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Review

HFpEF in the Elderly: Exercise-Based Immunomodulatory Interventions and New Strategies

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Abstract: To examine the immunopathological mechanisms underlying heart failure with preserved ejection fraction (HFpEF) in elderly patients and evaluate exercise training as an immunomodulatory intervention for managing disease complications. A narrative literature review was conducted using PubMed, Embase, and Cochrane Library databases (2010–2023), focusing on immune dysfunction, aging, and exercise interventions in HFpEF. HFpEF pathophysiology in elderly patients involves complex interactions between innate and adaptive immunity, characterized by elevated pro-inflammatory cytokines, NLRP3 inflammasome activation, and immune cell dysfunction. Major complications—frailty syndrome, sarcopenia, and malnutrition—share common inflammatory pathways that perpetuate disease progression. Exercise training fundamentally alters this inflammatory profile through multiple mechanisms: suppressing pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6), promoting anti-inflammatory immune cell phenotypes, and enhancing tissue regenerative capacity. Unlike pharmacological interventions targeting single pathways, exercise exerts pleiotropic effects across the immune-inflammatory network, simultaneously addressing cardiac dysfunction and systemic complications. Structured exercise programs effectively interrupt inflammatory cascades, improve functional capacity, and enhance quality of life in elderly HFpEF patients. Exercise training represents a cornerstone intervention that directly targets the fundamental immunopathology of HFpEF. Implementation of specialized exercise-based cardiac rehabilitation programs tailored to elderly patients is urgently needed to optimize clinical outcomes in this growing population.

Keywords: Clinical Syndrome; Complications; Elderly; Exercise Training; HFpEF; Immune Inflammation

1. Introduction

Over the past two decades, heart failure with preserved ejection fraction has been of significant interest, yet various aspects of its diagnosis and treatment remain challenging. Heart failure (HF), a clinical syndrome characterized by symptoms and/or signs due to structural or functional cardiac abnormalities, is corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. Globally, HF affects at least 26 million individuals, with prevalence rising steadily due to aging populations. The healthcare cost of HF is substantial and will rise sharply as the population ages [1]. With the aging population, the number of elderly with HF will significantly increase. The population of elderly people aged 60 and above has exceeded 222 million, and over 80% of HF patients are over 65 years old. Elderly patients with HF have a high risk of worsening

of HF leading to hospital readmission [2]. HF is often classified into different categories based on ejection fraction (**Table 1**), with HF with preserved ejection fraction (HFpEF), where the left ventricular ejection fraction (LVEF) ≥ 50% being the most common form of HF [3]. Among people aged ≥ 65, HFpEF is reported to be more common (40%–80%) [4], making Heart Failure with preserved ejection fraction (HFpEF) among the elderly a significant and growing concern, given the aging population worldwide [5].

Though extensive strides have been made in distinguishing and managing heart failure with reduced ejection fraction, the complicated pathophysiology underlying HFpEF—even sharing similar incidence and hospitalization rates—is less amenable to explanation. The associated clinical guidelines remain non-conclusive, and various aspects of HFpEF diagnosis and treatment continue to present significant challenges for clinicians. Despite advances in therapy, there is increasing urgency for accurate diagnosis and timely implementation of guideline-directed medical therapy, yet therapeutic challenges remain substantial [6].

By contrast with HFrEF in its underlying pathophysiology, systemic inflammation and immune dysfunction might play pivotal roles in HFpEF development. Obesity, hypertension, and diabetes are all comorbid conditions that underlie a systemic pro-inflammatory environment through increased circulating levels of inflammatory cytokines and immune cell infiltration in cardiac tissues [7]. This inflammatory environment leads to coronary microvascular endothelial dysfunction, which reduces nitric oxide bioavailability and cyclic guanosine monophosphate (cGMP) signaling in adjacent cardiomyocytes, promoting myocardial stiffness and fibrosis. Heart failure can occur in a multitude of conditions due to degeneration of tissues and various organs in aged subjects. The elderly also have multiple diseases concurrently, quality of life is severely damaged, and incidence and mortality are significantly increased yearly. The aging process itself is due to immunosenescence and inflammaging and predisposes immune-mediated myocardial injury in aged HFpEF patients. Recent studies have shown that nitrosative stress plays an important role in advancing HFpEF and have proved that increased activity of inducible nitric oxide synthase (iNOS) plays a part in cardiomyocyte dysfunction by disturbing central cellular processes [8].

Table 1. Classification of heart failure.

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤ 40%
HFimpEF (HF with improved EF)	Previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures
HFpEF (HF with preserved EF)	LVEF ≥ 50% Evidence of spontaneous or provokable increased LV filling pressures

Exercise training may serve as a powerful immunomodulatory intervention capable of addressing the underlying inflammatory pathophysiology of HFpEF. Unlike pharmacological interventions that target specific pathways, exercise training exerts pleiotropic effects on immune function, potentially reversing the chronic low-grade inflammatory state characteristic of elderly HFpEF patients. Exercise-based interventions have consistently demonstrated large, significant, clinically meaningful improvements in symptoms, objectively determined exercise capacity, and quality of life in HFpEF patients [9]. Research progress on exercise rehabilitation for heart failure with preserved ejection fraction has highlighted the potential of structured exercise programs to improve not only functional capacity but also the underlying pathophysiological abnormalities [10]. Furthermore, this success may be attributed to the pleiotropic effects of exercise, which may favorably affect the full range of abnormalities that contribute to exercise intolerance in HFpEF. However, the underlying immunological mechanisms remain poorly characterized.

