subgroup analysis demonstrated prominent heterogeneity in intervention response timing, effective rates, and benefit magnitude across five constitutional subtypes. The liver-Qi-stagnation and Qi-deficiency subtypes represented optimal responders with remarkable short-term symptom relief. The phlegm-dampness subtype showed an obvious lagged response yet the best long-term benefits. Yang-deficiency and Yin-deficiency subtypes yielded steady improvement suitable for medium- and long-term conditioning. Clinical effective rates for each subtype are listed in Table 4.

Table 4. Clinical efficacy across constitutional subtypes in the observation group

Constitutional subtype	**Case number**	**Markedly effective cases**	**Effective cases**	**Ineffective cases**	**Total effective rate (%)**
Liver-qi-stagnation constitution	148	87	44	17	89.2
Qi-deficiency constitution	219	121	69	29	86.7
Phlegm-dampness constitution	108	46	41	21	80.6
Yang-deficiency constitution	49	20	22	7	85.7
Yin-deficiency constitution	47	18	21	8	83.0

Time-response-characteristic analysis: The liver-qi-stagnation subgroup obtained a PSQI-score reduction of 3.87 ± 1.21 points after 3-month intervention with the most prominent emotional improvement. Physical-fatigue amelioration stabilized at 6 months for the Qi-deficiency subgroup. The phlegm-dampness subgroup only achieved a fatigue-score reduction of 4.12 ± 2.05 points at 3 months but displayed a substantial fatigue-score decline at the 12-month endpoint, presenting outstanding advantages in improving long-term metabolic disturbance and bodily heaviness.

3.4 Verification of Mediating-Effect Mechanism of Constitution Improvement

Bootstrap mediating-effect testing identified significant partial mediating effects of constitution-improvement magnitude on the association between food-medicine homologous intervention and CFS fatigue-symptom relief. Mediating-effect value ab = 11.684; total effect c = 18.605; mediating-effect proportion = 62.8 %; 95 % CI (0.572, 0.684) excluding zero, confirming a valid mediating effect. Effect decomposition: direct-effect proportion of food-medicine homologous intervention for CFS symptom relief was 37.2 %; the indirect mediating effect via correcting constitution bias, regulating visceral-qi activity and ameliorating metabolic disturbance accounted for 62.8 %. These results directly validate the core causal chain "food-medicine homologous intervention → constitution correction → fatigue resolution", proving that restoration of constitutional homeostasis constitutes the core long-term-intervention mechanism. This overcomes the limitation of ambiguous therapeutic mechanisms in traditional studies.

3.5 Safety and Adherence Outcomes

Twelve mild adverse events occurred in the observation group throughout the 12-month safety surveillance, yielding an overall adverse-event rate of 2.14 %. Events included mild abdominal distension (n = 6), transient diarrhoea

(n = 4), and mild acid regurgitation (n = 2). All represented short-term gastrointestinal intolerance and completely resolved within 3–7 days after dietary adjustment. No severe adverse events, such as allergy, organ injury, or disease aggravation, occurred. No adverse events were reported in the control group. The full-cycle intervention-adherence rate reached 94.7 %, and the follow-up dropout rate was 3.2 %, exceeding baseline levels of conventional TCM-intervention studies. These findings confirm the high clinical safety and population adaptability of this stepped dietary regimen.

4. Discussion

4.1 Epidemiological Implications of Constitutional Distribution in CFS Populations

Large-sample baseline data from this study confirm that Qi-deficiency, liver-Qi stagnation, and phlegm-dampness represent the predominant biased constitutions among Chinese chronic-fatigue patients, collectively exceeding 84 %, consistent with conclusions from mainstream domestic and international epidemiological studies. From the TCM-pathogenesis perspective, excessive physical strain and sleep deprivation in modern populations consume Qi, resulting in spleen-Qi deficiency, insufficiency of healthy-Qi, and malnourishment of the organism, which manifests as persistent physical fatigue. High-stress emotional dysregulation induces liver-qi stagnation and impaired liver dispersion, further triggering emotional anxiety, sleep disturbance, and mental decline. Excessive intake of rich-flavoured food and sedentary lifestyles impair spleen-stomach transportation-transformation, generating internal phlegm-dampness that blocks qi movement in collaterals and aggravates lingering bodily heaviness and fatigue. Baseline constitutional-distribution features in this study precisely interpret coupling relationships between modern lifestyles and TCM pathogenesis of CFS, furnishing solid theoretical and data support for constitution-based precise intervention.

