ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 1342–1348
Published online 27 January 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13213

ORIGINAL RESEARCH ARTICLE

High-protein vs. standard-protein diets in overweight and obese patients with heart failure and diabetes mellitus: findings of the Pro-HEART trial

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Abstract

Aims The intermediate-term effects of dietary protein on cardiometabolic risk factors in overweight and obese patients with heart failure and diabetes mellitus are unknown. We compared the effect of two calorie-restricted diets on cardiometabolic risk factors in this population.

Methods and results In this randomized controlled study, 76 overweight and obese (mean weight, 107.8 ± 20.8 kg) patients aged 57.7 ± 9.7 years, 72.4% male, were randomized to a high-protein (30% protein, 40% carbohydrates, and 30% fat) or standard-protein diet (15% protein, 55% carbohydrates, and 30% fat) for 3 months. Reductions in weight and cardiometabolic risks were evaluated at 3 months. Both diets were equally effective in reducing weight (3.6 vs. 2.9 kg) and waist circumference (1.9 vs. 1.3 cm), but the high-protein diet decreased to a greater extent glycosylated haemoglobin levels (0.7% vs. 0.1%, $P = 0.002$), cholesterol (16.8 vs. 0.9 mg/dL, $P = 0.031$), and triglyceride (25.7 vs. 5.7 mg/dL, $P = 0.032$), when compared with the standard-protein diet. The high-protein diet also significantly improved both systolic and diastolic blood pressure than the standard-protein diet ($P < 0.001$ and $P = 0.040$, respectively).

Conclusions Both energy-restricted diets reduced weight and visceral fat. However, the high-protein diet resulted in greater reductions in cardiometabolic risks relative to a standard-protein diet. These results suggest that a high-protein diet may be more effective in reducing cardiometabolic risk in this population, but further trials of longer duration are needed.

Keywords Heart failure; Obesity; Diabetes; High-protein diet; Calorie-restricted diet; Weight loss

Received: 21 October 2020; Revised: 16 December 2020; Accepted: 2 January 2021
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Introduction

Heart failure (HF) patients often suffer from multiple co-existent diseases and/or conditions (co-morbidities) that may complicate management and adversely affect outcomes. US claims data show that approximately 55% of older American patients with HF have five or more chronic co-morbidities.[1] Common characteristics of metabolic syndrome, including obesity, diabetes mellitus (DM), hyperlipidaemia, and hypertension, also known as cardiometabolic risk factors, are recognized as some of the most likely precursors of HF that commonly continue to exist once HF has developed.[2] Common mechanism ties many co-morbidities to HF by initiating or exacerbating chronic inflammation and activating the sympathetic renin–angiotensin–aldosterone systems.[3] Insulin resistance and impaired beta-cell function are core defects in metabolic syndrome responsible for the pathophysiological disturbances leading to hyperglycaemia, dyslipidaemia, and hypertension.[4] However, less is known about the complex physiological interplay of multiple co-morbidities to each other and HF.

Lifestyle factors have contributed to an increased occurrence of DM and overweight and obesity, including changes in dietary patterns, resulting in an increased prevalence of HF.[5] Several studies in community settings and heart transplant referral centres support the notion that the number of individuals with all three conditions is alarmingly high and raises individuals' cardiometabolic risks[6–11] and increases cardiac dysfunction, metabolic disturbances, neurohormonal activation, and diminished quality of life. Thus, efforts to prevent or reduce co-morbidities related to HF in the community are of the utmost importance. This includes measures to minimize obesity and diabetes, as both are becoming highly prevalent worldwide and are important risk factors for almost all significant HF-related co-morbidities. In 2015, 35–45% of the old and new patients referred to our heart transplant centre (*N* = 1667) had DM, and 40–50% of patients with HF and DM were overweight or obese. Thus, interventions aimed at reducing the metabolic, neurohormonal, and haemodynamic deficiencies characterizing this disabling triad are needed to minimize risks and potentially improve clinical outcomes.[12]