Despite significant advances in pharmacological treatment of heart failure with preserved ejection fraction (HFpEF) in recent years, non-pharmacological treatment strategies, particularly exercise interventions based on immunomodulatory mechanisms, remain insufficiently explored. Currently, there is a lack of comprehensive reviews that systematically integrate the immunopathological mechanisms of HFpEF with the immunomodulatory effects of exercise training. This review aims to fill this knowledge gap and provide novel non-pharmacological therapeutic strategies based on immune-inflammatory regulation for elderly patients with HFpEF. How to promote survival rate and quality of life in aged HFpEF patients through regulated regulation of immune response, reduction in inflammation response, and intervention through exercise may become a future therapeutic challenge [11].

2. Methods

This narrative review synthesized literature from PubMed, Embase, and Cochrane Library databases covering January 2010 to December 2023. Search terms included combinations of "heart failure with preserved ejection fraction", "HFpEF", "elderly", "aging", "immune dysfunction", "inflammation", "exercise training", "cardiac rehabilitation", "frailty", "sarcopenia", and "malnutrition". Inclusion criteria encompassed original research articles, systematic reviews, and clinical guidelines published in English focusing on HFpEF pathophysiology, immunological mechanisms, and exercise interventions in elderly populations. Exclusion criteria included case reports, editorials, and studies exclusively examining HFrEF. Reference lists of selected articles were manually searched for additional relevant publications. The literature selection process was conducted independently with a focus on studies reporting immunological parameters and exercise outcomes in elderly HFpEF patients.

3. Characteristics of HFpEF

3.1. Exercise Intolerance and Cardiopulmonary Dysfunction

Exercise intolerance (EI) is a key clinical manifestation in HFpEF patients, reflecting underlying immune-mediated pathophysiology rather than simply cardiac dysfunction. In HFpEF, systemic inflammation contributes to EI through multiple mechanisms. Pro-inflammatory cytokines, particularly TNF-α, IL-1β, and IL-6, directly impair skeletal muscle function and metabolism, while simultaneously promoting endothelial dysfunction. In elderly HFpEF patients, circulating levels of these inflammatory mediators often inversely relate to exercise capacity as measured by peak oxygen uptake (VO_2 peak). The NLRP3 inflammasome activation in both cardiac and skeletal muscle tissue creates a self-perpetuating cycle of inflammation and tissue dysfunction that manifests clinically as fatigue and dyspnea during exertion, significantly reducing quality of life.

Cardiorespiratory fitness (CRF) reflects the integration of ventilation (pulmonary function), circulation (systemic and pulmonary hemodynamics), and metabolism (skeletal and respiratory muscle efficiency) to support oxygen delivery and utilization during dynamic aerobic activity (**Figure 1**). CRF is now recognized as a clinical vital sign due to its prognostic value in assessing health trajectories, diagnosing unexplained exertional symptoms (e.g., dyspnea), and evaluating responses to therapeutic interventions [12].

In patients with heart failure with preserved ejection fraction (HFpEF), the decline in CRF is primarily driven by impairments in peripheral oxygen diffusion and utilization, which reduce oxygen absorption capacity. However, recent studies suggest that peripheral oxygen utilization can be quantitatively assessed through the arterial-mixed venous oxygen content difference [$C(a\text{-}v)O_2$]. Peak $C(a\text{-}v)O_2$, which reflects peripheral oxygen extraction efficiency, is a critical determinant of exercise capacity in HFpEF patients [13]. Abnormalities in peak $C(a\text{-}v)O_2$ may contribute to: i) Hemodynamic dysregulation, ii) Exercise-induced pulmonary injury, iii) Skeletal muscle dysfunction [14].

3.2. Immune Dysfunction in HFpEF

Immune system dysfunction plays a crucial role in the pathophysiology of HFpEF, involving complex interactions between innate and adaptive immunity that collectively drive cardiac dysfunction. In HFpEF patients, a chronic low-grade inflammatory state represents a significant feature, with comorbidities triggering systemic inflammation that affects cardiac function through coordinated immune responses (**Figure 2**). The innate immune system, particularly macrophages, plays a vital role in HFpEF pathogenesis and serves as the primary responder to tissue damage and metabolic stress. Significantly increased macrophage infiltration occurs in the myocardial tissue of HFpEF patients, with these macrophages promoting cardiac fibrosis and remodeling through secretion of pro-fibrotic factors. Cardiac macrophages directly contribute to diastolic dysfunction in HFpEF through complex inflammatory mechanisms [15]. These activated innate immune cells subsequently influence adaptive immunity through antigen presentation and cytokine production, where macrophage-derived cytokines polarize T cell responses, while T cell-derived factors further activate and sustain macrophage inflammatory functions, creating a self-perpetuating inflammatory cascade. The PROMIS-HFpEF study provided substantial evidence that the complex inflammatory network in HFpEF involves elevated levels of pro-inflammatory cytokines, which serve as both characteristics of HFpEF patients and independent predictors of disease prognosis [16].

