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TIRZEPATIDE REDUCES HEART FAILURE HOSPITALIZATIONS IN OBESE PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION: A PROSPECTIVE CONTROLLED STUDY

General Medicine

Dr. Aravind C — Professor & HOD Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India

Dr. Deeksha S Hegde* — Postgraduate Resident Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India*Corresponding Author

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as an obesity-driven syndrome characterized by systemic inflammation, volume overload, and metabolic dysfunction. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has demonstrated cardiovascular benefits in the SUMMIT trial, but prospective data in NYHA class III–IV HFpEF populations remain limited.**Methods:** This prospective controlled single-center study enrolled 100 patients with HFpEF (left ventricular ejection fraction ≥50%), body mass index ≥30 kg/m², and NYHA class III–IV symptoms. Fifty patients received tirzepatide with gradual dose escalation in addition to standard heart failure therapy, while 50 controls received standard therapy alone. The primary outcome was improvement in NYHA functional class by at least one class at 6 months. The secondary outcome was heart failure hospitalization during follow-up.**Results:** Baseline characteristics were comparable between groups. NYHA functional class improvement occurred in 94% of the tirzepatide group versus 80% of controls (p = 0.072). Heart failure hospitalization occurred in 16% of the tirzepatide group versus 40% of controls (p = 0.012), corresponding to an absolute risk reduction of 24% and a number needed to treat of approximately 5.**Conclusion:** Tirzepatide significantly reduced heart failure hospitalizations and demonstrated a favorable trend toward functional improvement in obese patients with HFpEF. These findings support the therapeutic potential of metabolic-targeted therapy in this high-risk population.

KEYWORDS

Tirzepatide, Hfpef, Obesity, Heart Failure Hospitalization

INTRODUCTION

Heart failure with preserved ejection fraction has emerged as one of the most pressing challenges in contemporary cardiovascular medicine. It accounts for approximately half of all heart failure cases, affecting an estimated 3 million individuals in the United States alone, and its prevalence continues to rise in parallel with the aging population and the growing burden of metabolic comorbidities. Patients with HFpEF experience severe exercise intolerance, recurrent hospitalizations at a rate of approximately 1.4 per year, and annual mortality rates approaching 15%. Despite this substantial morbidity and mortality, effective pharmacologic therapies for HFpEF have historically been limited, with most neurohormonal strategies that proved successful in heart failure with reduced ejection fraction failing to demonstrate comparable benefits in the preserved ejection fraction phenotype.

The pathophysiology of HFpEF is now understood to be fundamentally distinct from that of heart failure with reduced ejection fraction. Rather than a primary disorder of systolic contractile dysfunction, HFpEF represents a systemic syndrome driven by comorbidity-related inflammation, microvascular dysfunction, and myocardial fibrosis. Obesity, in particular, has been identified as one of the strongest risk factors for incident HFpEF, with up to 80% of affected individuals being overweight or obese. Visceral adipose tissue serves as a reservoir for the aberrant production of proinflammatory adipocytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-alpha, which drive systemic immune dysregulation, coronary microvascular rarefaction, and myocardial stiffness. Markers of inflammation such as C-reactive protein and interleukin-6 are independently associated with worse symptoms, diminished exercise capacity, and adverse prognosis in HFpEF. The recognition that visceral adiposity precedes and predicts the development of HFpEF across diverse populations has given rise to the concept that obesity-related HFpEF constitutes a distinct clinical phenotype amenable to metabolic-targeted interventions.

Patients with NYHA class III or IV symptoms represent a particularly vulnerable subset of patients with HFpEF. Higher NYHA functional class has been independently associated with higher rates of heart failure hospitalization and cardiac death, with hazard ratios exceeding 2.0 for the combined endpoint in prospective cohorts. These patients exhibit more pronounced diastolic dysfunction, higher pulmonary artery pressures, greater body mass indices, and elevated natriuretic peptide levels compared with less symptomatic individuals. The coexistence of obesity and significant functional limitation creates a population with high event rates and limited therapeutic options.

