Pathogenesis of Hypertension-Related Frailty in Older Adults and Mechanisms of Exercise Intervention: Research Advances (Postprint)

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Abstract

With the acceleration of China' s aging process, frailty, as a common geriatric syndrome, has become a public health issue of great concern. Hypertension and frailty frequently coexist in older adults, resulting in multiple adverse health outcomes. This article analyzes the epidemiological status and pathogenesis of hypertension-related frailty in the elderly, including inflammatory response, oxidative stress response, insulin resistance, and hormonal metabolism disturbances, etc., summarizes the possible mechanisms through which exercise intervention improves hypertension-related frailty, and aims to provide novel insights for conducting targeted exercise intervention research in elderly patients with hypertension-related frailty.

Full Text

Preamble

Research Progress on the Pathogenesis and Exercise Intervention Mechanisms of Hypertension-Related Frailty in Older Adults

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Abstract

As China' s population aging accelerates, frailty—作为一种常见的老年综合征—has emerged as a significant public health concern. Hypertension and frailty frequently coexist in older adults, leading to multiple adverse health outcomes. This article analyzes the epidemiological status and pathogenesis of hypertension-related frailty in the elderly, including inflammatory response, oxidative stress, insulin resistance, and hormonal metabolic disorders. We also summarize the potential mechanisms through which exercise intervention may improve hypertension-related frailty, aiming to provide novel insights for developing targeted exercise interventions for elderly patients with hypertension-related frailty.

Keywords: elderly; hypertension; frailty; mechanism; intervention

Introduction

Hypertension is a complex cardiovascular syndrome triggered by numerous interacting factors and represents one of the most prevalent chronic diseases among older adults, posing serious threats to their health. According to the 2019 "Chinese Hypertension Health Management Guidelines," the prevalence of hypertension among individuals over 65 years old in China exceeds 50%, imposing a substantial burden on both public health and socioeconomic development [1]. The "Chinese Expert Consensus on Frailty Assessment and Intervention in Elderly Patients" defines frailty as a nonspecific state of decreased physiological reserve in older adults that increases vulnerability and reduces stress resistance [2]. Current research indicates that frailty and hypertension often coexist in older populations, with frailty representing a critical risk factor for increased mortality among elderly hypertensive patients [3]. This review examines the epidemiological status, pathogenesis, and exercise intervention mechanisms of hypertension-related frailty in older adults, providing a reference for targeted exercise intervention research.

1 Epidemiological Status of Hypertension-Related Frailty in Older Adults

Hypertension and frailty are significantly correlated and mutually influential in older adults. On one hand, frailty serves as an independent risk factor for

hypertension, signaling increased risk for its development. On the other hand, hypertension can trigger frailty. In a Korean cross-sectional survey, Kang et al. [4] screened 4,352 community-dwelling adults over 65 using the Frailty Index, revealing that among frail older adults, the prevalence of hypertension reached 67.8%—significantly higher than the 49.8% observed in healthy older adults. Similarly, Brazilian researchers Aprahamian et al. [5] surveyed 619 outpatient older adults using the FARIL Frailty Scale, finding that 83% of frail patients had hypertension compared to 51.7% in the healthy group. These findings demonstrate that hypertension prevalence is higher among frail older adults than in the general elderly population.

Conversely, the detection rate of frailty is also elevated among older adults with hypertension. Ma et al. [3] assessed frailty status in 5,844 older patients using the Comprehensive Geriatric Assessment Frailty Index, reporting a frailty prevalence of 13.8% among hypertensive patients—higher than the 7.4% in the control group. Chen et al. [6] screened 304 community-dwelling older adults with hypertension using a frailty scale, finding an even higher frailty prevalence of 38.1%. These results underscore the close relationship between hypertension and frailty in older adults: frailty increases hypertension risk, while hypertensive older adults are more susceptible to frailty than their non-hypertensive counterparts.