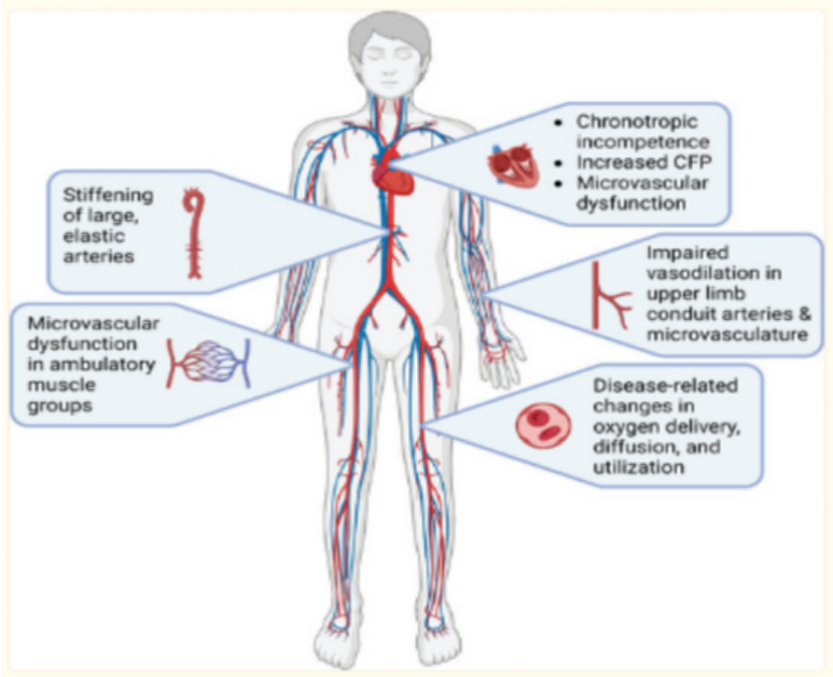

Figure 1. Overview of disease-related changes in cardiac, vascular and skeletal muscle function that contribute to exercise intolerance in patients with HFpEF.

Note: The figure displays a human body outline with labeled pathophysiological alterations: chronotropic incompetence, increased cardiac filling pressure (CFP), microvascular dysfunction in ambulatory muscle groups, stiffening of large elastic vessels, impaired vasodilation in upper limb/coronary arteries/microvasculature, and disease-related changes in oxygen delivery, diffusion, and utilization. (From: Experimental Physiology).

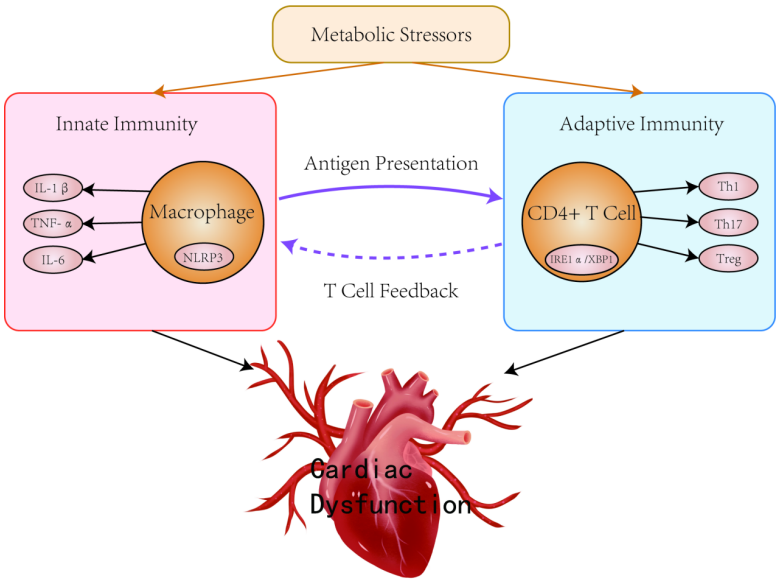

Figure 2. Immune dysfunction and cardiac pathophysiology in HFpEF.

Note: The diagram illustrates metabolic stressors activating macrophages, NLRP3 inflammasome activation, cytokine release (TNF-α, IL-1β, IL-6), antigen presentation to CD4+ T cells, T cell activation with IRE1α/XBP1 pathway dysfunction, and resulting myocardial fibrosis, diastolic dysfunction, and microvascular dysfunction. Arrows indicate interaction pathways between innate and adaptive immune responses.

The adaptive immune system's role in HFpEF involves CD4+ T cells, which play important functions in HFpEF pathophysiology. Research discovered enhanced infiltration of CD4+ T cells in the myocardium in experimental HFpEF, demonstrating that dysfunction of the endoplasmic reticulum stress response (IRE1α/XBP1) pathway in-

duced a shift towards an inflammatory phenotype, with T cell-specific deficiency of XBP1 being accompanied by increased inflammatory responses that are responsible for adverse cardiac remodeling in cardiometabolic HFpEF [17]. The interaction between immune and metabolic systems plays an important role in the initiation and progression of HFpEF. The interaction between immune and metabolic systems plays an important role in the initiation and progression of HFpEF. Metabolic diseases like obesity and diabetes induce chronic inflammation through various mechanisms, with both arms of immunity being implicated in cardiomyocyte response and alterations in systemic and cardiac immune responses serving as key players in the disease pathophysiology [18]. Additionally, SGLT2 inhibition has been shown to modulate NLRP3 inflammasome activity through mechanisms involving ketone bodies and insulin signaling, suggesting potential therapeutic approaches targeting inflammation in HFpEF patients with metabolic comorbidities [19].

A comprehensive explanation of these immunological processes contributes to the design of innovative therapeutic strategies for HFpEF in which inflammasome inhibitors, cytokine antagonists, and immune cell-targeted therapy can contribute toward improving patient outcomes. Understanding the intricate crosstalk between innate and adaptive immunity provides a foundation for developing precision immunomodulatory approaches tailored to individual immune phenotypes in HFpEF patients.

3.3. Risk Factors for HFpEF

Based on a literature review of databases such as PubMed, Embase, and Cochrane Library (2010–2023), several key risk factors contribute to increased HFpEF prevalence.

3.3.1. Age and Gender Factors

Age represents a predominant risk factor for HFpEF development. About 2% of people under 60 years old suffer from heart failure, while the proportion rises dramatically to 10% in those over 75 years old [20]. While age-specific heart failure incidence is decreasing overall, this decline is less dramatic for HFpEF than for HFrEF, indicating HFpEF's stronger association with advancing age [21]. However, due to changes in dietary patterns, lifestyle modifications, and earlier onset of myocardial infarction, the age of HFpEF onset is also advancing, with increased incidence rates observed in people aged $\leq$ 45 years [22]. Gender differences also play a significant role, as women of the same age are more likely to develop HFpEF than men, with symptoms becoming more pronounced after menopause. This phenomenon relates to postmenopausal estrogen deficiency, as estrogen serves as an important regulator of lipid metabolism, reducing low-density lipoprotein while increasing triglyceride and high-density lipoprotein levels, thereby providing cardiovascular protection. However, epidemiological reports from the United States indicate that after adjusting for population composition and other heart failure-related risk factors, no significant difference in HFpEF risk exists between men and women [23].

