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The Physical Exercise Application in Frailty and its Underlying Mechanisms

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Abstract

Frailty is a kind of clinical state or a kind of complex pathological syndrome characterized by impaired physiological functions, weakened physical and mental resistance to stress, and reduced ability to maintain homeostasis in multiple systems. Several types of risk factors can affect the occurrence and development of frailty either independently or in conjunction with one another, including age, gender, and exercise habits; and multidimensional systemic treatment are often required to alleviate or improve frailty. Physical exercise is the various kinds of systematic and conscious activities, it has been demonstrated that regular exercise can promote the normal metabolism processes within the body, thereby preventing or alleviating the symptoms of various diseases. Physical exercise has the potential to regulate oxidative stress, immune response, and endocrine balance in the body of frail people by activating multiple signaling pathways including mitochondrial function, cytokine secretion, and regulation of inflammatory factors, its applications in frailty have been made significant progress and the underlying mechanisms have been further elucidated. In this review, we have summarized the recent progress on the applications of physical exercise in frailty and the potential mechanisms, hoping that our reviews may provide some helpful guidance for further research.

Keywords: Physical exercise, Frailty, Oxidative stress, Aging

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Introduction

Frailty is a complex syndrome of polyphysiological decline, and frailty often results in adverse health outcomes. These include reduced physiological function, physical and mental stress resistance, and reduced ability to maintain homeostasis. The occurrence of frailty is associated with several kinds of diseases, including neurodegenerative diseases, cardiovascular diseases, and sarcopenia; Additionally, the prevalence of frailty exhibits particular characteristics. An epidemiological study conducted in Europe demonstrated that the prevalence of frailty in the community and the non-community was 12% and 45%, respectively; there was a notable discrepancy between the two groups [1, 2]; and in China, the prevalence of frailty among individuals aged 65 and above was 18.8-50.9%; specifically, almost 10% individuals aged over 60 years old, 15% individuals aged between 75-84 years old, and approximately 25% of individuals aged over 85 years old were suffered from frailty, there is a significant correlation between the prevalence of frailty and age [3]. Statistical results of the World Health Organization (WHO) demonstrated that there were 1 billion people aged 60 years old or older in 2019, this figure is projected to reach 2 billion by 2050. The significant increase in the elderly population is accompanied by a corresponding rise in the number of individuals experiencing frailty. This has the potential to place a considerable enormous economic and mental burden on frail people and their families [4].

Physical exercise is a kind of regular activity that could improve human body development and working ability, maintain the balance of mind and body, and reduce the occurrence of many kinds of metabolic diseases. The accumulating evidence demonstrated that physical exercise could improve the metabolism, reduce oxidative stress, enhance the immunoregulation and antioxidant effect, and is emerging as a promising non-pharmacological intervention for reducing the incidence rate and mortality associated with various diseases. For example, Paddy C Dempsey *et al*. followed and studied the effect of physical activity (PA) volume and intensity on 88 412 middle-aged adults, and found that PA volume and physical activity intensity could decrease the risk of cardiovascular disease [5]; Qiaoyun Wang *et al*. [6] provided the evidence that physical exercise could reduce the incidence rate of cancer and improve the prognosis of cancer patients and had the better effects on various types of cancers at different stages by inhibiting the cancer cell proliferation and regulating the cancer mechanism. Similarly, frailty is a kind of complex polyphysiological decline syndrome, physical exercise is currently considered the preferred solution for preventing or treating frailty at present, and the applications of physical exercise in frailty are manifold and include improvements in physical function, quality of life, and mental health, which exhibit the irreplaceable advantages.

In this review, we have summarized the recent progress on the applications of physical exercise in frailty and the potential mechanisms, hoping that our reviews may provide some helpful guidance for further research.

Results and Discussion

Clinical manifestations, risk factors, and pathogenesis of frailty

The main clinical manifestations of frailty are the decline in the function of multiple organs in the body, including extreme fatigue, unexplained weight loss, and recurrent lung or urinary tract infections [4, 7]. Exactly, frailty could result in a decrease of mitochondria in muscle cells and the functional muscles, further weakening the muscle strength and coordination [8]; leading to worsening of cardiovascular disease and poor prognosis [9]; affecting the activity of nerve cells in patients, to reduce their cognitive function; decrease the number of T and B cells in the body, to further affect their immune function; even decrease the glomerular filtration rate of patients and to affect their renal function [10-12].

