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ORIGINAL RESEARCH

Pragmatic Weight Management Program for Patients With Obesity and Heart Failure With Preserved Ejection Fraction

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BACKGROUND: Obesity is associated with heart failure with preserved ejection fraction (HFpEF). Weight loss can improve exercise capacity in HFpEF. However, previously reported methods of weight loss are impractical for widespread clinical implementation. We tested the hypothesis that an intensive lifestyle modification program would lead to relevant weight loss and improvement in functional status in patients with HFpEF and obesity.

METHODS AND RESULTS: Patients with ejection fraction >45%, at least 1 objective criteria for HFpEF, and body mass index ≥30 kg/m^2 were offered enrollment in an established 15-week weight management program that included weekly visits for counseling, weight checks, and provision of meal replacements. At baseline, 15 weeks, and 26 weeks, Minnesota Living With Heart Failure score, 6-minute walk distance, echocardiography, and laboratory variables were assessed. A total of 41 patients completed the study (mean body mass index, 40.8 kg/m^2), 74% of whom lost >5% of their baseline body weight following the 15-week program. At 15 weeks, mean 6-minute walk distance increased from 223 to 281 m (P=0.001) and then decreased to 267 m at 26 weeks. Minnesota Living With Heart Failure score improved from 59.9 to 37.3 at 15 weeks (P<0.001) and 37.06 at 26 weeks. Changes in weight correlated with change in Minnesota Living With Heart Failure score (r=0.452; P=0.000) and 6-minute walk distance (r=−0.388; P<0.001).

CONCLUSIONS: In a diverse population of patients with obesity and HFpEF, clinically relevant weight loss can be achieved with a pragmatic 15-week program. This is associated with significant improvements in quality of life and exercise capacity.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02911337.

Key Words: exercise ■ heart failure with preserved ejection fraction ■ left ventricular hypertrophy ■ obesity ■ quality of life ■ weight loss

Many large population studies have shown strong and graded associations between obesity and incident heart failure (HF).[1–3] This association appears to be much stronger for HF with preserved ejection fraction (HFpEF) than for HF with reduced ejection fraction.[1,4] The prevalence of HFpEF is increasing out of proportion to that of HF with reduced ejection fraction.[5] This shift is thought to be driven in substantial part by a continually increasing prevalence of obesity[6] and low levels of physical activity, particularly in younger patients.[7,8]

Most treatments that improve outcomes in patients with HF with reduced ejection fraction have not had a significant impact on HF hospitalizations or mortality in HFpEF.[9–11] This highlights the need for an alternative approach for the treatment of HFpEF. Recent studies have shown that large amounts of weight loss achieved through bariatric surgery protect against

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CLINICAL PERSPECTIVE

What Is New?

- Obesity is strongly associated with incident heart failure, particularly with preserved ejection fraction.
- An intensive lifestyle management program produced ≈7% loss of body weight in patients with documented heart failure with preserved ejection fraction; this was associated with relevant improvements in exercise capacity, quality of life, metabolic markers, and echocardiographic measures of filling pressures.

What Are the Clinical Implications?

- A relatively standard, commercially available lifestyle modification program that includes physical activity recommendations, but not supervised exercise, is safe and effective, even in people with limited exercise capacity.

Nonstandard Abbreviations and Acronyms

6MW	6-minute walk
E/e′	ratio of mitral early diastolic flow velocity/mitral annular velocity
HFpEF	heart failure with preserved ejection fraction
MLWHF	Minnesota Living With Heart Failure

incident HF.[12–14] However, lifestyle modification is applicable to a much broader segment of the population with HFpEF and, if effective, would likely be more cost effective than surgical weight loss.

Only one prior prospective study has directly addressed weight loss as a therapy for HFpEF with obesity.[15] Diet and exercise were both shown to be associated with weight loss and improved exercise capacity. However, the diet intervention involved the provision of 2 complete meals/day for the duration of the study, and the exercise intervention included supervised exercise 3 days/week. Although the study design was robust and produced proof of concept, the intervention used is not readily scalable to routine clinical practice. Furthermore, supervised exercise programs are relatively costly and will be impractical for the foreseeable future because of the effects of the COVID-19 pandemic. Therefore, it remains uncertain whether weight loss and its benefits could be safely and practically achieved using a more easily disseminatable program. The purpose of the current study was to use a pragmatic design to test the efficacy of a locally run, fee-for-service lifestyle intervention program that is similar to those available in many parts of the country. Although physical activity was prescribed, supervised exercise was not part of the program, which makes the findings easier to apply in the current healthcare environment.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Protocol and Design

This was a prospective, single-center, unblinded trial of intensive lifestyle modification in patients with a clinical diagnosis of HFpEF as well as objective measures confirming the diagnosis. The study protocol was approved by the institutional review board at the Medical University of South Carolina. The trial was registered at clinicaltrials.gov (NCT02911337). All patients signed an informed consent. Inclusion criteria included the following: left ventricular (LV) ejection fraction >45%, aged 18 to 80 years, body mass index (BMI) >30 kg/m^2, and the ability to complete a 6-minute walk (6MW) test (maximum distance, 850 m). Patients had to have typical symptoms and/or signs of HF (ie, dyspnea on exertion, weight gain, orthopnea, paroxysmal nocturnal dyspnea, bendopnea, edema, elevated jugular venous pressure, and pulmonary rales), requirement for diuretic therapy, and 1 major or at least 2 minor criteria. Major criteria included the following: brain natriuretic peptide (BNP) level >200 ng/L, presence of pulmonary edema on chest radiography or computed tomography, or elevated LV filling pressures (pulmonary capillary wedge pressure >15 mm Hg at rest or >25 mm Hg with exercise, or LV end-diastolic pressure >18 mm Hg). Minor criteria included the following: left atrial enlargement on echocardiography (left atrial volume >68 mL or anterior-posterior diameter >4.0 cm), increased LV wall thickness (≥1.1 cm), ratio of early transmitral inflow velocity/early diastolic velocity of the mitral annulus (E/e′) >14 (average of medial and lateral mitral annular velocity) by echocardiography, or intermediate level of BNP (60–199 ng/L). Exclusion criteria included severe chronic obstructive pulmonary disease, estimated glomerular filtration rate <20 mL/min, severe hepatic disease, major psychiatric condition, and active malignancy (other than skin cancers). A complete list of exclusion criteria is presented in Data S1.