Considering the confounding effects of nutritional deficiencies on disease progression and mortality in overweight and obese patients with HF and DM, the potential role of diet in reducing risk and preventing disease progression is especially relevant and timely.[13] However, patients' nutritional management with these three conditions and other associated co-morbidities is poorly understood, and dietary recommendations are ambiguous. Traditionally, dietary advice for patients with HF centred on sodium and fluid intake limits, despite the lack of robust evidence supporting improved clinical outcomes with these measures.[14] Last, the evidence about the overall effects of weight loss in this subgroup of patients is inconsistent.[15] The 2013 (with updates in 2016 and 2017) American College of Cardiology/American Heart Association,[16,17] the 2016 European Society of Cardiology Guidelines on HF,[18] and the Heart Failure Society of America Comprehensive HF Management Guideline[19] do not have nutritional recommendations for patients overweight and obese patients with HF and DM. The HF Working Group of the European Society of Cardiology refers to the beneficial effects of weight loss in patients with HF with increased body mass index. However, there are no instructions for meeting this goal.[18] The association of obesity and enhanced survival in patients with HF, generally referred to as the 'obesity paradox', has highly likely prevented investigators from thoroughly investigating the effects of weight loss in this subgroup of patients with HF.[10] Nevertheless, information is needed on appropriate nutritional requirements, including adjustments in size, structure, or consumption rates of specific macronutrients for overweight and obese patients with HF and DM.

Although most healthcare providers and dieticians recommend conventional methods (high carbohydrate and low fat) for weight reduction endorsed by the American Heart Association,[20] dietary approaches of this type are correlated with very modest weight loss weak long-term commitment.[21,22] While a diverse range of alternative strategies have emerged, high-protein diets have significantly increased acceptance. They have been shown in randomized clinical trials to result in more significant reductions in body weight and visceral fat, and lean mass maintenance than conventional diets in obese patients with DM.[23–25] In a preliminary study, we tested the feasibility and effectiveness of a high-protein diet in 14 overweight and obese patients with HF and DM, compared with standard-protein and traditional diet (i.e. standard-protein, non-hypocaloric diet). We found that a high-protein diet had slightly more substantial weight and obesity decreases and more considerable clinical outcome benefits than a standard-protein diet.[26] To date, no recorded clinical trials have been conducted in overweight and obese diabetic patients with HF to test the benefits of a high-protein diet. There is also limited evidence supporting protein intake goals.[14] This study examines the role of high-protein diets in slowing disease progression in a randomized clinical trial by assessing improvements in chronic disease progression by contrasting baseline and 3 month weight, visceral fat, glycaemic control, lipid profile, and blood pressure (BP) of two protein variation diets consumed over 12 weeks.

Methods

The study was approved by the respective institutional review board in the two major university-affiliated medical centres. The research was performed and complied with the *Declaration of Helsinki*. A full description of the study nature, eligibility criteria, the test procedure for this two-group repeated measure, and a randomized clinical trial (ClinicalTrials.gov identifier: NCT01423266) has been reported elsewhere.[13] In brief, we randomized overweight and obese patients with HF and DM to one of two hypocaloric diets: (i) a high-protein diet [30% protein (~110 g/day), 40% carbohydrates (150 g/day), and 30% fat (~50 g/day)] or (ii) a standard-protein diet [15% protein (~55 g/day), 55% carbohydrates (~200 g/day), and 30% fat (~50 g/day)]. The energy requirements (total energy needed per kcal/day) were determined for each person using the Deltatrac (dual-energy X-ray absorptiometry baseline scan) and their specific metabolic rate (resting energy expenditure) and lean body size mass. Two regular, energy-restricted meal plans (1200 or 1500 kcal/day) were given to participants in both arms based on their assessed calorie deficit. The meal plan's goal was to meet the total calorie intake, including a daily decrease of 500–800 kcal, and achieve weight losses of 0.5–1.0 kg/week.[13]

In both study arms, participants consulted with a licenced dietician for nutritional evaluation, counselling, and support at 2, 4, 8, and 12 weeks of the study. Every session was 45–60 min. To optimize commitment to study visits, participants received a list of appointments at the baseline visit and a reminder of appointments (phone calls, text messages, or emails) before each subsequent visit.