3.3.2. Chronic Inflammation

A growing body of research describes chronic low-grade inflammation as a key risk factor for HFpEF progression. Increased levels of inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been independently linked to HFpEF development and suggest a unique inflammatory pattern in its pathogenesis [24]. The ongoing presence of inflammation creates a feed-forward response where inflammatory processes result in cardiac fibrosis and increased stiffness, further fueling enhanced inflammatory responses. The activation of NLRP3 inflammasome, a protein complex responsible for processing pro-inflammatory cytokines, plays a crucial role in understanding HFpEF mechanisms [25]. Comorbid conditions such as obesity, diabetes, and hypertension drive an enhanced systemic pro-inflammatory environment, leading to inflammation in the coronary microvascular endothelium and ultimately myocardial stiffness and fibrosis. Recent clinical evidence has demonstrated that canakinumab therapy targeting inflammation resulted in reduced heart failure hospitalizations, particularly in patients with increased inflammatory biomarkers [26], reinforcing the mechanistic relationship between inflammation and HFpEF while identifying potential therapeutic avenues.

3.3.3. Lifestyle and Behavioral Factors

Unhealthy lifestyle patterns, including smoking, alcohol abuse, and physical inactivity, represent closely related risk factors for HFpEF occurrence and development. Research demonstrates that cigarette smoking was

similarly associated with both HFpEF and HFrEF risk, with adjusted hazard ratios of approximately 2.0 for both conditions [27]. Additionally, smoking significantly increases the risk of adverse outcomes in HFpEF patients, suggesting that timely smoking cessation strategies may help improve patient outcomes [28]. Conversely, regular physical activity provides protective benefits, as HFpEF patients exercising for more than 150 minutes per week show significantly reduced hospitalization risk (HR = 0.70, 95% CI 0.49–1.00) [29]. The sedentary lifestyle prevalent in modern society, combined with poor dietary habits, creates a synergistic effect that amplifies cardiovascular risk and promotes the development of metabolic comorbidities that predispose individuals to HFpEF.

3.3.4. Metabolic Risk Factors

Obesity serves as an important cardiovascular risk factor and high-risk predictor of HFpEF. More than 80% of HFpEF patients are obese or overweight, with research demonstrating a U-shaped relationship between body mass index (BMI) and HFpEF risk [30]. For every 1 kg/m^2 increase in BMI within the 25 to 35 kg/m^2 range, heart failure risk increases by 5% in men and 7% in women [31]. Other significant metabolic risk factors form a cluster of interconnected conditions that frequently coexist in HFpEF patients. Hypertension is present in 90% of cases, representing the most common comorbidity and contributing to increased cardiac afterload and subsequent diastolic dysfunction. Hyperlipidemia affects 62% of patients and promotes endothelial dysfunction and accelerated atherosclerosis. Diabetes mellitus occurs in 52% of cases and creates a state of chronic inflammation while impairing myocardial metabolism. Obesity and related cardiometabolic traits, including insulin resistance, are more strongly associated with risk of future HFpEF versus HFrEF, with this differential risk being particularly pronounced among women [32]. These metabolic comorbidities often cluster together, creating a synergistic effect that amplifies individual risk factors and promotes the chronic inflammatory state characteristic of HFpEF pathophysiology.

4. Complications in HFpEF

Elderly patients with HFpEF frequently develop multiple complications, including frailty syndrome, sarcopenia, and malnutrition, which significantly impact prognosis and quality of life. These complications share common immunoinflammatory pathways that both contribute to and result from the underlying HFpEF pathophysiology (**Table 2**).

Table 2. Summary of HFpEF complications: immunological mechanisms and clinical impact.

Complication	Definition	Prevalence in HFpEF	Key Inflammatory Markers	Primary Immune Mechanisms	Clinical Consequences	Exercise Training Benefits
Frailty Syndrome	Decreased physiological reserve with reduced stress tolerance	19–52% in heart failure patients; 94% in HFpEF studies	↑IL-6, ↑TNF-α, ↑CRP, ↓IL-10	Inflammaging, NF-κB activation, immune cell senescence	15-fold ↑ death/ hospitalization risk	↓Inflammation, ↑functional capacity
Sarcopenia	Progressive loss of muscle mass, strength, and function	30–52% in chronic HF; up to 98% in acute HF	↑TNF-α, ↑IL-6, ↓IL-10, ↑myokines	Ubiquitin-proteasome activation, satellite cell dysfunction	↑MACE risk, ↓quality of life, ↓exercise capacity	↑Muscle protein synthesis, ↓inflammation
Malnutrition	Inadequate nutrient intake/ absorption with altered body composition	Variable, higher in elderly	↓Short-chain fatty acids, ↓IL-10, ↑bacterial translocation products	Gut dysbiosis, intestinal barrier dysfunction, systemic inflammation	Volume overload, cardiac structural changes, ↑mortality	↑Gut health, ↓systemic inflammation

Note: ↑ = increased; ↓ = decreased.