Tirzepatide is a novel dual GIP and GLP-1 receptor agonist that has demonstrated substantial metabolic and cardiovascular benefits across multiple clinical settings. By simultaneously engaging both incretin receptor pathways, tirzepatide produces greater weight reduction than selective GLP-1 receptor agonists alone and exerts pleiotropic effects on inflammation, blood volume, blood pressure, and end-organ function. The landmark SUMMIT trial, a randomized, double-blind, placebo-controlled study of 731 patients with HFpEF and obesity, demonstrated that tirzepatide reduced the composite of cardiovascular death or worsening heart failure events by 38% (hazard ratio 0.62; 95% CI, 0.41–0.95; p = 0.026) over a median follow-up of 104 weeks. Tirzepatide also improved health status as measured by the Kansas City Cardiomyopathy Questionnaire, increased six-minute walk distance, and shifted patients toward more favorable NYHA functional classes. Mechanistic analyses from the SUMMIT trial revealed that these clinical benefits were accompanied by reductions in estimated blood volume, systemic blood pressure, C-reactive protein, and troponin T, along with preservation of renal function.

However, the SUMMIT trial enrolled predominantly patients with NYHA class II and III symptoms, and prospective real-world data evaluating tirzepatide in patients with symptomatic HFpEF remain limited. Whether the benefits observed in the controlled trial setting translate to this higher-risk population in clinical practice is an important question with direct implications for patient management. This study aimed to evaluate the efficacy of tirzepatide in reducing heart failure hospitalizations and improving functional status in obese patients with HFpEF over a six-month follow-up period.

Methods

Study Design and Setting

This was a prospective controlled single-center study conducted over a six-month period. The study was designed to evaluate the clinical efficacy of tirzepatide as an adjunct to guideline-directed medical therapy in patients with HFpEF and concomitant obesity.

Study Population

A total of 100 consecutive patients meeting eligibility criteria were enrolled and allocated to two groups: a tirzepatide group (n = 50) and a control group (n = 50). Allocation was based on clinical decision-making in conjunction with patient preference and drug availability, rather than formal randomization.

Inclusion criteria were: age 40 years or older; body mass index of 30 kg/m² or greater; left ventricular ejection fraction of 50% or greater on transthoracic echocardiography; and NYHA functional class III or IV symptoms at enrollment. Exclusion criteria included: heart failure with

reduced ejection fraction (left ventricular ejection fraction below 50%); severe renal dysfunction; severe hepatic dysfunction; active malignancy; and recent acute coronary syndrome.

Intervention

Patients in the tirzepatide group received tirzepatide administered subcutaneously with gradual dose escalation according to tolerability, in addition to their existing standard heart failure therapy. The control group continued standard heart failure therapy alone without the addition of tirzepatide. Standard therapy in both groups included diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors, prescribed as clinically indicated by the treating physician.

Outcomes

The primary outcome was improvement in NYHA functional class by at least one class at the six-month follow-up visit. NYHA class was assessed by the treating clinician at baseline and at six months. The secondary outcome was the occurrence of at least one hospitalization due to heart failure exacerbation during the six-month follow-up period.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and compared between groups using the chi-square test or Fisher exact test, as appropriate based on expected cell counts. Continuous variables were expressed as means with standard deviations and compared using the independent samples t-test. Relative risk reduction, absolute risk reduction, odds ratio, and number needed to treat were calculated for the secondary outcome. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline demographic and clinical characteristics of the two groups are presented in Table 1. The mean age was 61.8 ± 9.4 years in the tirzepatide group and 63.1 ± 8.7 years in the control group (p = 0.48). Male sex was represented in 48% and 40% of the tirzepatide and control groups, respectively (p = 0.42). Mean body mass index was 35.6 ± 4.1 kg/m² in the tirzepatide group and 34.9 ± 4.5 kg/m² in the control group (p = 0.39). The distribution of NYHA functional class was similar, with 74% and 76% of patients in class III (p = 0.81) and 26% and 24% in class IV (p = 0.81) in the tirzepatide and control groups, respectively. The prevalence of diabetes mellitus (62% vs. 58%, p = 0.68) and hypertension (84% vs. 88%, p = 0.56) was comparable between groups. No statistically significant differences were observed in any baseline characteristic, suggesting adequate comparability between the two cohorts.