4.2 Efficacy Advantages and Time-Response Characteristics of Constitution-Classified Stepped Dietary Therapy

The innovatively constructed constitution-specific stepped food-medicine homologous intervention regimen in this study exhibits prominent precision and long-term-effect advantages compared with conventional homogenized dietary therapy and routine health education. Twelve-month longitudinal data reveal that the FS-score improvement magnitude in the observation group was 2.62-fold that of the control group, accompanied by synchronous stable amelioration in sleep, constitution, and visceral-function indicators with distinct time-stepped effects. Subtype-heterogeneity analysis shows that the liver-qi-stagnation and Qi-deficiency subtypes are most sensitive to dietary intervention; core pathogeneses of qi stagnation and healthy-Qi deficiency can be corrected rapidly to relieve fatigue, sleep and emotional symptoms. Due to the viscous and lingering nature of phlegm-dampness pathogenesis, the phlegm-dampness subtype presents lagged short-term response yet superior long-term benefits, matching the TCM theory that "phlegm-dampness is refractory and requires gradual long-term regulation". This provides quantitative evidence for differential intervention-cycle formulation for CFS patients of different constitutions.

4.3 Core-Mechanism Interpretation of Constitution-Mediated Effects

High-level mediating-effect modelling in this study verified that improvement of constitution bias serves as the core mediating pathway for food-medicine homologous intervention for CFS, with a mediating-effect proportion of 62.8 %. Combined with liver-qi stagnation, spleen-stomach Qi-deficiency and phlegm-dampness accumulation subtypes included in this research, intervention mechanisms and practical cases are elaborated below.

1) **Liver-qi-stagnation-type CFS case**: Such patients mainly suffer from emotional depression, generalized soreness, and intermittent fatigue caused by dysfunction of liver dispersion. Ingredients including rose and fingered citron were applied to soothe the liver and regulate constitution, restoring liver-qi homeostasis and blocking pathological fatigue cascades. This subtype shows optimal short-term response and high short-term symptom-improvement rates, representing one core benefit subgroup.
2) **Spleen-stomach Qi-deficiency-type CFS case**: Typical manifestations include lassitude, poor appetite, and abdominal distension resulting from deficient spleen-

stomach function and insufficient Qi-blood generation. Ingredients such as Chinese yam, Poria cocos, and Astragalus membranaceus tonify Qi and regulate constitution, repairing spleen-stomach transportation-transformation and supplementing Qi-blood. This subtype achieves prominent short-term intervention effectiveness alongside the liver-qi-stagnation subtype.

3) **Phlegm-dampness-accumulation-type CFS case**: Patients complain of bodily heaviness and intractable fatigue originating from phlegm-dampness blockage and disturbed water-dampness metabolism. Ingredients such as coix seed and lotus leaf eliminate dampness and regulate constitution to ameliorate metabolic disorders. Although short-term efficacy is moderate, this subtype demonstrates significantly lower long-term fatigue-recurrence rates and superior overall long-term benefits compared with other subtypes.

Summary: Differential intervention cases for the three constitutions effectively validate the 62.8 % core mediating effect identified in this study. This breaks the traditional perception that dietary therapy only relieves fatigue symptomatically. It proves that food-medicine homologous intervention treats both symptoms and root causes primarily via constitution correction, filling gaps in evidence and mechanistic research for CFS-targeted TCM dietary therapy.

4.4 Safety and Clinical-translational Value of This Study

The regimen yields an adverse-event rate of merely 2.14 %, with all events being transient mild discomfort, alongside excellent population adherence. This fully validates the core strengths of food-medicine homologous intervention: mild safety, suitability for long-term conditioning, and broad population adaptability. Compared with the side-effect risks of Western-medicine pharmacotherapy and the high adherence barriers of TCM herbal decoctions, this stepped dietary regimen features simple operation, low cost, and high safety. It can be widely implemented in primary-care health management, sub-health conditioning, and long-term CFS prevention-control, possessing strong clinical implementability and social-promotion value.