4.1. Frailty Syndrome

Frailty is a common geriatric syndrome characterized by decreased physiological reserve capacity and reduced tolerance to stressors, manifesting as disability, functional decline, and increased vulnerability to adverse outcomes, including hospitalization and death [33]. The prevalence of frailty among heart failure patients ranges from 19.0% to 52% [34]. In patients aged ≥ 80 years with heart failure, frailty incidence exceeds 70%, compared to 10% to

20% in the general population aged ≥ 65 years. Among HFpEF patients specifically, frailty prevalence reaches 94%, likely related to the older age and higher comorbidity burden characteristic of this population [35,36]. The core immunological mechanism underlying frailty involves "inflammaging"—a state of chronic low-grade inflammation characterized by persistently elevated pro-inflammatory cytokines, including IL-6, TNF-α, and CRP, with relatively decreased anti-inflammatory factors like IL-10. Frail HFpEF patients exhibit elevated inflammatory markers that promote chronic systemic inflammation, serving as a key driver of both frailty and HFpEF pathogenesis [37]. This inflammatory state activates the NF-κB signaling pathway across multiple tissues, promoting cellular senescence and tissue dysfunction. Additionally, immune cell senescence, particularly in the adaptive immune system, results in reduced T cell repertoire diversity and increased pro-inflammatory T cell subsets, further exacerbating the systemic inflammatory environment. Frailty substantially increases morbidity and mortality in HFpEF patients. The risk of death and hospitalization in patients with chronic heart failure combined with frailty increased approximately 15-fold compared with non-frail patients [38]. The presence of frailty complicates treatment decisions and necessitates tailored therapeutic approaches that consider reduced physiological reserve. Annweiler et al. emphasized that practical management of frailty in older heart failure patients requires comprehensive geriatric assessment and multidisciplinary interventions to optimize clinical outcomes [39].

4.2. Sarcopenia

Sarcopenia is a geriatric clinical syndrome characterized by age-related progressive, systemic loss of skeletal muscle mass and/or decreased muscle strength and physiological function [40]. In HFpEF, sarcopenia primarily affects skeletal muscles and often precedes weight loss [41]. Sarcopenia affects approximately 10% of elderly individuals (≥ 65 years) in the general population, with incidence rates rising to 25–50% among those ≥ 85 years old [42]. Among chronic heart failure patients, 30% to 52% develop sarcopenia, with HFpEF patients exhibiting higher rates. In acute decompensated heart failure, up to 98% of elderly patients present with sarcopenia [43,44]. The immunological mechanisms of sarcopenia in HFpEF involve a complex cytokine network promoting muscle catabolism. Pro-inflammatory cytokines, particularly TNF-α and IL-6, activate the ubiquitin-proteasome system in skeletal muscle, accelerating protein degradation while suppressing protein synthesis pathways [45]. These inflammatory mediators also impair satellite cell function, limiting muscle regenerative capacity. Furthermore, chronic inflammation enhances the production of myokines that can further exacerbate systemic inflammation, creating a detrimental cycle between cardiac dysfunction and skeletal muscle wasting. HFpEF-related vascular endothelial damage and dysfunction affect skeletal muscle structure and function by impairing oxygen supply and vasodilation, making it difficult to maintain metabolic balance and oxygen supply, ultimately leading to exercise intolerance [46]. Sarcopenia significantly reduces quality of life and physical fitness in HFpEF patients. Heart failure patients with sarcopenia are typically older, have more comorbidities, and exhibit higher B-type natriuretic peptide (BNP) levels [43]. Sarcopenia not only increases heart failure incidence in the elderly but also significantly elevates the risk of major adverse cardiovascular events (MACE) [44].

4.3. Malnutrition

Malnutrition in HFpEF encompasses inadequate nutrient intake, absorption, or utilization, leading to altered body composition and impaired physiological function. Primary causes include gastrointestinal congestion resulting in appetite loss and nutrient malabsorption, complex dietary restrictions, and poor adherence to nutritional recommendations. While specific prevalence data for malnutrition in HFpEF patients varies across studies, elderly heart failure patients demonstrate particularly high susceptibility to nutritional deficiencies due to multiple contributing factors, including medication effects, dietary restrictions, and underlying pathophysiology. Recent evidence suggests that malnutrition in HFpEF associates with gut microbiota dysbiosis and intestinal barrier dysfunction. Malnourished HFpEF patients exhibit altered gut microbial composition with increased intestinal permeability [47]. This dysbiosis promotes bacterial translocation, allowing bacterial products to enter circulation, activating immune cells, and triggering systemic inflammation. The resulting inflammatory environment contributes to myocardial stiffness, fibrosis, and worsening diastolic function characteristic of HFpEF. Malnutrition increases inflammatory factor levels within the body, reducing nitric oxide utilization, weakening cyclic guanosine monophosphate response, and accelerating cardiomyocyte atrophy and contraction, leading to fibrosis and diastolic dysfunction [48]. Additionally, impaired intestinal function in malnourished patients results in intestinal flora shifts, with flora metabolites such as short-chain fatty acids and indoles acting as "messengers" to activate various pathways

affecting brain cells, influencing host appetite and endocrine regulation, leading to decreased growth hormone and insulin-like growth factors [49,50]. Malnutrition contributes significantly to mortality in elderly HFpEF patients through multiple mechanisms. Malnourished patients experience low protein levels, reduced intravascular colloid osmotic pressure, and severe water and sodium retention, resulting in cardiac volume overload and structural cardiac changes. As HFpEF progresses in elderly patients, nutritional status gradually deteriorates, potentially leading to cardiac cachexia.

4.4. Evidence from Clinical Trials

Table 3 summarizes the key clinical trials and meta-analyses evaluating exercise interventions in elderly HFpEF patients. The evidence consistently demonstrates that structured exercise programs, whether aerobic, resistance, or combined training, lead to significant improvements in functional capacity, quality of life, and clinical outcomes. These benefits are observed across different exercise modalities and patient populations, supporting exercise training as a cornerstone therapy for elderly HFpEF patients.

Table 3. Summary of Key Clinical Trials and Meta-Analyses on Exercise Interventions in Elderly HFpEF Patients.