Patients underwent assessment at baseline, at completion of the 15-week lifestyle intervention, and at 26-week follow-up. Primary end points were taken at the 15-week time point. Measurements done at 26 weeks were preplanned and intended to assess

whether there was maintenance of benefits. However, measurements at this time point were primarily exploratory. The clinical assessment included measurement of weight, waist circumference, blood pressure, Minnesota Living With Heart Failure (MLWHF) score, 6MW test, serum laboratory variables (creatinine, blood urea nitrogen, electrolytes, hemoglobin A1c, lipids, BNP, and hs-CRP [high-sensitivity C-reactive protein]), and echocardiography.

The coprimary end points at 15 weeks were as follows: (1) change in quality of life (QOL), measured with MLWHF score, and (2) change in 6MW distance. Secondary/exploratory end points included echocardiographic measures of cardiac structure and function (left atrial volume, LV chamber dimensions, LV mass, LV ejection fraction, E/e′, E deceleration time, and tricuspid regurgitation velocity). Safety end points included significant changes in serum electrolytes, estimated glomerular filtration rate, hypotension, arrhythmias, hypoglycemia, and hospitalizations.

All patients received standard medical treatment for coexisting conditions, such as hypertension and diabetes. During the study period, medications, such as antihypertensive agents, diuretics, or glucose-lowering agents, were adjusted as clinically indicated.

Weight Loss Program

We used a multidisciplinary 15-week, intensive lifestyle program ordinarily offered on a fee-for-service basis but provided at no cost to study participants. The program uses a structured dietary intervention that includes provision of shakes and nutrition bars to replace 2 meals/day for the first 8 weeks, followed by a food-based hypocaloric diet. Weekly 30- to 60-minute meetings alternated among exercise specialists, dieticians, and psychologists or other behavioral specialists. Patients work directly with a dietitian to learn about hypocaloric, high-quality food choices. Although *supervised* exercise was not part of the program, patients met with an exercise physiologist who provided information, motivation, and a personalized prescription for an exercise program and active leisure. This exercise plan was reviewed at all subsequent visits. Patients were provided a wrist-worn activity monitor to record their daily steps. This was used as a motivational tool, but data from the devices were not collected for the study. An emphasis on long-term, lifestyle choices is used to encourage patients to make healthy behavior changes that they can sustain after completing the program. The program is outlined in detail in Data S2.

Clinical Assessments

Height and weight were measured using a digital scale and a stadiometer. Waist circumference was measured at the midpoint between the iliac crest and the lowest rib. Seated blood pressure was measured using an automated cuff placed over the brachial artery. The average of 2 readings was reported. Finally, serum was collected to monitor renal function, electrolytes, lipids, inflammation, and BNP.

Outcomes

The MLWHF questionnaire assesses disease-specific QOL using a total score that ranges from 0 to 105, with higher scores indicating worse HF-related QOL. The 6MW test has been validated for assessment of HF limitations.[16] Administration of the MLWHF and the 6MW test was performed by study coordinators who were aware of the patient's stage in the program. Following the 6MW test, subjects quantified their sensation of dyspnea and fatigue (or perceived exertion) using the modified Borg scale (range, 0–10, with 10 indicating maximal dyspnea or exertion).

Echocardiography

Echocardiography was performed by an experienced sonographer in accordance with the American Society of Echocardiography guidelines.[17] All echocardiograms were interpreted by a single, level 3 trained echocardiologist (S.E.L.). All key measurements were performed by the cardiologist who was blinded to the individual weight changes of the study participants.

Statistical Analysis

A preliminary power analysis was completed using data from previously published studies in patients with HFpEF who reported 6MW distance and MLWHF scores.[18] Baseline 6-minute walk distance was 1480 feet (SD, 225 feet) and MLWHF score was 32 (SD, 20). With a planned enrollment of 65 patients and an assumed dropout rate of 20%, we had >90% power to detect a 10% change in 6MW distance and a 20% change in the total MLWHF score. Changes of this magnitude are believed to be clinically relevant and have been seen in other studies of interventions for HF.[18–20] An α level of 0.05 was used for power calculations.

Statistical analyses were performed using Sigma Plot (Systat Software, San Jose, CA). Normally distributed data are presented as mean±SD or nonnormally distributed as median (interquartile range) for continuous variables. Discrete variables are shown as percentages. Primary analyses were conducted using 2-tailed, paired *t*-tests and 1-way ANOVA. We compared variables collected at baseline, at the 15-week end point, and at 26-week follow-up. The coprimary end points were the change in 6MW distance and the change in the MLWHF score at 15 weeks. The 6MW distance and MLWHF score were treated as 2 independent end points and were analyzed as such.

Additional clinical end points included New York Heart Association score, Borg dyspnea scale, and Borg fatigue scale. Echocardiographic end points were considered to be preliminary as the study did not have sufficient power to detect changes in these parameters. Echocardiographic parameters of interest included change in E/e′, change in LV mass, and change in left atrial volume.

