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Advanced Therapies for Heart Failure with Preserved Ejection Fraction and Amyloidosis: The Role of Weight Loss and Genetic Interventions

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Abstract

Effective weight loss treatment strategies for patients with heart failure with preserved ejection fraction (HFpEF) encompass a multifaceted approach, integrating lifestyle modifications, nutritional interventions, and, in some cases, surgical options. Lifestyle modifications, including dietary changes and increased physical activity, are crucial for managing weight and improving overall health in heart failure patients. These changes can significantly impact weight loss and symptom management, although they may receive less attention compared to pharmacological treatments. Nutritional interventions that focus on reducing caloric intake while enhancing nutritional quality are also vital, as they can aid in achieving sustainable weight loss. For patients experiencing significant fluid retention, diuretic therapy remains a cornerstone of treatment. This approach helps manage weight by alleviating congestion and improving cardiac function, although careful monitoring is necessary to avoid potential adverse effects. In cases of morbid obesity, bariatric surgery presents a viable option, particularly for patients with advanced heart failure. This surgical intervention can lead to substantial weight loss, potentially allowing patients to meet eligibility criteria for heart transplantation. Overall, a combination of these strategies tailored to individual patient needs can optimize weight management in HFpEF, ultimately enhancing quality of life and clinical outcomes.

Keywords: Weight loss, Heart failure, Gene editing, Cardiac amyloidosis

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Introduction

HFpEF represents nearly 50% of all heart failure cases worldwide, making it a substantial burden on healthcare systems (Figure 1) [1]. The condition is particularly prevalent among individuals with obesity, which is considered one of the primary risk factors contributing to its development. Obesity drives a complex interplay of pathophysiological changes, including increased blood volume, heightened cardiac output, and systemic inflammation, all of which place additional stress on the heart's diastolic function. These changes ultimately result in impaired left ventricular filling, elevated filling pressures, and reduced exercise tolerance, hallmark features of HFpEF [2, 3]. In addition to its cardiovascular effects, obesity is frequently accompanied by comorbid conditions such as hypertension, diabetes mellitus, and obstructive sleep apnea, which further exacerbate HFpEF symptoms and worsen long-term outcomes [4, 5].

The rising incidence of HFpEF aligns closely with the global obesity epidemic, which has seen rates triple since the 1970s [6]. As obesity rates continue to climb, particularly in aging populations, the prevalence of HFpEF is projected to increase, creating an urgent need for effective weight management strategies to mitigate its impact (Figure 2) [1]. Research suggests that intentional weight loss can alleviate many of the hemodynamic and metabolic abnormalities associated with obesity in HFpEF, thereby improving cardiac function and quality of life [7]. However, achieving sustainable weight loss in this population remains a challenge due to factors such as limited physical activity tolerance and the complex interplay of hormonal and metabolic dysregulation [8]. Despite these barriers, recent advances in lifestyle interventions, pharmacological therapies, and bariatric procedures offer promising avenues for addressing obesity and improving outcomes in HFpEF patients [9, 10].

Moreover, the link between obesity and HFpEF extends beyond mechanical and hemodynamic burdens to include systemic inflammation and adipose tissue dysfunction [11]. Obesity is associated with the release of pro-inflammatory cytokines and adipokines, which contribute to endothelial dysfunction, oxidative stress, and myocardial fibrosis-key pathophysiological processes in HFpEF [12, 13]. Excess visceral adiposity also promotes ectopic fat deposition around the heart, such as epicardial adipose tissue, which has been shown to directly impair myocardial function and exacerbate diastolic dysfunction