Frailty could increase the risk of disability, functional decline, hospitalization, and even death when the elderly are under stress because frail elderly people need long-term care and treatment, usually bringing increasing medical expenses for the patients and their families [13]. The accumulative evidence demonstrated that many kinds of risk factors, including genetic factors, aging, economic conditions, education level, unhealthy lifestyle, and geriatric syndrome could result in the occurrence and deterioration of frailty, increasing difficulty of screening and identifying biomarkers of frailty [14, 15]. Zekun Zheng *et al*. [10] recruited and analyzed the data of 500 000 middle-aged and older adults in the United Kingdom from 2006 to 2022, found that there was a statistical correlation between frailty and polygenic risk score on Parkinson's disease; Zhou *et al*. [16] investigated and analyzed the data of 7471 older adults aged over 80 years from 2002 to 2014 from in China, results demonstrated that there were 2,930 cases of frailty were identified, and the people with the polygenic risk score$>2.47\times10^{-4}$ suffered from frailty at the higher risk, this evidence suggested the correlation between genetic factors and frailty; Galluzzo *et al*. [17] provided the evidence that the prevalence and incidence of frailty in women was higher than that in men, and increased with the advancing age, demonstrated the relationship between aging and frailty; Sirven *et al*. [18] provided the data that the elderly people with the bad economic conditions can easily to withstand the frailty symptoms compared to people with better economic conditions in Europe, demonstrating that economic conditions also become the risk factor of frailty. To validate the relationship between unhealthy lifestyles and frailty, Li *et al*. [19] analyzed 3,279 volunteers from Dongfeng-Tongji in China, the analysis results demonstrated that unhealthy lifestyles including smoking, drinking alcohol, and physical inactivity on cognitive impairment had a significant relationship with frailty.

Brain deterioration, cardiovascular dysfunction, and deprivation of muscle function are the main manifestations of frailty, the evidence demonstrated that the high level of cerebral white matter, impaired cerebral perfusion, the occurrence of neuroinflammation [20, 21], increased inflammation, reduced physical activity [22], and increased inflammatory inflammation [23] were highly associated with the process of frailty. Further evidence demonstrated physical inactivity could alter the brain structure, reduce neurogenesis, synaptic plasticity, and angiogenesis in frail people [24], and physical activity levels were closely correlated with the total brain volume and cerebral white matter volume [25]; and reduced physical activity could decrease the synthesis of nitric oxide, which could result in arterial stiffness and cardiovascular dysfunction in frail people [26].

Exercise applications in frailty

Physical exercise and frailty

Physical exercise is a regular aerobic physical exercise that is used to improve the speed, strength, endurance, coordination, agility, and flexibility of the body, there are numerous forms of physical exercise including jogging, push-ups, squats, sit-ups, single-leg pull-ups, and sitting forward bends, those different kinds of physical exercises could activate multiple physical functions and reduce the occurrence and development of multiple diseases [27]. This evidence demonstrated that physical exercise can also increase muscle density and mass, enhance cardiopulmonary function, accelerate metabolism in the body, regulate the excitability and inhibition processes of the central nervous system, improve immune regulatory function, and exhibit superior therapeutic effects on frailty [28-30]. In particular, there are several kinds of physical exercises, including aerobic exercise, strength training, flexibility training, and balance training. Given that the specific methods of exercise, the desired outcomes, and the energy consumption expenditure involved vary from one exercise to another, these different physical exercises also have different advantages in alleviating frailty.