Study Type	Population	Intervention	Primary Outcomes	Key Findings
Edelmann et al. [51]	64 HFpEF patients (age 65 ± 7 years, 56% female)	Supervised endurance/resistance training vs UC for 3 months	Peak VO2, diastolic function, QoL	Peak VO_2 improved; E/e' decreased from 12.2 ± 3.5 to 10.1 ± 3.0; improved physical QoL
Pandey et al. [52]	276 patients from 6 RCTs	Exercise training	Exercise capacity, safety	No exercise-related major adverse events reported; consistent improvements in exercise capacity
Fukuta et al. [53]	5 RCTs on exercise (245 patients), 8 RCTs on drugs (1080 patients)	Exercise training vs pharmacotherapy	Functional capacity, QoL	Exercise training improved functional capacity and QoL; mean difference in MLWHFQ: −5.8 points
Nolte et al. [54]	64 HFpEF patients (65 ± 7 years, 56% female)	ET (n = 44) vs UC (n = 20) for 3 months	QoL dimensions, depression	Improved physical, mental, and social dimensions of QoL; reduced depression symptoms
Baral et al. [55]	14 RCTs, 629 participants (mean age 68.1 years, 63.2% female)	Endurance training (10 studies), IMT (3), FES (1)	Peak VO2, 6MWT, QoL	WMD in peak VO_2: 2.25 ml/kg/min (95% CI 1.81–2.70); significant improvement in 6MWT distance
Edelmann et al. [56]	322 HFpEF patients (mean age 70 years, 59.6% female)	Combined endurance/resistance training vs UC for 12 months	Modified Packer score	20.5% improved in ET vs 8.1% in UC; significant improvements in peak VO_2 and NYHA class

5. The Role of Exercise Training in HFpEF

5.1. Immunological Basis of Exercise Training in HFpEF

The immunological effects of exercise in HFpEF operate through several key mechanisms that fundamentally alter the inflammatory profile characterizing this condition (**Figure 3**). Regular physical activity shifts the immune environment from a pro-inflammatory state toward an anti-inflammatory milieu, directly addressing the underlying pathophysiology of HFpEF. Exercise decreases circulating levels of pro-inflammatory cytokines including, TNF-α, IL-1β, and IL-6, while increasing anti-inflammatory mediators such as IL-10 and IL-1ra [57]. These changes collectively attenuate the chronic low-grade inflammation that underlies HFpEF pathogenesis and contributes to exercise intolerance, cardiac dysfunction, and associated complications.

Exercise training regulates specific immune cell populations involved in HFpEF pathophysiology. In cardiac and skeletal muscle tissue, exercise reduces infiltration of pro-inflammatory M1 macrophages while promoting an anti-inflammatory M2 phenotype. Contracting skeletal muscles release myokines during exercise, particularly IL-6, which paradoxically exerts anti-inflammatory effects by inducing IL-10 and IL-1ra production [58]. Additionally, regulatory T cells increase with regular exercise, enhancing immunosuppressive capacity and limiting excessive

inflammatory responses that contribute to cardiac dysfunction. At the molecular level, exercise inhibits the NF-κB signaling pathway, a master regulator of inflammation controlling numerous pro-inflammatory genes implicated in HFpEF. Exercise also suppresses NLRP3 inflammasome activation in cardiac and skeletal muscle tissue, reducing production of IL-1β and IL-18 that otherwise promote myocardial stiffness and fibrosis characteristic of HFpEF [59]. Exercise training can effectively target the chronic inflammatory state characteristic of HFpEF, making it a promising immunomodulatory therapy that addresses multiple pathophysiological mechanisms simultaneously [60].

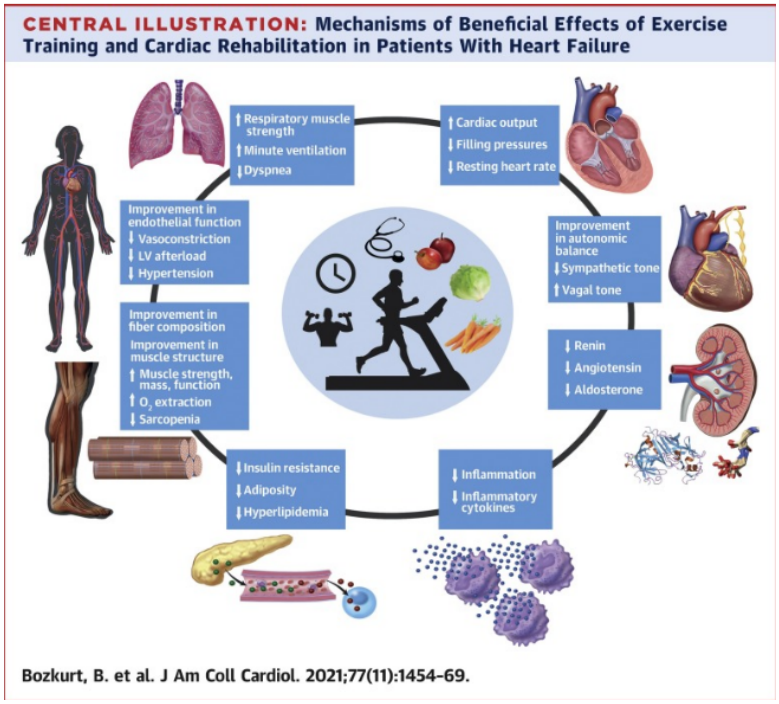

Figure 3. Mechanisms of beneficial effects of exercise training and cardiac rehabilitation in patients with heart failure.

Note: Central figure shows a runner with surrounding organ systems displaying specific improvements: respiratory (enhanced muscle strength, improved ventilation), cardiac (increased output, reduced filling pressures), vascular (improved endothelial function, reduced afterload), skeletal muscle (increased strength/mass, enhanced oxygen extraction), autonomic (improved balance, reduced sympathetic tone), neurohormonal (reduced RAAS activation), metabolic (decreased insulin resistance, reduced adiposity), and anti-inflammatory effects (reduced cytokines). (Adapted from: Bozkurt et al. 2021).