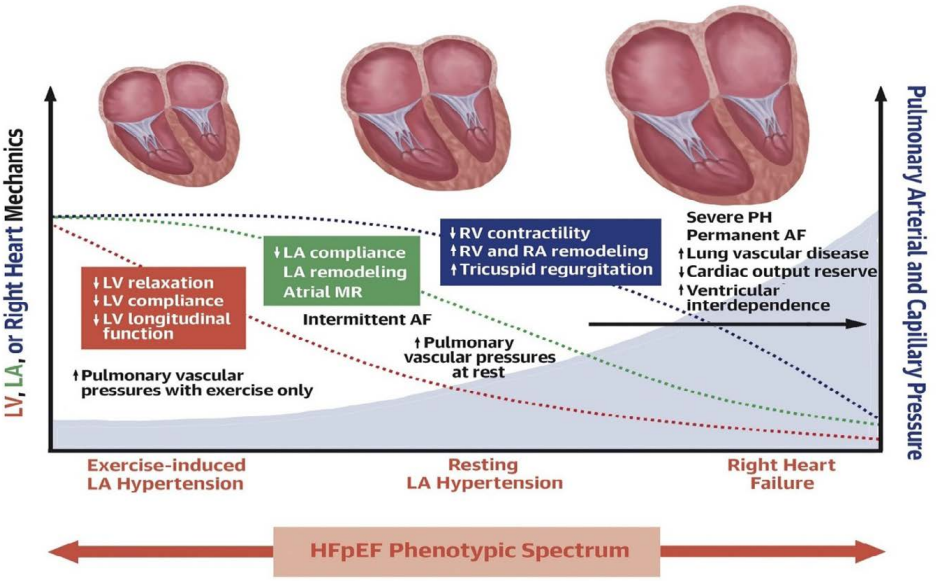

Figure 1: Disease progression in HFpEF reproduced from [1].

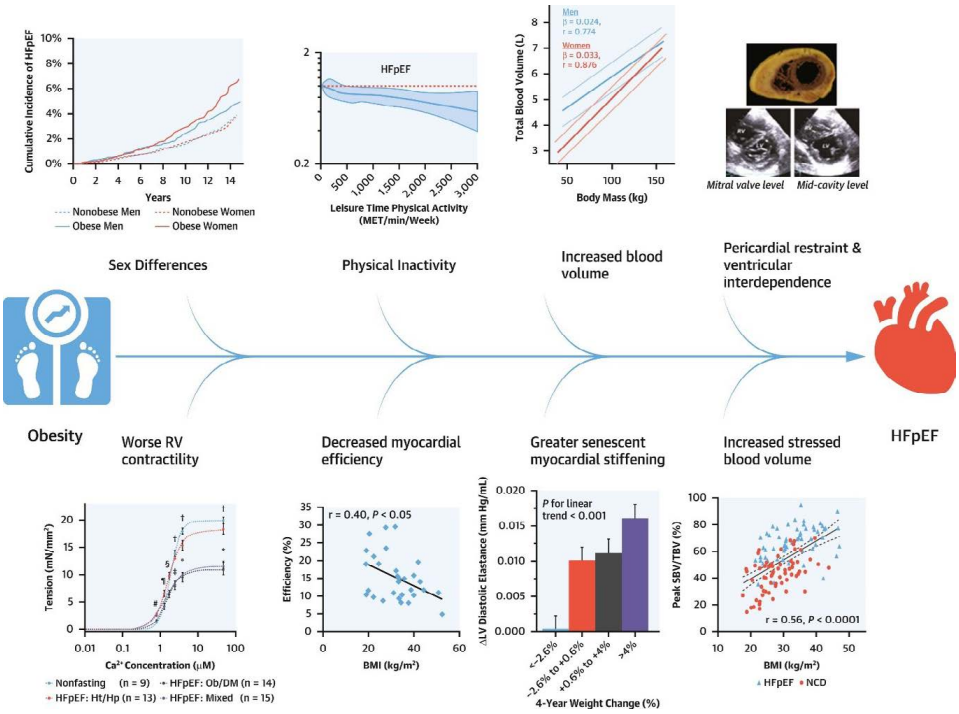

Figure 2: Obesity related HFpEF reproduced from [1].

[14, 15]. Furthermore, obesity-related metabolic abnormalities, such as insulin resistance and altered lipid metabolism, add another layer of complexity to the management of HFpEF [11]. These metabolic disturbances not only worsen cardiovascular outcomes but also reduce the efficacy of conventional heart failure therapies, emphasizing the need for targeted interventions. As such, addressing obesity through a combination of lifestyle changes, pharmacological treatments, and innovative approaches like anti-inflammatory therapies could play a pivotal role in alleviating the burden of HFpEF in this high-risk population [16].