Aerobic exercise and frailty

Aerobic exercise is a type of exercise that primarily provides the energy requirement for exercise through the process of aerobic metabolism [31]. In the human body, when the level of exercise is not high, the main source of energy supply for the body comes from the aerobic metabolism of sugar. During aerobic exercise, oxygen can fully decompose and consume sugars and fats in the body, enhancing and improving cardiovascular function, preventing osteoporosis, and regulating psychological and mental states [32, 33]. Recent evidence has demonstrated the efficacy of aerobic exercise applications in the treatment of frailty, with significant advancements being made in this field. For example, Bisset *et al*. [34] analyzed the effect of aerobic exercise on C57Bl/6 mice, comprising 12 male mice and 22 female mice, and found that aerobic exercise could delay the development of frailty in both male and female mice, and extend the life expectancy of female mice; similarly, Lefferts *et al*. [35] compared the effect of total steps/day and faster aerobic steps/day (≥60 steps/min) on frailty in individuals with hypertension, demonstrated that aerobic steps/day could decrease the incidence of developing frailty compared with total steps/day; Zhang *et al*. [36] investigated the correlation between aerobic exercises and frailty from 2008 to 2011 in China, found that aerobic exercise could decrease the risk of aerobic exercise, it was determined that the NMJ pathway-related genetic risk was one of the key regulators of frailty, and aerobic exercise could partly decrease the effect of NMJ pathway-related genetic risk on frailty.

Strength exercise and frailty

Strength exercise is a form of exercise that has been demonstrated to enhance bone, muscle, and ligament strength, improve joint function, increase bone density and metabolism, and further control or slow down the progression of various chronic diseases, including osteoporosis and cardiovascular disease. Consequently, strength exercise also could retard the progression of frailty. For example, Weng *et al*. [37] collected and analyzed recent articles about the applications of strength exercise in frailty, and the data demonstrated that strength exercise had a partial effect on alleviating the process of frailty; Similarly, Aas *et al*. [38] investigated the effect of strength training with protein supplementation on frailty, found that acute strength training could alleviate the symptoms of frailty by regulating the expressions of LC3-I and LC3-II, and by activating the ubiquitin-proteasome system and mitochondrial fission. Winters-Stone *et al*. [39] designed a single-blind, randomized controlled trial to study the effects of strength training or Tai Ji Quan on frailty cancer people, the results demonstrated that both strength training and tai ji quan could alleviate the symptoms of frailty, especially, strength training resulted in a three-fold reduction in inactivity, and had the better effects in women than that in men. Baltasar-Fernandez *et al*. [40] investigated the effect of a 6-week resistance training and fast walking interval training program on frail older adults aged above 75 years old and found that this kind of 6-week training could effectively decrease the frailty index, alleviate the symptoms of frailty, offering a promising avenue for frailty treatment.

Balance exercise and frailty

As frailty progresses, the proliferation of muscle cells turns to slow, muscle tissue begins to atrophy, and muscle function begins to decline in individuals with frailty. Impaired balance and lower limb muscle strength are some of the main symptoms of frailty, they also represent a significant risk factor to result in falls in older adults [41]. Much evidence demonstrated that exercise could increase the strength of muscles and reduce the risk of frailty. For example, Costa *et al*. [42] recruited 22 volunteers to investigate the effect of short-term balance exercise on frailty, the results demonstrated that this kind of balance exercise could alleviate the symptoms of frailty including muscle strength, psychological status, and postural balance; Similarly, Karagül *et al*. [43] designed a randomized prospective trial to assess the effectiveness of balance exercise, results demonstrated that the symptoms of frailty were improved in frail older adults after six weeks of balance exercise.

Traditional Chinese exercise on frailty

Traditional Chinese exercise is a form of exercise which formed under the guidance of traditional Chinese medicine and traditional Chinese martial arts. The Yellow Emperor's

Inner Canon has recorded a variety of exercise and health preservation methods, including walking, guiding, and breathing [44], these methods have been further developed into traditional Chinese exercise, including Tai Chi, Baduanjin, and Yijinjing; these forms of exercise can be considered the inheritances and manifestations of traditional Chinese exercise [45-47]. It has been demonstrated that traditional Chinese exercise can prevent and alleviate the symptoms of diseases by smoothing the Qi and blood meridians, activating muscles and bones, and regulating and harmonizing the internal organs; furthermore, it has also been proven to improve muscle strength, cardiovascular function, and respiratory function [48, 49]. The accumulative evidence demonstrated that traditional Chinese exercise also showed effectiveness in frailty. For example, Xia *et al*. [50] compared the effect of the 24-week Baduanjin on frailty people with cognitive functions, and found that Baduanjin exercise could improve the cognitive and physical functions of frailty people; similarly, Wang *et al*. [51] evaluated the effect of Baduanjin exercise on frailty people, the results demonstrated that Baduanjin exercise could significantly improve the working memory and cognitive flexibility of frailty people after a 24-week treatment; Jiayuan *et al*. [52] provided the evidence that Tai Chi Chuan could alleviate the cognitive and physical function in frailty people; and Kasim *et al*. [53] demonstrated that Tai Chi could improve the antioxidant capacity and vascular function, thereby alleviating the symptoms of frailty including physical and mental fatigue.