Each patient's baseline data were used as the control condition and compared with the same variables measured at the 15- and 26-week time points. Patients were excluded from analysis if they did not complete the initial 15-week program. The primary end point was the 15-week data, and all patients were used for this analysis. Findings at 26-week follow-up were a secondary end point. For the 26-week analysis, we excluded the patients who completed 15 weeks, but were lost to follow-up at 26 weeks (5 of the 41 patients). Finally, we analyzed the relationship between change in weight and change in outcome variables at 15 weeks using each as a continuous variable. Linear regression was used to test for associations between weight loss and the primary outcomes.

RESULTS

Study Participants' Baseline Characteristics

A total of 65 patients with documented HFpEF and a BMI >30 kg/m^2 signed consent. Five of these never began the program, and 19 who started, did not complete the 15-week weight loss program (31.6%) and were excluded from the analysis. These 19 patients were younger (57.5±12.8 versus 67.0±9.2 years old; P=0.002) but otherwise did not differ in demographics from those who completed at least 15 weeks (Table S1). Of the 41 remaining patients, 37 returned at 26 weeks. The study flow is shown in Figure 1. The mean age of the study participants was 66.9±9.2 years (Table 1). Fourteen (34%) of the study participants were men, 21 (56%) were White race, and 17 (42%) were Black race (Table 1). Baseline characteristics, including associated comorbidities and medications used at the time of the study, are listed in Table 1.

Anthropometrics and Hemodynamic Parameters

Patients were categorized as having class 2 or 3 obesity, with mean BMI of 43 kg/m^2, and all met criteria for abdominal obesity based on sex-specific waist circumference cutoffs (Table 2). Significant decreases in weight, body surface area, and BMI were observed following the completion of the 15-week weight loss program (–6.7%, –3.4%, and –6.6% versus baseline, respectively; P<0.00001; Table 2). At 26 weeks, there was slight weight regain but differences from baseline persisted (–5.3%, –3%, and –5% versus baseline, respectively; P<0.00001; Table 2).

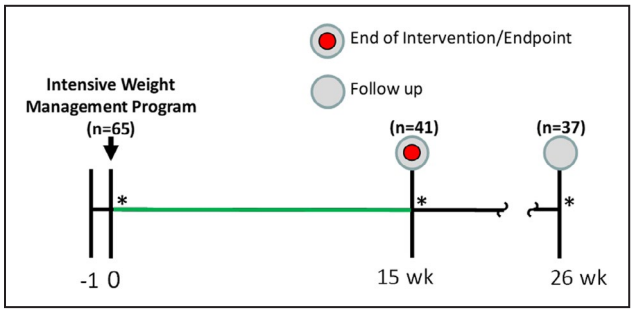

Figure 1. Study design.
Sixty-five patients were initially enrolled in the study. Twenty-four dropped out, and 41 successfully completed the 15-week weight loss program. A total of 37 of the 41 study participants returned at 26 weeks for data collection. *The interval for quality-of-life questionnaires (Minnesota Living With Heart Failure, New York Heart Association, and Borg dyspnea and fatigue scores, as well as laboratory, echocardiographic, and 6-minute walk testing).

At the 2-week assessment, we observed a transient elevation of blood urea nitrogen from a median of 22 mg/dL (interquartile range, 16–30 mg/dL) at baseline to 29 mg/dL (interquartile range, 20.5–48.5 mg/dL; P=0.001). In all cases, this resolved. Eight patients had reductions in diuretic doses (Table S2), 3 had reductions in blood pressure medications, and 2 had reductions in diabetes medications. By 15 weeks, there were no differences in measures of renal function (Table 3). There was a significant reduction in hemoglobin A1c at 15 weeks (–6.1% relative change versus baseline; P=0.0035; Table 3), and a nonsignificant yet strong trend toward reduction in fasting glucose and triglyceride levels compared with baseline (–12.9% and –11.4% relative change, respectively; Table 3). Low- and high-density lipoproteins and BNP did not change.

Effect of Weight Loss on Primary Outcomes

Completion of the program at 15 weeks was associated with significant improvement in both primary end points of 6MW distance and MLWHF score. The 6MW distance increased from 223 to 281 m, and MLWHF score decreased from 59.9 to 37.3, at 15 weeks (29% increase [P=0.001] and 37% decrease [P=0.00002], respectively, versus baseline; Figure 2). These improvements persisted at 26 weeks (24.2% [P=0.03] and –36.4% [P=0.0003], respectively, versus baseline; Figure 2); P<0.05 by 1-way ANOVA. Changes in weight correlated with change in MLWHF score (r=0.452; P<0.001) and 6MW distance at 15 weeks (r=–0.388; P<0.001).

Table 1. Baseline Characteristics of Study Participants

Variable	Values
Age, mean±SD, y	67.0±9.2
Men, n/total (%)	14/41 (34.2)
Race, n/total (%)	
White	21/41 (56.1)
Black	17/41 (41.5)
Other	1/41 (2.4)
Comorbidities, n/total (%)	
Diabetes	24/41 (58.5)
Hypertension	37/40 (92.5)
CKD	9/41 (21.9)
Atrial fibrillation	9/41 (21.9)
Prior ablation	4/41 (9.76)
COPD	13/41 (31.7)
Asthma	14/41 (34.1)
OSA	32/41 (78.1)
PE	3/41 (7.3)
CAD	11/41 (26.8)
CABG	2/41 (4.8)
DES	9/41 (21.9)
Arthritis	33/41 (80.5)
Pacemaker, n/total (%)	3/41 (7.3)
Abdominal surgery, n/total (%)	13/41 (31.7)
Bariatric surgery, n/total (%)	1/41 (2.44)
Recent HF admission, n/total (%)	6/41 (14.6)
Alcohol use, n/total (%)	8/41 (19.5)
Medications, n/total (%)	
β Blocker	20/41 (48.8)
ACEi or ARB	21/41 (51.2)
MRA	20/41 (48.8)
Loop diuretic	33/41 (80.5)
Thiazide	8/41 (19.5)
Calcium channel blocker	13/41 (31.7)
Antiarrhythmic	3/41 (7.3)
Nitrate	11/41 (26.8)
Albuterol	9/41 (21.9)
Antiplatelet	17/41 (41.5)
Anticoagulant	7/41 (17.1)
Statin	17/41 (41.4)
Insulin	9/41 (21.9)
Metformin	6/41 (14.6)
Sulfonylurea	5/41 (12.2)
Pioglitazone	1/41 (2.4)
SGLT2 inhibitor	1/41 (2.4)

ACEi indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DES, drug-eluting stent; HF, heart failure; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; PE, pulmonary embolism; and SGLT2, sodium-glucose transport protein 2.