The most effective weight loss treatments for patients with HFpEF in conjunction with gene editing therapies for cardiac amyloidosis involve a combination of lifestyle interventions and advanced gene therapy techniques [17]. The treatment of HFpEF in combination with gene editing for cardiac amyloidosis presents a multifaceted approach to managing complex cardiovascular conditions. HFpEF, often associated with obesity, is a prevalent form of heart failure with limited treatment options. Weight loss interventions have shown promise in improving outcomes for HFpEF patients, while gene editing offers

potential therapeutic avenues for cardiac amyloidosis, a condition characterized by protein misfolding and deposition in the heart [17, 18]. Lifestyle interventions, particularly those focusing on diet and exercise, have shown significant benefits in reducing body weight and improving cardiovascular health in HFpEF patients [19]. Concurrently, gene editing therapies, such as CRISPR-Cas9, offer promising avenues for addressing the genetic underpinnings of cardiac amyloidosis, a condition often associated with HFpEF [20]. Table 1 summarizes the general information about the combination of weight loss treatment in patients with HFpEF and gene editing for the treatment of cardiac amyloidosis.

Weight loss and gene editing therapies have shown promising potential in impacting the progression of cardiac amyloidosis in patients with HFpEF. These interventions target different aspects of the disease, offering a multifaceted approach to treatment. Weight loss primarily addresses the metabolic and hemodynamic aspects of heart failure, while gene editing therapies focus on the molecular pathology of amyloidosis [21]. Together, they may provide synergistic benefits in managing cardiac amyloidosis in HFpEF patients.

Weight Loss in HFpEF

Weight loss through lifestyle interventions has been associated with improved outcomes in HFpEF patients. Intentional weight loss has emerged as a promising therapeutic approach to mitigate these adverse effects. A study demonstrated that an intensive lifestyle management program resulted in approximately 7% body weight reduction in patients with HFpEF and obesity, leading to significant improvements in exercise capacity and quality of life [22]. A systematic review and meta-analysis found that weight loss led to significant reductions in body weight, blood pressure, and improvements in aerobic capacity and quality of life [23]. In animal models, weight loss improved cardiac function and energy metabolism, suggesting potential benefits in reducing cardiac hypertrophy and enhancing insulin signaling [24]. For patients with severe obesity, bariatric surgery has been associated with reductions in heart failure hospitalizations and improved medium-term mortality. It is considered a viable option for achieving significant weight loss and improving heart failure outcomes [25]. Several clinical trials (Table 2) have investigated the efficacy of weight loss interventions in this population, demonstrating significant improvements in symptoms, exercise capacity, and quality of life.

Table 1: Summary of the general information.

Aspect	Weight loss in HFpEF	Gene editing for cardiac amyloidosis
Condition	HFpEF	Cardiac amyloidosis (specifically ATTR)
Primary goal	Improve heart function, reduce symptoms, and enhance quality of life through weight loss	Reduce misfolded TTR protein deposition in the heart, improve heart function
Mechanism	Weight loss reduces hemodynamic stress, enhances cardiac function, and reduces inflammation	Gene editing (e.g., CRISPR-Cas9) to decrease TTR production, preventing amyloid fibril deposition
Common interventions	Caloric restriction, physical activity and pharmacological treatments (GLP-1 agonists and bariatric surgery)	Gene editing technologies like CRISPR-Cas9 to target and modify TTR gene expression
Target population	Obese individuals with HFpEF	Patients with hereditary or wild-type TTR amyloidosis (affects the heart and other organs)
Recent studies/trials	Several clinical trials (e.g., STEP-HFpEF, SUMMIT, and Wegovy)	CRISPR-based treatments (e.g., NTLA-2001 trial and Intellia Therapeutics)
Potential outcomes	Reduction in symptoms, improved exercise capacity, quality of life, and weight loss	Significant reduction in circulating TTR, stabilization or improvement in disease progression
Challenges	Adherence to weight loss regimens and managing comorbidities	Delivery of gene-editing therapies, long-term safety and efficacy concerns
Clinical significance	Significant improvements in HFpEF symptoms and quality of life in obese individuals	Potential for permanent disease modification, offering hope for advanced cases of cardiac amyloidosis
References	STEP-HFpEF, SUMMIT, and other obesity-related HFpEF studies	Clinical trials such as NTLA-2001, Intellia's phase 1 study, and related studies on CRISPR

Table 2: Summarizes the interventions and key clinical outcomes.