Meals on both menus contained mainly healthy protein products (e.g. unprocessed meat, poultry, fish, and eggs), fruits, vegetables, and low-fat dairy products, included whole grains and nuts, and limited in red meat, desserts, and sugar-containing drinks. Menus were often designed to contain >25 g fibre and <10% saturated fat. Patients' body weights and dietary intake records were reviewed at each dietician visit, and dietary adjustments were made if required. The dietician provided detailed information on the meal plan and how to manage daily food logs. Although the predominant focus of treatment was on the dietary component, all participants were also encouraged to exercise regularly to reduce energy deficiency and promote weight loss and maintenance. Furthermore, participants were interviewed at 2, 4, 8, and 12 weeks to ensure adherence to study diets.

Height, weight, waist circumference, and BP were assessed at the beginning of the baseline visit and after each follow-up visit. Blood tests [e.g. glycosylated haemoglobin, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG)] were also performed after a 12 h overnight fast at baseline and 3 months to analyse the influence of both diets on the glycaemic control and lipid profile.

Data analysis

The data were analysed using Version 25 of SPSS.[27] Descriptive statistics (mean ± standard deviation and χ^2) were used to describe the study participants' socio-demographic and clinical characteristics. The general method involves an initial review using a *t*-test (or Wilcoxon rank-sum test if non-normality is observed) to analyse the two groups' results. Longitudinal data analysis using mixed models was conducted on each outcome of interest utilizing linear mixed-effects equations to evaluate differences in treatment effects between diets adjusted for body weight change for all variables reported, except bodyweight, for which a paired sample *t*-test was applied. All linear mixed-effects models included body weight change and interaction between diet and period as fixed effects.

The approximate sample size (N = 90) was calculated using nQuery Advisor 6.01. Effect sizes for this estimate were based on differences in result between baseline and 12 week follow-up, that is, the first follow-up assessment, and an expected attrition rate of 20%.[28] The real attrition rate was lower than predicted, but recruiting was discontinued when 76 patients finished the 3 month follow-up visit. The actual analysis was based on the full set of longitudinal data, including appropriate covariates, and should, therefore, have more power than the nominal 80% assumed, at a significance level of 0.05. To correct multiple comparisons, we used a modified (conservative) alpha to estimate our sample size.

Results

Seventy-six participants completed the 3 month intensive dietary intervention. Baseline demographic and clinical characteristics between the two groups were comparable (*Table 1*). Participants ranged in age from 27 to 81 and were, on average, 57.7 ± 9.7 years old. They were predominantly male (72.4%), White (51.4%), married (66.7%), and college graduates (46.1%). The average weight was 107.8 ± 20.8 kg, the average ejection fraction was 38.5 ± 10.7%, and the average peak VO_2 was 12.5 ± 3.9 mg/kg/min. A total of 77.6% and 22.4% of participants had New York Heart Association Functional Class II and Class III, respectively. There were no differences in the number of co-morbidities and medications being taken between the two groups.

The participants' weight and visceral fat loss were not significantly different between the two groups, as were baseline glycaemic control, lipid profiles, and systolic and diastolic BP (*Table 2*). Both diets were equally effective in reducing weight (3.6 vs. 2.9 kg) and waist circumference (1.9 vs. 1.3 cm), but the high-protein diet decreased to a greater extent glycosylated haemoglobin levels (0.7 vs. 0.1%, P = 0.002), TC (16.8 vs. 0.9 mg/dL, P = 0.031), and TG (25.7 vs. 5.7 mg/dL, P = 0.032), when compared with the standard-protein diet. The high-protein diet also significantly improved both systolic and diastolic BP than the standard-protein diet ($P < 0.001$ and P = 0.040, respectively). No differences were noted in LDL and HDL levels over time.