Table 2. Allometric Data and Vital Signs

Variable	Baseline (n=41)	15 wk (n=41)	26 wk (n=37)
Height, cm	166.97±13.05	…	…
Weight, kg	120.76±19.05	112.65±20.18*	114.332±19.8†
Body surface area, m^2	2.36±0.25	2.28±0.26*	2.29±0.25†
Body mass index, kg/m^2	43.65±8.42	40.75±8.87*	41.46±9.44†
Waist size, cm	125.54±14.32	118.86±16.24*	121.86±15.30
Systolic blood pressure, mm Hg	129.22±18.97	127.55±17.94	134.36±22.17
Diastolic blood pressure, mm Hg	76.14±12.87	77.30±10.93	78.31±13.97
Heart rate, beats/min	88.19±18.09	85.29±16.50	85.71±16.72
O_2 saturation, %	94.97±4.79	95.65±2.67	95.96±2.76

Reported values are expressed as means±SD.
*P<0.05, baseline vs 15 weeks.
†P<0.05, baseline vs 26 weeks.

Effect of Weight Loss on Secondary Outcomes

The New York Heart Association class modestly, but significantly, improved from a mean of 2.73 at baseline to 2.46 at 26 weeks (P=0.005; Figure 3). Weight loss was associated with improved Borg dyspnea score at the completion of the 15-week program (–34.7% decrease [P=0.006] versus baseline; Figure 3). The reduction in the subjective sensation of dyspnea persisted at 26 weeks (–32.9% [P=0.042] versus baseline; Figure 3). Furthermore, the Borg fatigue score, a self-assessment of perceived exertion, was significantly improved at the completion of the 15-week program (–36.4% [P=0.017] versus baseline; Figure 3). The reduction in fatigue persisted at 26 weeks (–27.3% [P=0.034] at 26 weeks versus baseline; Figure 3). We further analyzed the data using a 1-way ANOVA, but no significant changes were observed in the secondary end points. Overall, these secondary outcomes further support the favorable impact of short-term weight loss on functional status and quality of life.

Cardiac Structure and Function

No significant changes were observed in resting systolic blood pressure, diastolic blood pressure, heart rate, and O_2 saturation (Table 2). We did not observe significant changes in LV end diastolic volume, LV wall thickness, LV mass, or left atrial volume (Table 4) Likewise, LV ejection fraction did not change. This was expected because the ejection fractions were all normal or minimally reduced at baseline by study design. There was no change at 15 weeks in E/e′. However,

Table 3. Laboratory Measurements

Variable	Baseline (n=41)	15 wk (n=41)	26 wk (n=37)
Creatinine, mg/dL	1.34±0.49	1.32±0.56	1.35±0.55
BUN, mg/dL	25.3±12.33	26.1±13.84	29.03±19.45
eGFR, mL/min	45.84±11.51	47.69±11.65	46.41±12.61
Hemoglobin A1c, %	6.9±1.51	6.48±1.53*	6.81±1.65
Glucose, g/dL	148.73±71.31	129.54±74.65	135.97±70.44
LDL, mg/dL	91.68±36.12	91.8±35.5	95.21±33.89
HDL, mg/dL	44.39±15.14	43.31±12.18	45.94±13.26
Triglyceride, mg/dL	161.66±108.3	143.23±77.5	154.94±111.13
BNP, pg/mL	108.85±161.3	114.7±230.44	110.09±247.69
Hemoglobin, g/dL	12.93±1.93	13.1±1.93	12.84±1.99
hs-CRP, mg/L	1.08±1.07	0.95±0.91	1.26±2.09

Reported values are expressed as means±SD. BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

*P<0.05, baseline vs 15 weeks.

we observed a significant decrease in E/e′ at 26 weeks (–14.8% [P=0.0024] versus baseline; Table 4). Estimated pulmonary artery systolic pressure showed a mild decline, but it was not significant, likely because of low numbers (only 70% of patients had measurable tricuspid regurgitation velocities). Overall, there were no definitive changes in cardiac structure or function, other than a suggestion of reduction in LV filling pressures at the 26-week time point.

Safety

Twenty-one adverse events occurred in 16 unique patients and were associated with emergency department visits during the study period (Table S3). Of these adverse events, only 7 were cardiac in nature. Only 4 patients with adverse events started but did not complete the study: 1 died of a pulmonary embolism in the setting of a newly diagnosed malignancy, 1 had a chronic

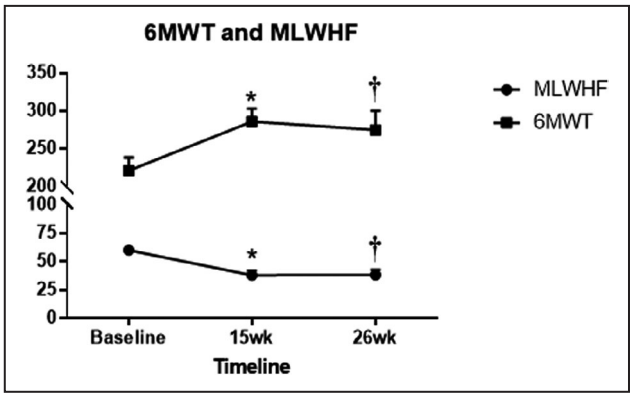

Figure 2. Weight loss at 15 weeks was associated with significantly improved 6-minute walk test (6MWT) and Minnesota Living With Heart Failure (MLWHF) score, indicative of improved quality of life.
The beneficial effects of the weight loss intervention on 6MWT and MLWHF score persisted until 26 weeks. Statistical significance is denoted. *P<0.05, baseline vs 15 weeks; †P<0.05, baseline vs 26 weeks.