Furthermore, because no gold standard currently exists for frailty definition and assessment, prevalence rates vary considerably depending on the evaluation instrument used, ranging from 4.0% to 59.1% [7]. This highlights the need for further research on standardized frailty assessment tools.

2 Pathogenesis of Hypertension-Related Frailty in Older Adults

Frailty represents a significant risk factor for hypertension onset, and numerous studies suggest that the progression of hypertension-related frailty is complex, potentially involving inflammatory response, oxidative stress, insulin resistance, and hormonal metabolic disorders.

2.1 Inflammatory Response

Hypertension pathogenesis involves vascular inflammatory responses that participate in vascular remodeling processes, damaging endothelial cells lining the vascular surface. This reduces their ability to activate, generate, and release various active substances, thereby diminishing cardiovascular regulatory capacity and accelerating hypertension progression. Additionally, aging and microinflammation in blood vessels, as risk factors for cardiovascular disease, elevate blood pressure by releasing multiple inflammatory cytokines that affect endothelial function, vascular elasticity, and structure.

Research demonstrates that hypertensive patients exhibit overexpression and

activation of various inflammatory factors, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) [8]. IL-6, a typical pro-inflammatory cytokine, plays a crucial role in triggering cascading inflammatory activation. Studies also indicate that microRNAs (miRNAs) can serve as regulatory targets for inflammation-related factors such as IL-1, IL-6, IL-8, and TNF-α, with increased miRNA levels promoting decreased expression of various pro-inflammatory cytokines in skeletal muscle. Therefore, elevating miRNA levels may improve the overexpression of pro-inflammatory cytokines and aging-related skeletal muscle inflammation, thereby alleviating frailty [9].

Yang et al. [10] confirmed in their research on inflammatory factor levels in frail patients that frailty exhibits a linear positive correlation with serum levels of IL-6, soluble intercellular adhesion molecule-1, and homocysteine. These inflammatory factors contribute to frailty by affecting musculoskeletal metabolism and damaging the endocrine system, suggesting that inflammatory responses during hypertension progression represent an important mechanism promoting frailty. Consequently, controlling systemic inflammatory responses may slow the progression of hypertension-related frailty.

2.2 Oxidative Stress Response

Oxidative stress occurs when the balance between oxidation and antioxidation is disrupted, with oxidants gaining dominance and damaging tissues and cells [11]. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a key activator predominantly distributed in tissues with high energy metabolism, such as skeletal muscle and liver. PGC-1α regulates mitochondrial metabolism, influences oxidative stress levels, and plays a critical role in the development of cardiovascular diseases including atherosclerosis and hypertension [12]. Additionally, PGC-1α may be associated with aging and frailty. When overexpressed, PGC-1α affects normal mitochondrial energy metabolism, inhibits FOXO3-mediated overactivation of the ubiquitin-proteasome system, and reduces abnormal degradation of atrogin-1 and muscle ring finger-containing protein 1 (MuRF1), thereby regulating reactive oxygen species (ROS) levels, reducing skeletal muscle mass loss, and preventing skeletal muscle aging [13]. Conversely, aging can decrease PGC-1α activity, triggering age-related skeletal muscle atrophy and promoting frailty [14].

With advancing age, elevated oxidant levels and decreased antioxidant activity and content may render oxidative stress responses more pronounced in older adults with hypertension. This likely relates to oxidative damage and redox imbalance leading to excessive ROS accumulation. While ROS play important mediating roles in normal physiological activities, pathological states involving ROS-mediated redox imbalance can cause mitochondrial dysfunction, damage DNA, proteins, and lipids, trigger vascular endothelial dysfunction, and cause vascular injury that promotes hypertension when oxidative damage exceeds the antioxidant system' s self-purification capacity.