5.2. Exercise Training Effects on HFpEF Complications

5.2.1. Frailty Syndrome

Exercise training directly counteracts the inflammaging process underlying frailty by modulating immune cell function and cytokine production. Regular physical activity enhances the anti-inflammatory capacity of immune cells while reducing pro-inflammatory signaling cascades. Exercise promotes the expansion of regulatory T cells and shifts macrophage populations toward anti-inflammatory phenotypes, effectively reversing the immune dysfunction characteristic of frailty syndrome.

Cardiac rehabilitation programs incorporating both aerobic and resistance training show substantial improvements in functional capacity, reduced inflammatory biomarkers, and enhanced quality of life measures. Exercise interventions consistently demonstrate improvements in physical performance, reduced hospitalization rates, and enhanced independence in activities of daily living among frail HFpEF patients.

Exercise training reduces frailty severity and its associated clinical consequences in HFpEF patients. Regular physical activity improves physiological reserve capacity, enhances tolerance to stressors, and reduces the risk of adverse outcomes, including hospitalization and functional decline. The multidisciplinary approach incorporating tailored exercise programs, nutritional counseling, and comprehensive geriatric assessment optimizes clinical outcomes in frail HFpEF patients [39].

5.2.2. Sarcopenia

Exercise training addresses sarcopenia through dual mechanisms of reducing inflammatory muscle catabolism and promoting anabolic pathways. Physical activity suppresses TNF-α and IL-6-mediated activation of the ubiquitin-proteasome system while simultaneously enhancing satellite cell function and muscle regenerative capacity. Exercise-induced myokines create a favorable local environment for muscle protein synthesis while reducing systemic inflammation that otherwise promotes muscle wasting.

Resistance training emerges as the most effective intervention for sarcopenia in HFpEF patients. Even nonagenarians can achieve substantial muscle strength gains through high-intensity resistance training [61], while short-term heavy resistance training can eliminate age-related deficits in muscle mass and strength in healthy older males [62]. Combined resistance and aerobic training significantly improves functional capacity and quality of life in obese HFpEF patients [63]. Quiriarte et al., using a multiomic approach, demonstrated that exercise therapy can rescue dysfunctional skeletal muscle lipid and branched-chain amino acid oxidation while restoring exercise capacity in cardiometabolic HFpEF, highlighting the importance of skeletal muscle metabolism in exercise intolerance [64]. Exercise training enhances skeletal muscle oxidative capacity [65], improves neuromuscular function, and increases walking speed in elderly HF patients [66].

Exercise training significantly improves muscle mass, strength, and functional performance in HFpEF patients with sarcopenia. Regular physical activity reduces the risk of major adverse cardiovascular events, enhances exercise tolerance, and improves quality of life across physical, psychological, and social dimensions. Exercise-induced improvements in skeletal muscle function translate to enhanced cardiac metabolism, reduced insulin resistance, and improved overall cardiovascular health through beneficial muscle-heart crosstalk [67].

5.2.3. Malnutrition

Exercise training addresses malnutrition-related immune dysfunction by improving gut microbiota composition and reducing systemic inflammation. Physical activity enhances intestinal barrier function, reduces bacterial translocation, and promotes the growth of beneficial gut bacteria that produce anti-inflammatory metabolites, including short-chain fatty acids. Exercise also improves appetite regulation and nutrient utilization through favorable effects on hormonal and metabolic pathways.

Exercise programs improve nutritional status and reduce malnutrition-related complications in elderly HF patients. Cardiac rehabilitation incorporating nutritional assessment and counseling shows significant improvements in dietary adherence, nutrient intake, and nutritional biomarkers. Exercise training enhances the effectiveness of nutritional interventions and reduces the progression of malnutrition in HFpEF patients.

Exercise training improves nutritional status, reduces inflammation-related nutrient losses, and enhances the clinical response to nutritional interventions. Regular physical activity helps maintain adequate protein levels, improves intravascular oncotic pressure, and reduces fluid retention. Exercise programs that include nutritional education and monitoring demonstrate superior outcomes in preventing progression to cardiac cachexia and improving long-term prognosis [68].

Across all HFpEF complications, exercise training consistently improves health-related quality of life through multidimensional benefits encompassing physical health, emotional well-being, social relationships, and environmental factors (**Figure 4**). These comprehensive improvements demonstrate the holistic impact of exercise interventions beyond specific pathophysiological targets, emphasizing the value of exercise training as a cornerstone therapy for elderly HFpEF patients with multiple complications.

5.3. Exercise as an Integrated Immunomodulatory Strategy in HFpEF

Exercise training represents a unique therapeutic modality that simultaneously addresses multiple pathophysiological mechanisms underlying HFpEF and its complications through coordinated immunomodulatory effects. Unlike pharmacological interventions that typically target single pathways, exercise exerts pleiotropic effects across the immune-inflammatory network, making it particularly well-suited for the complex, multisystem nature of HFpEF in elderly patients. The 2023 American Heart Association and American College of Cardiology Scientific Statement emphasizes that exercise-based interventions have consistently demonstrated large, significant, clinically meaningful improvements in symptoms, objectively determined exercise capacity, and quality of life in HFpEF pa-

tients, attributing this success to the pleiotropic effects of exercise that favorably affect the full range of abnormalities contributing to exercise intolerance [53]. The immunological benefits of exercise training create a beneficial cascade that improves not only individual complications but also their interconnected pathophysiology.

The integrated approach of exercise training addresses the shared inflammatory pathways underlying frailty, sarcopenia, and malnutrition simultaneously. By reducing systemic inflammation, improving immune cell function, and enhancing tissue regenerative capacity, exercise training breaks the vicious cycles that perpetuate these complications in HFpEF patients [49]. The anti-inflammatory effects of exercise complement the cardioprotective benefits, creating synergistic improvements in cardiac function, exercise tolerance, and quality of life.