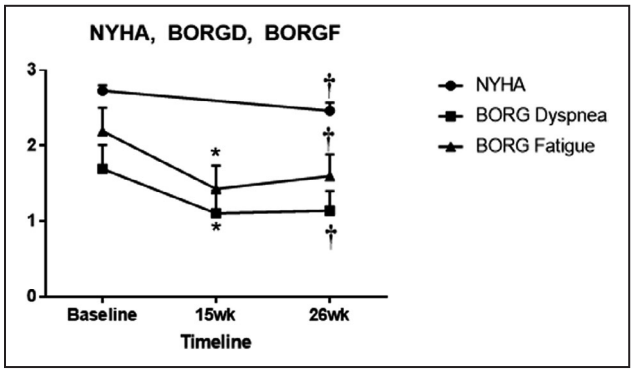

Figure 3. Weight loss significantly improved New York Heart Association (NYHA) functional score, as well as the Borg dyspnea (BORGD) and Borg fatigue (BORGF) scores at both 15 and 26 weeks.
Statistical significance is denoted. *P<0.05, baseline vs 15 weeks; †P<0.05, baseline vs 26 weeks.

Table 4. Echocardiographic Measurements

Variable	Baseline (n=41)	15 wk (n=41)	26 wk (n=37)
LV mass, g	232.25±74.05	223.06±57.76	232.71±65.68
LVEDV, mL	110.31±40.19	107.93±32.96	111.79±31.91
LVESV, mL	41.05±29.16	36.25±17.46	34.61±16.56
Posterior wall thickness, mm	1.23±0.49	1.24±0.49	1.31±0.77
Septal wall thickness, mm	1.25±0.27	1.24±0.22	1.18±0.22
LAESV, mL	75.1±29.84	73.44±26.04	78.65±18.37†
LVEF, %	65.6±7.96	64.5±6.9	66.06±9.4
E, cm/s	92.8±26.5	87.1±23.6*	89.5±28.2
E deceleration time, ms	230.3±51.6	240.4±65.1	214.5±65.9
A, cm/s	82.8±38.8	81.7±43.0	89.2±43.8
E/A	1.16±0.75	1.06±0.60	1.02±0.45
e' Septal, cm/s	6.95±2.22	6.50±2.38	7.36±2.24
e' Lateral, cm/s	7.89±2.5	8.06±2.3	8.75±2.29†
E/e′	13.93±6.84	13.59±7.88	11.87±5.59†
RV diameter, mm	40.49±5.91	40.40±8.42	42.19±6.66
TAPSE, mm	23.09±4.68	21.23±5.28	23±4.46
RAP, mm Hg	3.65±2.33	3.58±1.81	3.76±1.82
RVSP, mm Hg	34.7±9.9	31.79±8.19	30.7±10.0

Reported values are expressed as means±SD. A indicates late diastolic mitral inflow velocity; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular tissue velocity; LAESV, left atrial end systolic volume; LV, left ventricular; LVEDV, LV end diastolic volume; LVEF, LV ejection fraction; LVESV, LV end systolic volume; RAP, right atrial pressure; RV diameter, right ventricular basal diameter; RVSP, right ventricle systolic pressure; and TAPSE, tricuspid annular plane systolic excursion.

*P<0.05, baseline vs 15 weeks.

†P<0.05, baseline vs 26 weeks.

obstructive pulmonary disease exacerbation secondary to an upper respiratory tract infection, 1 had an HF exacerbation after increased dietary salt consumption, and 1 presented with severe hyponatremia secondary to psychogenic polydipsia. Medication changes occurred throughout the study to curtail potential adverse events. Of the 8 patients requiring reduced diuretic dosing, 5 had elevation of serum blood urea nitrogen or creatinine detected on routine laboratory testing. Of the 3 patients requiring reduced antihypertensive dosing, 2 were hypotensive during routine follow-up and 1 presented to the emergency department with hypotension. Of the 2 patients requiring reduced antiglycemic dosing, 1 had asymptomatic hypoglycemia on routine follow-up.

DISCUSSION

Obesity and HFpEF

Many epidemiological studies have shown strong and graded links between obesity and incident HF.[1,3,4] The persistently growing prevalence of obesity is thought to contribute specifically to the increasing incidence of HFpEF.[21] Some investigators have suggested there is a unique phenotype of HFpEF associated with obesity in which excess fat both directly and indirectly leads to increases in LV mass and cardiac filling pressures.[22,23] Thus, weight reduction seems like an obvious target for patients with HFpEF, but weight management is surprisingly not well studied for this purpose. This is probably caused, at least in part, by the fact that meaningful weight loss is difficult to achieve and more difficult to sustain in any population.[24] The challenge of producing and maintaining significant fat loss may be particularly pronounced in patients with exercise limitations resulting from HF. In the current pragmatic study, a structured, short-term weight loss program for participants with HFpEF with obesity was associated with clinically relevant weight reduction; and the degree of weight loss correlated with improved QOL and increased submaximal exercise capacity. More important, the intervention was an existing multidisciplinary lifestyle modification program incorporating the core elements of similar programs shown to produce meaningful weight loss. The program offers exercise counseling but does not incorporate a supervised exercise component. This is important because supervised exercise is relatively costly and will be less feasible in the foreseeable future because of the ongoing effects of the COVID-19 pandemic. That this type of program is safe, effective, and capable of producing clinically relevant weight loss and positive impacts on QOL implies broad applicability to the large population with HFpEF and obesity.