Research also indicates that during aging, excessive ROS accumulation following oxidative stress may regulate multiple signaling pathways, disrupting muscle protein homeostasis and damaging satellite cell function to reduce muscle content, while also impairing neuromuscular junction and excitation-contraction coupling function, decreasing muscle quality, strength, and function, and leading to sarcopenia [15]. Sarcopenia resulting from decreased skeletal muscle mass and strength serves as a key driver of frailty, accelerating its progression [16]. Furthermore, oxidative stress can increase intracellular calcium concentration to enhance proteasome activity, accelerating skeletal muscle breakdown and promoting frailty development [17]. Thus, oxidative stress represents a common pathogenic mechanism linking hypertension and frailty, with oxidative stress responses in hypertensive patients potentially accelerating frailty progression.

2.3 Insulin Resistance

Insulin resistance refers to decreased insulin sensitivity in peripheral tissues, reducing insulin' s biological effectiveness. On one hand, insulin resistance induces hypertension through multiple pathways, including increased renal sodium reabsorption, accelerated vascular smooth muscle cell proliferation, activation of the renin-angiotensin-aldosterone system, and stimulation of the sympathetic nervous system [18]. On the other hand, insulin resistance alters the content of different muscle fiber types, causes intramuscular fat infiltration, and affects normal skeletal muscle function [19]. Since frailty positively correlates with reduced skeletal muscle mass, insulin resistance may contribute to frailty through its effects on skeletal muscle.

Research shows that insulin resistance affects pancreatic β-cell secretory function, reduces insulin-like growth factor-1 (IGF-1) levels, decreases protein synthesis, and diminishes its muscle growth-promoting effects. Additionally, insulin resistance can inhibit glucose uptake by skeletal muscle cells, causing muscle contraction dysfunction, reducing skeletal muscle content, and promoting frailty [20]. Moreover, insulin resistance positively correlates with age, suggesting its impact may be more significant in older patients with both hypertension and frailty. Therefore, addressing insulin resistance should be considered when improving frailty status in older hypertensive patients.

2.4 Hormonal Metabolic Disorders

Hormone levels are closely related to hypertension. Studies show that postmenopausal women experience significant estrogen decline that negatively correlates with systolic and diastolic blood pressure, with hypertension prevalence increasing more rapidly in postmenopausal women than in men—likely related to altered hormone secretion patterns after menopause [21]. On one hand, decreased estrogen weakens its blood pressure-lowering effects; on the other hand, estrogen deficiency reduces elastin content and promotes excessive collagen deposition in arteries, accelerating vascular wall remodeling and increasing arterial stiffness, thereby raising hypertension incidence [22]. Additionally, vascular

dysfunction serves as an important biological marker of aging, and insufficient estrogen secretion reduces large artery compliance and impairs endothelium-dependent vasodilation, potentially becoming a key factor accelerating frailty progression in older women with hypertension [23].

Current research identifies estradiol, free testosterone, and dehydroepiandrosterone as primary sex hormones affecting frailty. Carcaillon et al. [24] found that elevated estradiol levels correlate with frailty occurrence in postmenopausal women. Dehydroepiandrosterone effectively regulates bone metabolism and improves physical and cognitive function in frail patients, with deficiency exacerbating functional decline. Furthermore, studies show that IGF-1, parathyroid hormone, and vitamin D affect frailty progression by influencing musculoskeletal systems. Decreased grip strength, physical decline, and falls represent frailty risk factors, with IGF-1 levels being lower in populations with declining grip strength and physical function. Further research has demonstrated that IGF-1 levels correlate with frailty progression [25], while high parathyroid hormone levels independently associate with fall risk and may worsen frailty. Thus, hormones influence not only blood pressure changes but also affect frailty progression through multiple pathways, though their specific mechanisms in hypertension-related frailty require further investigation.

3 Mechanisms of Exercise Intervention in Hypertension-Related Frailty

Multiple guidelines and consensus statements affirm that exercise intervention represents an important means of preventing and delaying frailty progression [26-27]. Long-term regular exercise helps lower blood pressure and improve frailty status. However, current research on exercise interventions for hypertension-related frailty remains limited, and the mechanisms through which exercise improves this condition require further exploration.