Future development of exercise-based interventions should focus on personalized approaches that consider individual inflammatory profiles, comorbidity burdens, and functional capacities. The integration of exercise training with emerging technologies, including wearable sensors and artificial intelligence algorithms, may enhance treatment personalization and optimize clinical outcomes. Such comprehensive, immunologically-informed exercise programs represent a promising non-pharmacological strategy for improving outcomes in the growing population of elderly patients with HFpEF.

Despite exercise training's immunomodulatory benefits, several barriers limit its implementation in elderly HFpEF patients. These include physical limitations, fear of exertion, lack of specialized programs, and insufficient healthcare provider awareness. Addressing these challenges requires the development of graduated exercise protocols starting with low-intensity activities, comprehensive patient education about safety and benefits, and training of healthcare professionals in exercise prescription for HFpEF. Additionally, home-based exercise programs with remote monitoring may improve accessibility and adherence, particularly for frail elderly patients who face transportation barriers. The establishment of specialized HFpEF exercise clinics within cardiac rehabilitation centers could provide the expertise and resources necessary to optimize outcomes in this complex patient population.

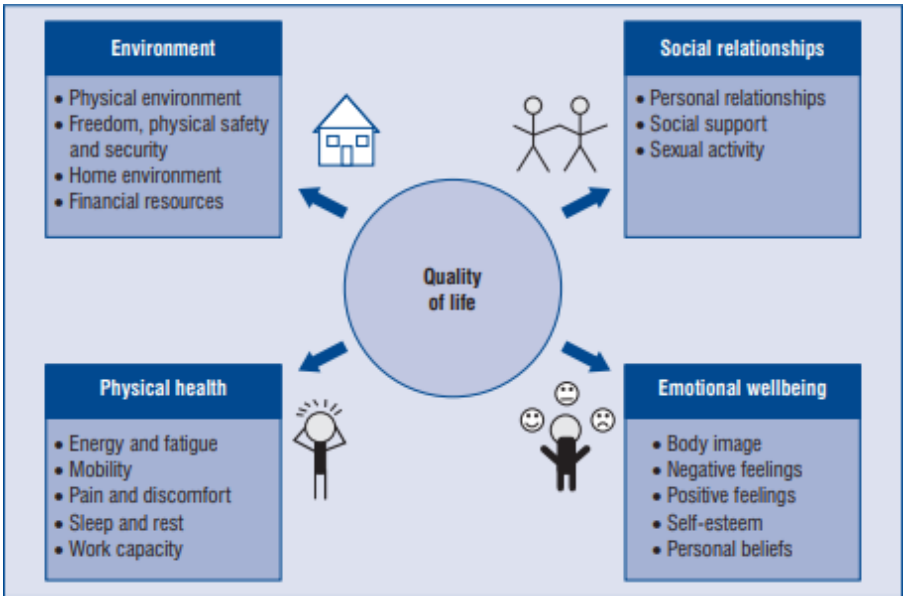

Figure 4. Dimensions of health-related quality of life.

Note: The figure shows four primary dimensions: Physical health (including energy/fatigue, mobility, pain/discomfort, sleep/rest, work capacity), Emotional wellbeing (including body image, negative/positive feelings, self-esteem, personal beliefs), Social relationships (including personal relationships, social support, sexual activity), and Environment (including physical environment, safety, home environment, financial resources).

6. Conclusion

HFpEF in the elderly represents a complex syndrome driven by chronic inflammation and immune dysfunction, manifesting as multiple debilitating complications that severely impact quality of life and prognosis. The interplay between aging, comorbidities, and immune dysregulation creates a challenging clinical scenario where traditional pharmacological approaches often yield limited success. This review has demonstrated that exercise training offers a unique therapeutic approach by directly targeting the underlying immunopathological mechanisms through

coordinated anti-inflammatory effects. Unlike conventional treatments that address symptoms or single pathways, exercise intervention fundamentally modulates the immune-inflammatory network that perpetuates disease progression.

Exercise training's unique value lies in its ability to simultaneously target multiple pathophysiological mechanisms—suppressing NLRP3 inflammasome activation, enhancing regulatory T cell function, and shifting macrophage phenotypes. This multifaceted approach not only improves cardiac function but also addresses the debilitating complications of frailty, sarcopenia, and malnutrition through enhanced muscle oxidative capacity and reduced systemic inflammation. The resulting positive feedback loop, where improved exercise tolerance further reduces inflammation and promotes tissue regeneration, represents a therapeutic advantage that single-target pharmacological interventions cannot achieve. Such comprehensive immunomodulation positions exercise training as an essential therapeutic strategy rather than merely supportive care.

Future research should prioritize developing precision exercise medicine approaches tailored to the heterogeneous HFpEF population. This includes identifying specific biomarker profiles that predict exercise responsiveness, determining optimal exercise modalities and intensities for different HFpEF phenotypes, and elucidating the temporal dynamics of exercise-induced immunomodulation. Mechanistic studies should investigate how exercise timing, duration, and intensity influence inflammatory resolution and tissue repair processes. The integration of emerging technologies offers opportunities for continuous monitoring and real-time adjustment of exercise prescriptions based on individual physiological and inflammatory responses.

Elderly HFpEF patients should undergo initial cardiopulmonary exercise testing and frailty screening before starting exercise programs. Structured programs should prescribe moderate-intensity exercise (50–70% peak VO_2) three times weekly, progressing from aerobic training to combined aerobic-resistance training after 4–5 weeks. Supervised sessions for the first 3 months are essential to ensure safety and proper technique. Implementation of specialized exercise-based cardiac rehabilitation programs, specifically designed for the unique needs of elderly HFpEF patients, represents both an urgent clinical priority and a promising therapeutic frontier for improving outcomes in this rapidly growing patient population.

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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