Obesity likely plays both direct (ie, mechanical, hemodynamic, or hormonal) and indirect (ie, via associated comorbidities) roles in the pathophysiological characteristics of HFpEF. LV hypertrophy or concentric LV remodeling and left atrial enlargement are frequent in obese patients.[4] These changes in cardiac geometry may contribute to the symptoms of HF, at least in part, because of impaired LV diastolic filling. In addition, the size and location of fat depots, particularly epicardial fat, have been hypothesized to contribute to the pathophysiological characteristics of HFpEF.[25] More important, there is no direct treatment to reduce epicardial fat other than systemic weight loss. This study could not assess changes in the volume of specific fat beds. However, prior work shows that weight loss is associated with greater reductions in visceral and epicardial adipose tissue than reductions in subcutaneous adipose tissue.[26]

Beneficial Effects of Weight Loss on HFpEF

Multiple studies have shown that surgically induced weight loss is associated with improvements in cardiac structure and function in severely obese patients.[12,13,27] In the Utah Obesity Study, weight loss achieved by bariatric surgery was associated with reduction in LV mass, reduction in left atrial volume, and improved midwall fractional shortening compared with a matched control group.[12] Surgical weight loss is also associated with reduction in visceral and epicardial fat volumes.[26] However, there are no prospective studies evaluating bariatric surgery specifically in patients with established HFpEF. Such studies will be difficult to perform as surgical weight loss procedures are costly and not practical for a large proportion of patients.

It is generally believed that weight loss of 7% to 10% is the amount needed to achieve significant improvement in hypertension, diabetes, nonalcoholic fatty liver disease, and atrial fibrillation events.[18,28,29] However, 5% placebo-subtracted body weight loss is the metric that has been used by the US Food and Drug Administration for approval of weight loss medications.[30] In the current study, mean weight loss was 8.1 kg (–6.7%). Although significantly more weight loss can be achieved with bariatric surgery, lifestyle approaches should be implemented first and are generally required as a precursor to performing surgical weight loss procedures. Other approaches using medical interventions in conjunction with lifestyle interventions have also proven effective for weight loss, as evidenced by recent data that showed 15% body weight loss with semaglutide.[31] However, those studies were conducted primarily on women in their mid-40s with no history of diabetes or heart disease.[31] In patients with diabetes, semaglutide produced a smaller weight loss of ≈9%, which is only modestly more than what was seen in the current study.[32] No published

studies have to date assessed the utility of semaglutide in patients with HFpEF or risk factors analogous to those in our subjects. The substantial costs of semaglutide and other newer weight loss medications may be prohibitive for many patients. Together, these factors highlight the importance of approaches to weight loss using combined lifestyle interventions.

Several small-medium sized studies have evaluated the role of exercise as a treatment for patients with HFpEF.[18–20] These studies have shown that exercise training is safe and moderately effective, with an increase in 6MW distance or peak oxygen consumption by 10% to 15%.[18–20] In the aforementioned studies, exercise alone was also associated with modest, but significant, improvements in MLWHF.[18–20] Weight loss was reported in only one of these studies and was modest (–4.3 kg).[33] The degree of improvement in 6MW distance (29%) in our study is comparable to, or better than, the increases in exercise capacity observed in the above studies, which tested more direct exercise interventions.

Only 1 prior study has evaluated hypocaloric diet as means of achieving weight loss and improving exercise capacity or QOL in patients with HFpEF and obesity.[15] Kitzman et al randomly assigned 100 patients with HFpEF to diet, exercise, exercise plus diet, or control.[15] In that study, the groups randomized to reduced calorie diet were supplied 2 complete, preprepared meals/day (lunch and dinner) for the duration of the study (20 weeks). Those assigned to exercise had supervised exercise (primarily walking) sessions 3 times per week for 20 weeks. Patients in the diet group lost 7% body weight, and those in the exercise group lost 3%. The study showed that both diet and exercise were associated with increased peak maximal oxygen consumption (8–9%), and the combination was more effective than either alone (17%).[15] Interestingly, they did not observe a significant change in MLWHF score or in echocardiographic parameters, including LV mass or E/e′, whereas LV mass measured by magnetic resonance imaging decreased slightly by 4 g.[15] Although the study design was elegant, it will be difficult to reproduce the intervention in routine clinical practice. Thus, we designed a pragmatic, prospective study to extend the findings of Kitzman et al to a potentially broader population.

Impact of Weight Loss on QOL in Obese Patients With HFpEF

In the present study, we demonstrated that loss of ≈7% body weight was associated with a 37% decrease in MLWHF score and a 29% increase in 6MW distance at completion of the 15-week program, compared with baseline. These changes persisted at the 26-week follow-up, with a 36.4% decrease in MLWHF and a 24.2% increase in 6MW distance compared with baseline. The magnitude of changes is in alignment with previous studies that assessed the impact of exercise training on QOL measures and cardiac function in patients with HFpEF.[18–20,33,34] Gary and colleagues demonstrated that a 12-week exercise and education program, targeting women with HFpEF, resulted in a 24.2% increase in 6MW distance (840–1043 feet) and a 41.5% decrease in MLWHF score (41 to 24).[34] Another study conducted by Kitzman and colleagues demonstrated that 16 weeks of supervised exercise for patients with HFpEF resulted in an 11% increase in 6MW distance (1494–1659 feet) and a 21.9% decrease in MLWHF score (32 to 25), without any significant differences in echocardiographic parameters.[18] Edelman and colleagues showed that a 24-week program of exercise therapy resulted in a 32% decrease in MLWHF score, which was associated with improvements in cardiac structural parameters.[19] Smart and colleagues reported that a 16-week exercise program resulted in a 13.9% decrease in MLWHF, without any associated alterations in cardiac structural parameters.[33] Our findings suggest that supervised exercise is not mandatory to achieve improvements in exercise capacity and that successful dietary weight loss and counseling are perhaps as important, or even more important, in achieving this goal.