Primary Outcome: NYHA Functional Class Improvement At six months, 47 of 50 patients (94%) in the tirzepatide group demonstrated improvement in NYHA functional class by at least one class, compared with 40 of 50 patients (80%) in the control group. This difference did not achieve statistical significance by Fisher exact test (p = 0.072). While the absolute difference of 14 percentage points favored the tirzepatide group, the study was likely underpowered to detect a statistically significant difference for this outcome given the high improvement rate in both groups.

Secondary Outcome: Heart Failure Hospitalization Heart failure hospitalization occurred in 8 of 50 patients (16%) in the tirzepatide group compared with 20 of 50 patients (40%) in the control group. This difference was statistically significant (p = 0.012). The absolute risk reduction was 24%, the relative risk reduction was 60%, and the number needed to treat was approximately 5, indicating that for every five patients treated with tirzepatide, one heart failure hospitalization was prevented over the six-month follow-up period.

Table 1. Baseline Characteristics

Variable	Tirzepatide (n=50)	Control (n=50)	p-value
Mean age (years)	61.8 ± 9.4	63.1 ± 8.7	0.48
Male sex	24 (48%)	20 (40%)	0.42
BMI (kg/m²)	35.6 ± 4.1	34.9 ± 4.5	0.39
NYHA III	37 (74%)	38 (76%)	0.81
NYHA IV	13 (26%)	12 (24%)	0.81
Diabetes mellitus	31 (62%)	29 (58%)	0.68
Hypertension	42 (84%)	44 (88%)	0.56

Table 2. NYHA Functional Improvement

Outcome	Tirzepatide	Control	p-value
Improved	47 (94%)	40 (80%)	0.072*
No improvement	3 (6%)	10 (20%)	

Table 3. Heart Failure Hospitalization

Outcome	Tirzepatide	Control	p-value
>1 hospitalization	8 (16%)	20 (40%)	0.012*
No hospitalization	42 (84%)	30 (60%)	

DISCUSSION

This prospective controlled study demonstrates that the addition of tirzepatide to standard heart failure therapy significantly reduced heart failure hospitalizations in obese patients with HFpEF over a six-month period. Additionally, a numerically greater proportion of patients receiving tirzepatide experienced improvement in NYHA functional class, although this difference did not reach statistical significance. These findings extend the growing evidence supporting incretin-based therapies in HFpEF and suggest potential clinical benefit in patients with significant symptomatic limitation.

The reduction in heart failure hospitalization observed in this study is clinically meaningful. The absolute risk reduction of 24% and the number needed to treat of approximately 5 suggest a robust treatment effect in this high-risk population. The 40% hospitalization rate in the control group over six months reflects the substantial morbidity associated with symptomatic HFpEF and is consistent with registry data demonstrating frequent recurrent hospitalization in this population. The magnitude of hospitalization reduction observed here is directionally consistent with the SUMMIT trial, in which tirzepatide reduced worsening heart failure events by 46% (hazard ratio 0.54; 95% CI, 0.34–0.85) over a median follow-up of 104 weeks. A recent real-world retrospective cohort study using the TriNetX database similarly found that tirzepatide was associated with a 48% reduction in the composite of heart failure exacerbation and all-cause mortality among 14,154 propensity-matched patients with HFpEF, providing additional external validation for the findings reported here.