Study name/type	Patient type (sample size)	Objective	Intervention	Clinical outcomes
STEP-HFpEF Trial [26]	HFpEF patients with obesity (n = 529)	To evaluate the effects of semaglutide on weight loss, symptoms, and quality of life in obese HFpEF patients	Semaglutide (GLP-1 agonist)	Weight loss: 13.3% (95% CI -11.9 to -9.4; $p < 0.001$). KCCQ score improvement: +16.6 points (95% CI 4.8 to 10.9; $p < 0.001$).
Caloric restriction and exercise [27]	HFpEF patients (n = 100)	To investigate the impact of caloric restriction and aerobic exercise on functional capacity in HFpEF patients	Diet and aerobic exercise	Peak oxygen consumption increases: 12% (95% CI 0.7 to 1.7; $p < 0.001$). Weight loss: 10.4%.
SUMMIT trial [28]	HFpEF patients with obesity (n = 630)	To assess the efficacy of tirzepatide in improving weight loss and heart failure outcomes in HFpEF patients	Tirzepatide (GIP/GLP-1 agonist)	-
Wegovy (Semaglutide) trial [29]	HFpEF patients with obesity (n = 478)	To study the effects of semaglutide on physical function and quality of life in obese HFpEF patients	Semaglutide	-
Weight loss and mortality study [30]	HFpEF patients (n = 1515)	To examine the relationship between intentional weight loss and mortality in HFpEF patients	Intentional weight loss	Weight loss was associated with higher risk of mortality (HR 1.42, 95% CI 1.06 to 1.89; $p = 0.002$). Weight gain had similar risk of mortality (HR 0.98, 95% CI 0.68 to 1.42; $p = 0.932$) compared with weight stability.
Semaglutide and NT-proBNP study [31]	Obese HFpEF patients (n = 1145)	To evaluate the impact of semaglutide on NT-proBNP levels and heart failure symptoms in HFpEF	Semaglutide	NT-proBNP reduction: Significant (0.82; 95% CI 0.74 to 0.91; $p = 0.0002$). Symptom improvement: Greater in patients with high baseline NT-proBNP (estimated difference: tertile 1: 4.5 points, 95% CI 0.8 to 8.2; tertile 2: 6.2 points, 95% CI 2.4 to 10.0; tertile 3: 11.9 points, 95% CI 8.1 to 15.7; $p = 0.02$; baseline NT-proBNP as a continuous variable: $p = 0.004$).

Lifestyle interventions

A systematic review and meta-analysis demonstrated that lifestyle interventions, including diet and exercise, significantly reduced body weight by over 5 kg and improved blood pressure, aerobic capacity, and quality of life in HFpEF patients [23]. These interventions are crucial as obesity exacerbates HFpEF symptoms and outcomes [32]. High-intensity interval training and low-intensity training have been particularly effective in improving exercise tolerance and quality of life, with high-intensity interval training showing the most significant improvements in peak oxygen uptake and Minnesota living with heart failure questionnaire scores [33]. A chronic lack of exercise is a risk factor for HFpEF in certain individuals (Figure 3) [34].

A randomized clinical trial assessed the impact of caloric restriction and aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with HFpEF. The study found that both interventions led to significant improvements in exercise capacity and quality of life measures. The combination of diet and exercise resulted in additive benefits, highlighting the importance of lifestyle modifications in this patient population [27]. The concept of the "obesity paradox" suggests that higher body mass index may confer a survival benefit in heart failure patients. However, intentional weight loss through structured interventions has been shown to improve functional capacity and quality of life in obese HFpEF patients, challenging the notion of the obesity paradox in this context [35].

Pharmacological approaches

Pharmacological interventions have also been explored to facilitate weight loss in HFpEF patients. Emerging treatments like glucagon-like peptide-1 (GLP-1) receptor agonists have shown efficacy in reducing appetite and achieving substantial weight loss, which can alleviate HFpEF symptoms [36]. The STEP-HFpEF trial investigated the efficacy of semaglutide, a GLP-1 receptor agonist, in this cohort. Results indicated that semaglutide treatment led to substantial weight reduction and improved physical function compared to placebo. Specifically, patients receiving semaglutide experienced greater weight loss and enhancements in heart failure-related symptoms [26]. These findings suggest that semaglutide may offer dual benefits of weight loss and symptomatic relief in obese HFpEF patients. A study published examined the associations of weight loss or gain with all-cause mortality risk in HFpEF patients. The findings suggested that intentional weight loss was associated with a reduced risk of mortality, emphasizing the potential benefits of weight management in this population [30].