Impact of Weight Loss on Cardiac Structure

Prior studies provide some conflicting evidence on whether short-term lifestyle interventions (mainly exercise) produce significant changes in cardiac structure and function. Kitzman and Smart did not observe any significant improvements in cardiac structural or functional parameters following a 16-week exercise program.[18,20,33] On the other hand, Edelman demonstrated that 24 weeks of exercise therapy were associated with a reduction in E/e′ (12.8 to 10.5), suggesting lowering of LV filling pressures.[19] In the present study, we observed no changes in cardiac structure, and the only suggestion of functional improvement was reduction in E/e′ at 26 weeks. This suggests that the benefits of the intervention on 6MW distance and QOL were likely related, at least in part, to noncardiac factors. Potential reduction in LV filling pressures could be contributory. Several prior studies suggest that peripheral adaptations, particularly in skeletal muscle, mediate much of the improvement in exercise capacity after completion of an exercise training program,[15] and our results are consistent with that interpretation.

In the present study, we observed changes in MLWHF score and 6MW test of a larger magnitude compared with most of the other published studies.[18–20,33] We think this is likely a direct benefit of weight

reduction, as little weight loss was seen with most isolated exercise interventions. The degree of weight loss that we observed was associated with modest but significant metabolic benefits, as evidenced by reduction in hemoglobin A1c (–6.1% relative decrease) and trends toward lower fasting glucose and triglyceride levels. At 11 weeks following successful completion of the program, we observed trends suggesting some degree of early weight regain and attenuation in the improvements in 6MW distance and Borg fatigue scale. This highlights the well-known challenge of maintaining long-term benefits from lifestyle interventions and highlights the need for studies addressing adjunctive approaches to maintaining and increasing the favorable effects of lifestyle interventions.

Our study had high percentages of female and Black participants. This is important because these subgroups are underrepresented in most cardiovascular trials. More important, female and Black patients have higher prevalence of obesity than most other demographic groups. Although these groups were too small for meaningful statistical analyses, we did not see any trends to suggest that their responses were different than those of the overall study cohort.

Study Limitations

Despite the direct clinical relevance of the findings, there are several limitations. First, the final sample size was relatively small. A total of 19 of the 60 (32%) who attended at least 1 visit did not complete the study. This was expected and likely reflects the success rates that might be achieved in real-world applications of dietary interventions. These data may inform the design of subsequent trials. Those participants who did not complete the intervention were not included in the analyses and may have had worse outcomes compared with those participants who completed the study. Current treatment options are limited in patients with HFpEF and obesity, and this growing population is in desperate need of a practical approach to combating the combined effects of these diseases. As such, both clinicians and patients might find it encouraging that two thirds of the patients were able to complete the intervention despite the substantial effort and time commitment required. Second, despite significant weight loss, BMI at the end of the study was still >40 kg/m^2. Thus, other treatments in addition to the lifestyle intervention will be needed to gain maximal benefit. Bariatric surgery might be such an option. However, our patients had a mean age of 67 years, a confirmed diagnosis of HFpEF, and frequent comorbidities, which collectively might make them suboptimal candidates for weight loss surgery. Third, the study lacked a control group, and QOL measures, including MLWHF score and 6MW, were performed by study coordinators who were aware of the patient's stage in the program. Fourth, in patients with HF, weight loss could be attributable to extravascular fluid loss, rather than reduction in fat stores. We think this is unlikely to be the main mechanism as all of the patients enrolled had stable HF and none had overt volume overload. Moreover, 8 of the 41 patients had reductions in diuretic dosing during the intervention. In addition, because we did not assess body composition, it is unknown what proportion of weight lost is attributed to adipose tissue versus muscle loss. Fifth, the amount of weight loss achieved was good for a lifestyle intervention and comparable to what is obtained with semaglutide in patients with diabetes, but much less than what can be produced with bariatric surgery. Sixth, it is difficult to determine whether the benefits were directly related to changes in cardiovascular function or improved metabolic state, skeletal muscle function, and other physiologic factors. Nonetheless, we saw substantial benefit on clinical and metabolic parameters. Last, this was a short-term intervention. Although our data show sustained benefits out to 6 months (≈3 months after completion of the program), gradual weight recidivism after this time point is likely. Strategies to maintain the short-term weight loss and associated benefits will be needed to improve longer-term outcomes.

CONCLUSIONS

In conclusion: (1) patients with symptomatic HFpEF can lose clinically relevant amounts of weight using a relatively standard lifestyle intervention that does not require supervised exercise, (2) this amount of weight loss was safe and associated with significant improvements in QOL and exercise tolerance that are comparable or greater in magnitude than those reported in many HF trials using other effective treatments, and (3) weight loss in patients with HFpEF can have a beneficial impact on cardiac function and metabolic parameters and may be associated with reductions in doses of diuretics, antihypertensive agents, and diabetes medications. Future studies will need to include a greater number of participants with longer duration of follow-up to determine whether the benefits can be sustained and if there are differences in outcomes, such as HF hospitalizations.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1–S2
Tables S1–S3

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Supplemental Material

Data S1.