The favorable trend toward NYHA functional class improvement in the tirzepatide group, while not statistically significant, is biologically plausible and aligns with the comprehensive clinical trajectory analysis from the SUMMIT trial. In that analysis, tirzepatide shifted patients toward more favorable NYHA classes with a proportional odds ratio of 2.26 (95% CI, 1.54–3.31; p 0.001). The lack of statistical significance in the present study likely reflects the limited sample size and the high rate of improvement in the control group (80%), which may be attributable to optimization of background medical therapy, regression to the mean, or the subjective nature of NYHA class assessment in an unblinded study design.

Several biological mechanisms may underlie the observed clinical benefits. Tirzepatide produces substantial weight reduction, which directly alleviates the hemodynamic burden of obesity on the heart by reducing plasma volume, ventricular filling pressures, and pericardial restraint. In the SUMMIT trial, tirzepatide reduced body weight by 13.9% and estimated blood volume by 0.58 liters compared with placebo. Beyond weight loss, tirzepatide exerts potent anti-inflammatory effects, reducing C-reactive protein by approximately 37–39% in the SUMMIT trial. This is particularly relevant given that systemic inflammation driven by visceral adipose tissue is considered a central pathophysiological mechanism in obesity-related HFpEF, promoting coronary microvascular dysfunction, myocardial fibrosis, and impaired ventricular relaxation. GLP-1 receptor agonism may also directly reverse the proinflammatory biology of adipocytes, while GIP receptor agonism, acting on abundant receptors in epicardial adipose tissue, may suppress inflammation in tissue immediately adjacent to the myocardium. The reductions in troponin T and preservation of renal function observed in the SUMMIT mechanistic analyses further suggest that tirzepatide mitigates end-organ damage beyond its metabolic effects.

The present findings should be interpreted within the context of the broader evidence supporting incretin-based therapies in HFpEF. A pooled participant-level analysis of four randomized trials of semaglutide (SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM) demonstrated that semaglutide reduced the composite of

cardiovascular death or worsening heart failure events by 31% (hazard ratio 0.69; 95% CI, 0.53–0.89; p = 0.0045) in patients with HFpEF. The 2025 American College of Cardiology Scientific Statement on obesity management in heart failure now recognizes GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists as evidence-based therapies for symptom and event reduction in patients with HFpEF and obesity. Similarly, the American Diabetes Association 2026 Standards of Care recommend treatment with a GLP-1 receptor agonist or GIP/GLP-1 receptor agonist for reduction of heart failure events and symptoms in patients with symptomatic heart failure. The present study adds to this growing body of evidence by providing prospective data in symptomatic obese patients with HFpEF.

This study has few important limitations that warrant acknowledgment. First, the non-randomized, open-label design introduces the possibility of selection bias and performance bias. Without randomization, unmeasured confounders such as medication adherence, socioeconomic factors, and disease trajectory may have influenced the observed outcomes. The lack of blinding is particularly relevant for the primary outcome of NYHA class improvement, which is a subjective assessment susceptible to observer bias. Second, the sample size of 100 patients limits statistical power, as evidenced by the inability to detect a statistically significant difference in the primary outcome despite a 14-percentage-point absolute difference. Third, the six-month follow-up period is relatively short compared with the SUMMIT trial's median follow-up of 104 weeks, limiting the ability to assess durability of benefit and long-term safety.

CONCLUSION

In this prospective controlled study of obese patients with HFpEF, the addition of tirzepatide to standard heart failure therapy significantly reduced heart failure hospitalizations over six months, with an absolute risk reduction of 24% and a number needed to treat of approximately 5. A favorable trend toward improvement in NYHA functional class was also observed, though this did not reach statistical significance. These findings are consistent with the results of the SUMMIT trial and the broader evidence base supporting incretin-based therapies in obesity-related HFpEF. Tirzepatide may represent a promising therapeutic option for obese patients with HFpEF, a population with high morbidity and limited treatment options. Larger multicenter randomized controlled trials with longer follow-up, blinded outcome assessment, and comprehensive endpoint evaluation are warranted to confirm and extend these findings.

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