The SUMMIT trial investigated the efficacy of tirzepatide, a dual GIP and GLP-1 receptor agonist, in adults with HFpEF and obesity. Tirzepatide demonstrated significant improvements in primary and secondary endpoints, including a 38% reduction in the risk of heart failure outcomes and a notable reduction in body weight compared to placebo [28]. The European Medicines Agency endorsed Novo Nordisk's Drug Wegovy (semaglutide) for easing heart failure in obese patients, marking its second approval beyond weight loss. A late-stage study indicated significant weight loss and a 16.6 point improvement on a 100 point health scale after one year on the drug [29]. The HuMAIN trial is investigating HU6, a mitochondrial uncoupling agent, which promotes weight loss by increasing fat oxidation while preserving muscle mass, potentially benefiting HFpEF patients with obesity [37].

Gene Editing for Cardiac Amyloidosis

Gene editing technologies, particularly CRISPR-Cas9, hold significant promise for treating cardiac amyloidosis, a condition that can lead to HFpEF [17]. This innovative approach targets the genetic underpinnings of the disease, offering potential for more effective and lasting treatments. CRISPR-Cas9 has been explored in clinical settings for its ability to edit genes responsible for Transthyretin Amyloidosis (ATTR), a common form of cardiac amyloidosis. The potential benefits

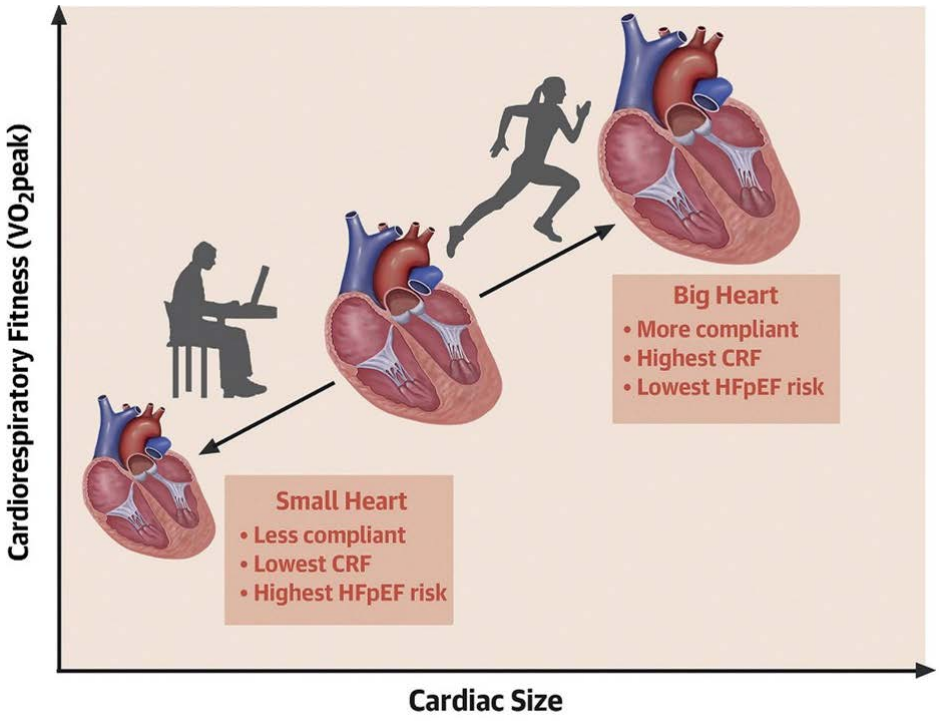

Figure 3: Correlation of physical activity and cardio fitness reproduced from [34].

and risks of using CRISPR for this purpose are multifaceted. Gene editing, particularly using CRISPR/Cas9, offers a promising approach to treating cardiac amyloidosis by correcting genetic mutations responsible for protein misfolding [38]. This method could potentially modify the disease course by targeting the underlying genetic causes.

Small interfering ribonucleic acid (RNAs) and antisense oligonucleotides are being explored to silence genes contributing to amyloid deposition, providing a disease-modifying therapy for cardiac amyloidosis [39]. These molecules disrupt the messenger RNA responsible for Transthyretin (TTR) synthesis, reducing amyloid fibril formation. Drugs like patisiran and inotersen have shown efficacy in treating ATTR, with ongoing trials exploring their impact on cardiac manifestations [39, 40]. Gene editing therapies, such as patisiran, a double-stranded RNA-based gene silencing therapy, have demonstrated significant reductions in cardiac amyloid burden. In a study, 45% of patients treated with patisiran showed cardiac amyloid regression, with a notable decrease in extracellular volume and improvement in functional capacity as measured by the six-minute walk test [41]. These therapies target the underlying genetic mutations responsible for amyloid production, offering a disease-modifying approach that can potentially halt or reverse disease progression [39, 42]. These strategies represent a shift from symptomatic treatment to addressing the root cause of the disease.