The underlying mechanisms of physical exercise application in frailty

Oxidative stress and frailty

Oxidative stress is a negative effect resulting from the presence of free radicals in the body, it is widely accepted that oxidative stress plays a pivotal role in the process of aging and the development of age-related diseases [54, 55]. It has been reported that oxidative stress is a significant contributing factor to a multitude of diseases, including neurodegenerative diseases, cardiovascular diseases, and chronic metabolic diseases, these conditions may directly or indirectly affect the development or progression of frailty [56, 57]. In a healthy body, excessive ROS can damage cellular proteins, lipids, and DNA, leading to fatal cell damage and the development of various pathologies under conditions of oxidative stress. For example, Chen *et al*. [58] reported that oxidative stress could regulate gut microbiota in frailty; Han *et al*. [59] provided evidence that H. pylori, a kind of microorganism isolated from gut microbiota has a high relationship with the development and progression of NAFLD. Besides its role in regulating gut microbiota, Wu *et al*. [60] conducted a longitudinal investigation of 11,277 older people in China between 2003 and 2018, and found a significant association between antioxidant index and frailty, indicating that oxidative stress plays a pivotal role in the development of frailty and its associated changes in antioxidant index. Gomes *et al*. [61] found that aging could lead to an increase in the levels of lipid peroxidation and reactive oxygen species (ROS) levels, and decrease glutathione levels (GSH) in older flies; aging was also found to improve the loss of locomotion and balance of flies and result in the iron accumulation, increase the ROS levels and lipid peroxidation levels in the fly body; indicated that oxidative stress may play a role in the pathogenesis of frailty. There is evidence demonstrating that physical exercise alleviates frailty by regulating oxidative stress; for example, de Barros *et al*. [62] reported that lasting regular exercise could regulate oxidative stress and immune response to reduce the risk and the symptoms of frailty. This evidence demonstrated that oxidative stress plays a role in the deterioration of frailty, and physical exercise can alleviate the process of frailty by regulating oxidative stress.

Inflammation and frailty

Inflammatory response represents a crucial component of the human body's intrinsic defense mechanisms. In the event of tissue damage or infection, the body's tissues will enter a state of normal self-protection and damage repair. Consequently, inflammation may be regarded as a defense response of the human body against environmental stimuli. Pro-inflammatory cytokines and anti-inflammatory cytokines are the main inflammatory factors that play important roles in the inflammatory response. The accumulative evidence demonstrated a strong correlation between the inflammatory response and frailty, inflammatory cytokines including interleukin IL-6, tumor necrosis factor-alpha (TNF-α), and nuclear factor κB (NF-κB), interleukin 10 could directly participate in process of frailty. For example, Arosio *et al*. [63] investigated 452 people between 43 and 114 years old in Italy, they found that inflammatory cytokines, including IFN-γ, IL-10, IL-6, IL-1β, TNF-α were increased significantly in older individuals, and Frailty Index could regulate the levels of Interferon-γ. Similarly, Cybularz *et al*. [64] analyzed the data of 120 participants and found that the expressions of interleukin IL-8 and CRP were increased, and the levels of intermediate monocytes were also elevated, demonstrating that there was a relationship between chronic systemic inflammation and frailty. Furthermore, Zhang *et al*. [65] demonstrated that the neutrophil-to-lymphocyte ratio, a biomarker of inflammation, was highly associated with frailty.

It has been demonstrated that physical exercise has the better effects on frailty by inhibiting the inflammation. Bisset *et al*. [34] reported that aerobic exercise led to an increase in the levels of pro-inflammatory cytokines (IL-

2, IL-3, IL-5, IL-6, IL-9, interferon γ) and a chemokine (KC) in female frail people, indicated that there were sex-based differences in the efficacy of aerobic exercise in alleviating the symptoms of frailty. Lavin *et al*. [66] found that aerobic exercise could reduce the expression of IL-1β, and increase IL-6 expression in younger people; furthermore, higher postexercise increased the expression of IL-8 and TNF-α; aerobic exercise increased the expression of muscle IL-1β and MCP-1. Especially, to understand the relationship between physical exercise and frailty, Marcos-Pérez *et al*. [67] evaluated the effects of a three-month exercise on 12 elder people and 12 aged C57BL/6 mice, found that pro-inflammatory biomarkers, including IL-6, CXCL-1, CXCL-10, IL-1β, IL-7, GM-CSF were decreased after exercise intervention, and CXCL-10 and IL-1β were identified as the potential biomarkers of functional improvement of frail people.