3.1 Exercise Improves Inflammatory Response via miRNA Regulation

Chen et al. [28] conducted a 16-week aerobic exercise program with 60 older male hypertensive patients, demonstrating that aerobic exercise effectively suppresses and even reverses the overexpression of inflammatory factors, suggesting exercise' s anti-inflammatory effects may prevent and treat hypertension. Additionally, exercise may improve inflammatory responses and affect frailty status by regulating miRNA levels. miRNAs are endogenous single-stranded non-coding RNAs that pair with target gene mRNA 3' untranslated regions to inhibit translation and accelerate degradation, playing crucial regulatory roles in organ differentiation, proliferation, and metabolism, as well as in exercise-induced metabolic processes [29].

Mercke et al. [9] showed that miRNA expression levels in skeletal muscle differed significantly between aged and young rhesus monkeys, with miR-181a and miR-181b levels markedly reduced in aged monkeys. Safdar et al. [30] mea-

sured miR-181 levels in mouse rectus femoris muscle after 90 minutes of acute treadmill exercise, finding significant elevation, suggesting exercise may improve inflammatory factor levels and frailty by increasing miR-181. Additionally, miR-1, miR-146a, and miR-185 may serve as frailty biomarkers, with level changes affecting frailty progression. However, whether exercise can improve inflammatory factor levels and frailty status in older hypertensive patients by regulating miRNAs requires further investigation.

3.2 Exercise Improves Oxidative Stress by Inducing Antioxidant Enzymes

Exercise can influence oxidative stress levels and affect skeletal muscle aging processes to regulate frailty. Research shows exercise induces activation of additional antioxidant enzymes, reduces ROS levels in aging skeletal muscle, and improves satellite cell function, thereby regulating skeletal muscle aging and alleviating microenvironmental oxidative stress [31]. PGC-1α serves as an important link between oxidative stress and endothelial dysfunction, regulating antioxidant factor levels, alleviating oxidative stress, and improving endothelium-dependent vasodilation to help maintain vascular wall integrity. This suggests that regulating PGC-1α levels may improve oxidative stress responses and significantly impact cardiovascular disease progression.

Exercise can also modulate ROS levels and alleviate oxidative stress-induced damage by regulating PGC-1α expression, thereby affecting frailty progression. Studies show exercise promotes expression of the stress-induced protein Sestrin2 (SESN2) in skeletal muscle of older mice, activating PGC-1α protein to maintain redox balance and increase skeletal muscle mass [32-33]. Feng et al. [34] noted that resistance and aerobic exercise can inhibit oxidative stress responses and reduce skeletal muscle mass loss in post-myocardial infarction mice, with the underlying mechanism involving activation of the SESN2/PGC-1α pathway. However, research on whether activating the SESN2/PGC-1α protein pathway can improve skeletal muscle mass and oxidative stress damage, thereby ameliorating hypertension-related frailty, remains lacking and warrants further exploration.

3.3 Exercise Improves Insulin Resistance by Elevating IGF-1 Levels

Skeletal muscle represents the key site where frailty induces insulin resistance, making improvement of skeletal muscle function and insulin sensitivity crucial for frailty prevention. Exercise intervention can stimulate skeletal muscle cells to secrete IGF-1, thereby alleviating sarcopenia [35]. Research shows both endurance and strength training can increase IGF-1 levels in older populations, activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway to reduce skeletal muscle cell apoptosis [36]. Additionally, when combined with protein supplementation, exercise elevates skeletal muscle anabolism in older adults, effectively preventing age-related sarcopenia. Studies show that in protein-supplemented mice undergoing exercise intervention, activation of the IGF-1/AKT/mTOR signaling pathway and inhibition

of the FOXO3/muscle atrophy protein pathway accelerate skeletal muscle anabolism, reduce protein ubiquitination degradation, regulate autophagy, and slow sarcopenia progression [37-38]. This suggests exercise may improve insulin resistance and skeletal muscle function via IGF-1-mediated pathways, thereby affecting frailty.