Innovations in gene editing, such as base and prime editors, enhance precision and efficiency, opening new possibilities for treating cardiomyopathies [43]. Gene editing has shifted the perception of cardiac amyloidosis from a fatal disease to one that is treatable with specific therapies. This approach could significantly improve the management of HFpEF by addressing one of its underlying causes [40].

In a landmark study, a single intravenous infusion of NTLA-2001, a CRISPR-Cas9-based therapy, was administered to six patients with hereditary TTR amyloidosis. The treatment resulted in a mean reduction of up to 87% in serum TTR levels on day 28, with no serious adverse events reported [44]. Further evidence from Intellia Therapeutics' ongoing Phase 1 study indicated that NTLA-2001 led to a rapid, deep, and durable reduction in serum TTR, accompanied by evidence of disease stabilization or improvement after a one-time treatment. Favorable trends were consistently observed across multiple markers of cardiac disease progression at month 12 compared to baseline in an ATTR-CM population with a high proportion of advanced heart failure patients [45]. Additionally, a study highlighted by the American Heart Association reported that NTLA-2001 significantly reduced circulating TTR protein levels by more than 90% in all patients after 28 days, demonstrating the potential of gene-editing therapy in treating ATTR amyloid cardiomyopathy [46].

Potential benefits

- Targeted gene editing: CRISPR-Cas9 can specifically target and edit the TTR gene, which is responsible for the production of misfolded proteins in ATTR amyloidosis. This precision allows for the reduction of pathogenic protein accumulation in cardiac tissues [44, 47].

- Clinical efficacy: In a phase 1 trial, the investigational therapy Nexiguran Ziclumeran demonstrated significant reductions in serum TTR levels, with a mean decrease of 90% at 12 months post-treatment. This suggests a durable therapeutic effect [48].

- Improvement in clinical outcomes: Patients treated with CRISPR-based therapies showed stabilization or improvement in heart function, as evidenced by changes in NT-proBNP levels and the New York Heart Association class [48].

3.2. Potential risks

- Adverse reactions: Some patients experienced transient infusion-related reactions and liver enzyme elevations, indicating potential side effects associated with CRISPR therapies [48].

- Heterogeneity of HFpEF: The diverse etiology of HFpEF, including cardiac amyloidosis, complicates treatment strategies. Identifying and targeting specific genetic causes within this heterogeneous group is crucial for effective therapy [49].

- Off-target effects: There is a risk of unintended genetic modifications, which could lead to unforeseen complications. However, advancements in delivery systems, such as echogenic liposomes, are being explored to enhance targeting specificity and minimize off-target effects [50, 51].

- Long-term safety: The long-term implications of CRISPR-based gene editing in cardiac tissues remain uncertain, necessitating further research to ensure safety and efficacy over extended periods [52].

While CRISPR-Cas9 offers a promising avenue for treating cardiac amyloidosis, it is essential to consider the broader context of gene therapy in cardiology. The field is rapidly evolving, with ongoing research into optimizing delivery methods and improving editing precision. These advancements could potentially extend the applicability of gene editing to other forms of heart disease, highlighting the transformative potential of this technology in cardiac care [38, 43].

Integration of Weight Loss and Gene Editing

The integration of weight loss interventions and gene-editing therapies presents an innovative, multimodal approach for managing complex cardiac conditions like HFpEF coexisting with cardiac amyloidosis. HFpEF is often exacerbated by obesity, which imposes additional hemodynamic stress on the heart and contributes to the development and progression of heart failure symptoms. Addressing this obesity-related stress through lifestyle modifications, such as caloric restriction and physical activity, or pharmacotherapy, such as GLP-1 receptor agonists (e.g., semaglutide), can significantly improve cardiac function and quality of life in HFpEF patients [37]. Studies have demonstrated that weight loss not only reduces adiposity but also improves left ventricular diastolic function and exercise capacity, which are key factors in the management of HFpEF [24]. In parallel, gene-editing therapies like CRISPR-Cas9 offer an opportunity to target the genetic mutations responsible for ATTR, a key contributor to restrictive cardiomyopathy. Recent clinical trials with CRISPR-based therapies have shown a significant reduction in TTR protein levels, providing hope for disease-modifying treatment options for patients with this devastating condition [53].