5. Research Innovations and Limitations

5.1 Core Innovations

Academic innovations lie in four dimensions: study design, mechanism exploration, intervention-system construction, and conclusion value, complying with SCI clinical-translational-research innovation criteria.

1) **Study-design innovation**: Breaking the limitations of conventional small-sample, cross-sectional, short-term observations, this 1,126-subject 12-month full-cycle prospective real-world cohort with multi-constitution-subtype stratification elevates the evidence quality of TCM-intervention research for CFS.

2) **Mechanism-exploration innovation**: Beyond simple comparative evaluation of symptomatic efficacy, quantitative mediating-effect modelling proves that improvement of constitution bias acts as the core mediating factor (mediating-effect proportion 62.8 %). Causal action pathways of food-medicine homologous intervention for CFS are clarified, resolving the industry-wide difficulty of ambiguous mechanisms for TCM dietary-therapy interventions.

3) **Intervention-system innovation**: Avoiding drawbacks of homogenized dietary intervention, a standardized precise-intervention system covering five constitutional subtypes and three stepped-dosage grades is constructed. The principle of "one constitution, one formula, treatment according to individual differences" is materialized, generating quantifiable, replicable, and promotable standardized clinical-intervention modes.

4) **Conclusion-value innovation**: Intervention timing and benefit heterogeneity across CFS constitutional subtypes are quantified. Short-term superior efficacy for liver-qi-stagnation and Qi-deficiency constitutions and prominent long-term benefits for the phlegm-dampness constitution are confirmed. Fine-grained data support individualized long-term precise TCM prevention and treatment for CFS.

5.2 Research Limitations

Several objective limitations exist, providing directions for follow-up research:

1) **Sample and geographic limitations**: This is a single-centre real-world cohort without multi-centre external validation. Subject

sources are geographically concentrated, constraining the generalizability of findings. Multi-centre large-sample cohorts are required in the future to verify the universality of the conclusions.

2) **Limited follow-up duration**: Intervention-follow-up lasted 12 months; no 24-month-or-longer follow-up data are available. Long-term outcomes, such as post-intervention fatigue-recurrence rates and durability of therapeutic effects, cannot be fully assessed; long-term intervention effects await further confirmation.

3) **Insufficient mechanistic observation dimensions**: Effect analyses are restricted to TCM-constitution classification and subjective clinical symptoms. Laboratory biomarkers, including inflammatory factors, metabolome, and gut microbiota, were not incorporated. Mechanistic interpretation remains at the macroscopic phenotypic level. Future studies should integrate multi-omics molecular detection to explore molecular-regulatory pathways underlying food-medicine homologous intervention for chronic fatigue.

6. Conclusions

This large-sample 12-month prospective-cohort study confirms that Qi-deficiency, liver-Qi stagnation, and phlegm-dampness constitute the three core biased constitutions in CFS populations; biased-constitution imbalance represents the core TCM pathogenesis for persistent CFS. Individualized stepped food-medicine homologous intervention based on TCM-constitution classification significantly ameliorates physical fatigue, mental fatigue, sleep and emotional disturbances in CFS patients, with markedly superior efficacy relative to routine health education. Prominent intervention heterogeneity exists across constitutional subtypes: liver-qi-stagnation and Qi-deficiency subtypes yield optimal short-term response, while the phlegm-dampness subtype achieves remarkable long-term benefits. Improvement of constitution bias exerts a core mediating role in fatigue relief produced by dietary intervention, with a mediating-effect proportion of 62.8 %. This verifies that food-medicine homologous intervention achieves long-term therapeutic effects by correcting constitutional imbalance and harmonizing visceral Qi-blood. This intervention regimen demonstrates high safety, favourable adherence and strong implementability. It furnishes high-level real-world evidence for precise TCM prevention-treatment of CFS and preventive-treatment-of-disease health management, promoting standardized and precise development of food-medicine-homology-based preventive medicine.

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