International research demonstrates that resistance exercise can also activate the IGF-1/mTOR/P70 ribosomal protein S6 kinase pathway in aged mice, increasing glucose transporter-4 levels, elevating skeletal muscle protein content, and enhancing glycogen metabolism efficiency to improve skeletal muscle mass [39]. In summary, endurance exercise, resistance training, and other exercise modalities can stimulate skeletal muscle cells to secrete IGF-1 through multiple pathways, regulating insulin resistance during aging to improve skeletal muscle function and modulate frailty. Furthermore, insulin resistance represents a risk factor for age-related diseases such as hypertension and atherosclerosis [40]. Research confirms that exercise can increase IGF-1 levels in hypertensive rats, activate the PI3K/nitric oxide synthase pathway, and enhance nitric oxide bioavailability to improve hypertension [41]. Thus, exercise holds promise for playing an important role in improving insulin resistance in aging-related diseases including hypertension and frailty.

3.4 Exercise Improves Hormonal Metabolic Disorders by Regulating Hormone Levels

Frailty is significantly associated with hormone levels, and exercise intervention can modulate hormone levels to improve frailty status. Testosterone has cardiovascular protective effects, and increasing testosterone levels can effectively delay frailty while positively influencing hypertension-related cardiovascular disease. Sgro et al. [42] showed that both submaximal and high-intensity exercise significantly increased serum testosterone levels in healthy men. Ha and Hon [43] conducted a 12-week combined aerobic and anaerobic training program (3 times weekly, intensity progressively increasing from 40% to 70% heart rate reserve) in older women, finding elevated serum estradiol content. Shi et al. [44] reported that 8 weeks of treadmill training (6 days/week, 1 hour/day, 25 m/min) increased muscle estradiol content in ovariectomized rats. These studies demonstrate that exercise can regulate hormone levels including testosterone and estradiol, though research on the specific mechanisms by which exercise improves hormone levels to alleviate frailty remains limited and requires further investigation.

Conclusion

Frailty and hypertension frequently coexist in older adults, with frailty exerting serious adverse effects on prognosis in elderly hypertensive patients. The pathogenesis of hypertension-related frailty may involve inflammatory response, oxidative stress, insulin resistance, and hormonal metabolic disorders. As an important intervention for improving hypertension-related frailty in older adults,

exercise can influence disease progression through multiple pathways: ameliorating inflammatory responses, reducing oxidative stress-induced damage, and regulating insulin resistance and hormone levels. However, current research on exercise mechanisms in hypertension-related frailty remains scarce, and different exercise modalities may exert differential effects. Future studies should further explore the specific targets and intervention effects of various exercise forms on hypertension-related frailty to provide novel approaches for its prevention and management.

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Literature Search Strategy

(1) Chinese databases including CNKI, Wanfang Data, and VIP Chinese Journal Service Platform were searched using Chinese keywords: “衰弱”(frailty), “衰老” (aging), “虚弱” (weakness), “老年” (elderly), “老年人” (older adults), “老年患者” (elderly patients), “高血压” (hypertension), “运动” (exercise), “机制” (mechanism).

(2) PubMed was searched using English keywords: “frail,” “frailty,” “Aged,” “old age,” “elderly patients,” “hypertension,” “exercise,” “Exercise therapy,” “mechanisms.”

(3) The search timeframe was from database inception to 2022.

Author Contributions

LIU Yameng, YANG Xiaoli, and ZHANG Caihong conceptualized and designed the article. LIU Yameng collected and organized literature and drafted the manuscript. YANG Xiaoli revised the manuscript. YANG Xiaoli and ZHANG Caihong were responsible for quality control and review. ZHANG Caihong provided overall supervision.

Conflict of Interest

The authors declare no conflict of interest.

Note: Figure translations are in progress. See original paper for figures.