Exclusion Criteria

-Uncontrolled blood pressure

-If BP > 160/95 mmHg at baseline and taking < 3 BP medications, increase BP medication before enrolling (target BP < 140/90)

-If resistant HTN, i.e., BP > 140/90 while taking 3 or more BP lowering medications, allow enrollment with BP up to 200/100 as weight loss may help to control resistant HTN

-Severe COPD (oxygen- or steroid-dependent, FEV1 or FVC < 80% predicted)

-Recurrent major depression, presence or history of suicidal behavior or ideation with intent to act, and current substantial depressive symptoms. Antidepressant drugs are allowed if the dose has been stable for 3 months.

-Other major psychiatric illness (schizophrenia, bipolar, dementia)

-Glomerular filtration rate (GFR) < 20 ml/min/1.73m^2

-Significant hepatic dysfunction (AST or ALT > 3 x the upper limit of normal, or total bilirubin > 1.5 mg/dl, unless there is a diagnosis of Gilbert's disease)

-Untreated clinically significant Hypothyroidism or Hyperthyroidism

-History of drug or alcohol abuse or dependency within the past 12 months

-Acute coronary syndrome without revascularization in the past 12 months

-Acute coronary syndrome with revascularization in the past 6 months

-CVA or TIA in the past 6 months

-Cancer or other terminal illness with life expectancy < 3 years

-History of medical noncompliance

-Significant anemia (Hb < 9 mg/dl)

-Life threatening or uncontrolled arrhythmia

-Hemodynamically relevant valvular heart disease

-Infiltrative heart disease including cardiac amyloidosis, sarcoidosis, Fabry's disease

-Genetic hypertrophic cardiomyopathy

-Significant pericardial disease

-Clinically relevant neuromuscular disease

-Pregnant or may become pregnant in next 6 months (instructed on contraception)

-Prior major organ transplant or intent to transplant (on transplant list)

-Pacemaker dependent

-Clinically significant congenital heart disease that may be cause of symptoms

Data S2.

Dietary Intervention

The program consists of a 3-phase dietary change, outlined below.

- Phase 1 (Weeks 1-8): For this first phase of the program, the diet consisted of approximately 1040-1200 calories per day, derived primarily from nutrition bars and shakes; patients consume 1 highly structured, food-based meal per day.
- Phase 2 (Weeks 9-10): Following the initial 8 weeks of the program, there was a transition to a partial meal replacement-based plan with 2 highly structured, food-based meals per day.
- Phase 3 (Weeks 11-15): At the end of 10 weeks, patients met with a registered dietitian who developed a nutritionally balanced hypocaloric diet designed to meet individual long-term nutritional requirements.

Table S1. Baseline Characteristics of Dropouts (n=19).

Variable	Values
Age (years, mean, SD)	57.5±12.8*
Male (%)	7/19 (36.8)
Race (%)	
White	13/19 (36.8)
Black	6/19 (31.6)
Comorbidities (%)	
DM	7/19 (36.8)
HTN	17/19 (89.5)
CKD	4/19 (21)
Atrial fibrillation	8/19 (42.1)
COPD	3/19 (15.8)
OSA	15/19 (79)
CAD	5/19 (26.8)
Bariatric Surgery (%)	2/19 (10.5)

*denotes p=0.002 compared to age (67.0±9.2) of the 41 patients that completed the 15-week program. Abbreviations: diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), coronary artery disease (CAD)

Table S2. Changes in Diuretic Doses.

Patient	Initial Dose (mg)	Subsequent Dose (mg)	Reason for Change
1	Torsemide 40 TID	Torsemide 40 BID	Weight loss, euvolemia
2	Bumetanide 2 BID	Bumetanide 1 BID	Acute kidney injury
3	Bumetanide 2 BID	Bumetanide 2 qD	Acute kidney injury
4	Furosemide 80 qD	Furosemide 40 qD	Acute kidney injury
5	Bumetanide 2 BID	Bumetanide 1 BID	Acute kidney injury
6	Bumetanide 2 BID	Bumetanide 1 BID	Acute kidney injury
7	Furosemide 40/20 (AM/PM)	Furosemide 20/20 (AM/PM)	Weight loss, euvolemia
8	Bumetanide 2 BID	Bumetanide 1 qD	Weight loss, euvolemia

Abbreviations: three times daily dosing (TID), twice daily dosing (BID), daily dosing (qD)

Table S3. Adverse Event.

Patient	Number of Events	Symptom	Diagnosis	Disposition
1*	2	Dyspnea	Non-cardiac	DC from ED
		Abdominal Pain	Malignancy	Deceased
2	3	Palpitations	Arrhythmia	DC from ED
3	1	Shoulder Pain	Musculoskeletal	DC from ED
4*	1	Confusion	Severe hyponatremia	DC from ED; Δ Rx
5*	1	Dyspnea	COPD Exacerbation	DC from ED
6	1	Weakness	Hypotension	DC from ED; Δ Rx
7	1	Hematochezia	Diverticulosis	DC from ED
8	1	Chest pain	Musculoskeletal	DC from ED
9	1	Palpitations	Atrial Fibrillation	DCCV; Inpatient DC
10	1	Chest pain	GERD	DC from ED
11	1	Palpitations	Atrial Fibrillation	DCCV; Inpatient DC
12	1	Not specified	Pneumonia and AKI	Not specified
13	2	Asymptomatic	Bradycardia	DC from ED; Δ Rx
		Hematochezia	Diverticulosis	DC from ED
14*	1	Dyspnea	CHF Exacerbation	Inpatient discharge
15	1	Not specified	Meningitis	Inpatient discharge
16	2	Dyspnea	Acute Bronchitis	DC from ED
		Foot pain	Musculoskeletal	DC from ED

Abbreviations: discharge (DC), emergency department (ED), medication changes made (Δ Rx), direct current cardioversion (DCCV); *denotes dropouts.