The combination of weight loss interventions and gene-editing therapies could therefore act synergistically, addressing both the phenotypic manifestations of HFpEF caused by obesity and the underlying genetic pathology of amyloid deposition. By reducing the burden of TTR amyloid fibrils in the heart and decreasing hemodynamic strain through weight reduction, these therapies could lead to improvements in both structural and functional aspects of heart disease. Clinical trials such as those examining NTLA-2001, a CRISPR-Cas9 gene-editing treatment for hereditary TTR amyloidosis, have demonstrated promising results in reducing amyloid burden and

stabilizing disease progression [44]. Furthermore, the complementary effects of these therapies might extend to a wider population, potentially benefiting patients with advanced stages of HFpEF and cardiac amyloidosis, who have historically had limited treatment options. With the continued development of both pharmacological and gene-editing strategies, this integrated approach holds significant potential for improving patient outcomes and altering the course of these complex cardiac diseases [54].

Addressing obesity-related hemodynamic stress through lifestyle modifications or pharmacotherapy, alongside correcting genetic abnormalities responsible for amyloid deposition, could synergistically improve patient outcomes. Future research should focus on optimizing these combined approaches, ensuring safety and efficacy, and identifying patient subgroups most likely to benefit from such personalized therapies. This comprehensive strategy holds the potential to transform the management of patients with overlapping cardiovascular and metabolic disorders.

Combining gene editing with weight loss could address both the genetic and lifestyle factors contributing to cardiac amyloidosis, offering a holistic treatment approach. Weight loss may improve the overall cardiac environment, making gene editing more effective by reducing the inflammatory and metabolic stress on the heart [55]. Ongoing research and clinical trials are essential to evaluate the efficacy and safety of these combined approaches. The integration of lifestyle, pharmacological, and genetic interventions requires careful consideration of patient-specific factors and comorbidities [56]. However, the durability and feasibility of these interventions in the long term require further investigation [24, 57].

Limitations and Future Prospects

Limitations

One of the key challenges in the management of HFpEF through weight loss is ensuring sustained adherence to weight management strategies. While caloric restriction and physical activity are widely recommended, achieving and maintaining long-term weight loss can be difficult, particularly among individuals with multiple comorbidities such as hypertension, diabetes, and sleep apnea, which are common in the HFpEF population [5]. Furthermore, weight loss interventions might have varied efficacy based on the degree of obesity, with more pronounced improvements seen in severely obese individuals, while the benefits are often more modest in those with mild obesity [24]. Weight loss may also exacerbate other cardiovascular conditions, such as sarcopenia, which could worsen muscle strength and function, leading to diminished exercise capacity in HFpEF patients [58]. These factors present a complex challenge in managing patients, necessitating individualized approaches to weight management.

Gene editing for ATTR, while promising, still faces significant limitations. The delivery of CRISPR-based gene editing therapies, such as NTLA-2001, is one of the primary obstacles. Gene-editing therapies rely on efficient delivery to the liver, where TTR is primarily produced. However, achieving precise targeting and delivery without unintended consequences, such as off-target mutations or immune responses, remains a concern [40]. Furthermore, while early clinical trials have demonstrated safety and efficacy in reducing serum TTR levels, the long-term effects of these gene-editing treatments are not yet fully understood. There is also a need for large-scale studies to assess the durability of these treatments and their impact on overall survival and quality of life in patients with advanced cardiac amyloidosis [44].

The potential synergy of combining weight loss strategies with gene-editing therapies for HFpEF and cardiac amyloidosis is an area of active research. Weight loss can help alleviate some of the hemodynamic stress on the heart in HFpEF patients, potentially improving cardiac function and enhancing the benefits of gene editing in TTR amyloidosis. However, the combination of these therapies is still largely unexplored in clinical settings. There is limited data on the safety and efficacy of using both strategies simultaneously, and the interaction between weight loss treatments and gene editing could lead to unforeseen complications [54]. Moreover, individual responses to gene-editing therapies may vary depending on genetic factors, disease stage, and the presence of other cardiovascular comorbidities, which complicates the design of combination treatment protocols.