Autophagy and frailty

Autophagy is a natural dynamic life process in that cells utilize lysosomal degradation to selectively clear damaged, aging, or excess biomolecules and organelles, releasing free small molecules for cellular recycling. Autophagy represents a significant protective mechanism, playing an important role in the development of cancer, neurodegenerative diseases, cardiovascular diseases, and infectious diseases to regulate the occurrence and development of diseases. Because frailty is a kind of polyphysiological decline syndrome associated with numerous diseases, including neurodegenerative diseases and cardiovascular diseases, autophagy also plays an important role in frailty. For example, Sasaki *et al*. [68] reported that IL-6 could regulate the expression of STAT3 and autophagy in myotubes via Fyn, Fyn could regulate the IL-6-STAT3-autophagy axis to affect the process of sarcopenia, exhibiting an autophagy-dependent signaling pathway in frailty. Sebastián *et al*. [69] investigated the effect of TP53INP2 on sarcopenia, and found that autophagy was increased in old transgenic mice, upregulation of autophagy improved the muscle atrophy in old mice, and re-expression of TRP53INP2 in aged mice improved muscle atrophy, enhanced mitophagy, and reduced ROS production. Wu *et al*. [70] provided evidence that Artemisia leaf extract could activate TRPML1 and downregulate autophagy/mitophagy to protect the neurons in Parkinson's disease. Similarly, physical exercise has been demonstrated to alleviate frailty by regulating autophagy. Zeng *et al*. [71] provided evidence that 12-week exercise training could regulate the expression of atrogin-1, MuRF1, and Beclin1, increase the LC3-II/LC3-I ratio, and improve the mitochondrial function in 21-month-old rats with sarcopenia. Li *et al*. [72] showed that exercise improved motor function and cognitive function in rats with Parkinson's disease by reducing ROS, cytokine levels, and mitochondrial autophagy. Similarly, Zhou *et al*. [73] demonstrated that exercise increased FNDC5/irisin levels in the nucleus pulposus, and FNDC5/irisin could activate autophagy to delay senescence and apoptosis. Notably, Kuramoto *et al*. [74] demonstrated that hepatic autophagy activation plays an important role in metabolic benefits, and provided that fibronectin (FN1) is a kind of an exercise-induced, muscle-secreted, autophagy-inducing circulating factor, and FN1-regulated the autophagy through IKKα/β-JNK1-BECN1 pathway, exhibiting a new signaling pathways for exercise application in frailty.

Conclusion

The efficacy of physical exercise in mitigating frailty has been substantiated by empirical evidence. A multitude of clinical studies have demonstrated that diverse forms of physical exercises, including aerobic exercise, strength exercise, balance exercise, and traditional Chinese exercise could alleviate the symptoms of frailty through the activation of distinct signaling pathways. However, there are still several issues that require further investigation. (1) Types of physical exercise, exercise forms, exercise intensity, and exercise duration are diverse, several clinical trials provided evidence that physical exercise has different therapeutic effects on frailty in different ages people and different sexes, some physical exercises have been shown to affect female older people but not male people, It is, therefore, necessary to consider how to ensure the uniformity and standardization of clinical application of physical exercise; (2) the underlying mechanisms of physical exercise application in frailty was were insufficient and not sufficiently elucidated. Although there is evidence that physical exercise can alleviate frailty by regulating oxidative stress, inflammation, or autophagy, there is a lack of direct evidence to prove the relationship among them, and the further mechanisms have not been explored; (3) the different frail people have the different medical histories, healthy statuses, endurance levels, and preferences, therefore, it is necessary to develop personalized or humanized exercise training.

In conclusion, the establishment of standardization of physical exercise applications in frailty, the deepening of basic research, and the development of diversified personalized physical training will facilitate the resolution of numerous applications and result in significant advancements in the field of physical exercise applications in frailty.

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