Future prospects

The future of weight loss treatment for HFpEF patients holds promise with emerging pharmacological interventions such as GLP-1 receptor agonists (e.g., semaglutide), which have shown efficacy in inducing weight loss and improving cardiovascular outcomes [37]. Additionally, the role of bariatric surgery as a potential treatment for severely obese HFpEF patients is gaining attention. Studies are exploring the benefits of bariatric procedures, such as gastric bypass, long-term cardiac function and quality of life in individuals with HFpEF [59]. Future research will likely focus on refining these treatments, exploring

Table 3: Summary of the limitations and future prospects.

Aspect	Weight loss treatment for HFpEF	Gene editing for cardiac amyloidosis
Adherence	Sustaining long-term adherence to weight loss strategies is difficult, especially in patients with comorbidities such as hypertension, diabetes, and sleep apnea	Efficient delivery of CRISPR-based therapies is challenging, with potential for off-target effects and immune responses
Efficacy	Weight loss interventions show varying efficacy based on the degree of obesity, with better results in severely obese individuals	Long-term effects of gene editing therapies are not yet fully understood, and there is a need for large-scale studies to assess their durability
Side effects	Weight loss can exacerbate other cardiovascular conditions like sarcopenia, potentially leading to worsened muscle strength and exercise capacity	Safety concerns related to gene delivery methods, especially in patients with advanced cardiac amyloidosis
Combination of therapies	Combining weight loss with gene-editing therapies is still largely unexplored, with limited data on the safety and efficacy of these combined approaches	The interaction between gene-editing therapies and other treatments could lead to unforeseen complications
Pharmacological advances	GLP-1 receptor agonists (e.g., semaglutide) are showing promising results for weight loss and improving cardiovascular outcomes	New gene-editing techniques and delivery methods, such as nanoparticles and lipid-based vectors, are being developed for safer and more efficient treatments
Bariatric surgery	Bariatric surgery (e.g., gastric bypass) is gaining attention for severely obese HFpEF patients and may improve long-term cardiac function	Combining gene-editing therapies with TTR stabilizers like tafamidis could maximize therapeutic benefit and improve patient outcomes
Expanded treatment scope	Future studies will explore the combined effects of weight loss with other heart failure interventions (e.g., TTR stabilizers)	Gene editing may eventually be used to treat broader amyloid-related diseases beyond TTR amyloidosis, including other forms of restrictive cardiomyopathy
Regulatory and clinical trials	Future research will focus on refining weight loss treatments and understanding their impact on biomarkers of heart failure progression	Regulatory approvals and ongoing clinical trials will be crucial for ensuring the safety and efficacy of gene-editing therapies in broader patient populations

their combined effects with other interventions, and understanding their impact on biomarkers of heart failure progression.

In the field of gene editing for cardiac amyloidosis, there is considerable optimism for further advancements. As CRISPR-Cas9 technology continues to evolve, newer, more efficient methods of gene delivery are being developed, including nanoparticles and lipid-based vectors, which might offer safer and more targeted delivery to the liver. Additionally, upcoming studies will explore combination therapies, such as pairing gene-editing techniques with other disease-modifying treatments, including TTR stabilizers like tafamidis, to maximize therapeutic benefit. It is also expected that gene editing could eventually be used in clinical practice for broader amyloid-related diseases beyond TTR amyloidosis, expanding its applicability in treating other forms of restrictive cardiomyopathy and systemic amyloidosis [53]. As the field progresses, regulatory approvals and more comprehensive clinical trials will play a critical role in ensuring that these treatments are both effective and safe in a wider patient population (Table 3).

Conclusion

While weight loss and gene editing present promising avenues for treating HFpEF and cardiac amyloidosis, challenges remain. The obesity paradox, where obese heart failure patients sometimes exhibit better survival rates, complicates the interpretation of weight loss benefits. Gene editing therapies are still emerging, and their long-term safety and efficacy need further validation. Additionally, weight loss interventions require sustained lifestyle changes, which can be difficult to maintain. Additionally, the long-term effects and ethical considerations of gene editing need thorough exploration. The sustainability of weight loss through lifestyle changes is often difficult, and the long-term effects of gene editing therapies are still under investigation. As research progresses, personalized treatment plans that incorporate these innovative strategies could transform the management of these complex conditions. Additionally, the integration of these treatments requires careful consideration of patient-specific factors and ongoing research to optimize outcomes [26].

Acknowledgements

None.

Conflict of Interest

None.

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