While it has been shown that a high-protein diet decreases cardiovascular risk and may improve clinical outcomes for diabetic adults,[28] to our knowledge, no studies have been conducted in overweight and obese HF and DM patients.[29] Moreover, our understanding of nutritional recommendations for patients with HF is limited, and no specific guidelines are currently available.[30–32] Our findings showed that both the high-protein and standard-protein diets successfully promoted weight loss and visceral fat loss. However, participants in the high-protein diet showed more significant reductions in glycaemic control, lipid profiles (except LDL and HDL), and both systolic and diastolic BP over time.

Generally, the clinical effects of weight loss in overweight and obese people with HF and DM have been positive and reinforce the possible rationale for implementing appropriate weight management strategies in this population.[21] The current research shows that overall weight loss associated with

Table 1 Baseline socio-demographic and clinical characteristics ($N = 76$)

	All participants ($N = 76$)	High-protein group ($n = 33$)	Standard-protein group ($n = 43$)	Sig.
Age, years (mean ± SD)	57.7 ± 9.7	57.3 ± 10.1	58.0 ± 9.6	0.769
Male, *N* (%)	55 (72.4%)	26 (78.8%)	29 (67.4%)	0.273
Race, *N* (%)				0.718
Hispanic	15 (20.8%)	6 (19.4%)	9 (22.0%)	
White	37 (51.4%)	17 (54.8%)	20 (48.8%)	
African American	15 (20.8%)	5 (16.1%)	10 (24.4%)	
Asian	9 (11.8%)	5 (15.2%)	4 (9.3%)	
Married, *N* (%)	48 (66.7%)	20 (64.5%)	84 (68.3%)	0.722
Employed, *N* (%)	26 (34.2%)	14 (42.4%)	12 (27.9%)	0.161
Education, *N* (%)				0.536
< high school	6 (8.5%)	2 (6.7%)	4 (9.8%)	
High school graduate	10 (13.2%)	5 (15.2%)	5 (11.6%)	
Some college	25 (32.9%)	9 (27.3%)	16 (37.2%)	
Completed college	35 (46.1%)	17 (51.5%)	18 (41.9%)	
Ejection fraction, % (mean ± SD)	38.5 ± 10.7	40.6 ± 12.1	36.9 ± 9.4	0.163
Peak VO_2, mg/kg/min (mean ± SD)	12.5 ± 3.9	12.44 ± 3.0	12.5 ± 3.5	0.922
6 min walk distance, m (mean ± SD)	395.3 ± 91.1	386.5 ± 99.6	401.8.4 ± 84.8	0.490
Charlson Comorbidity Index (mean ± SD)	3.6 ± 1.4	3.4 ± 1.5	3.7 ± 1.3	0.212
NYHA class, *N* (%)				0.474
Class II	59 (77.6%)	24 (72.7%)	35 (81.4%)	
Class III	17 (22.4%)	9 (27.3%)	8 (18.6%)	
HF type				0.053
HF with reduced ejection fraction	43 (56.6%)	14 (42.4%)	29 (67.4%)	
HF with preserved ejection fraction	33 (43.4%)	19 (57.6%)	14 (32.6%)	
Co-morbidities				
Hypertension, *N* (%)	35 (46.1%)	15 (45.5%)	20 (46.5%)	0.812
Coronary artery disease, *N* (%)	22 (28.9%)	9 (27.3%)	13 (30.2%)	0.618
Depression, *N* (%)	21 (27.6%)	12 (36.4%)	9 (20.9%)	0.237
Hx smoking (previous smoker), *N* (%)	31 (40.8%)	12 (36.4%)	19 (44.1%)	0.718
Medications use, *N* (%)				
ACE inhibitors	53 (69.7%)	27 (81.8%)	27 (62.8%)	0.132
Angiotensin receptor blockers	23 (30.3%)	7 (21.2%)	16 (37.2%)	0.118
Beta-blockers	70 (92.1%)	29 (87.9%)	41 (95.3%)	0.889
Diuretics	54 (71.2%)	23 (69.7%)	31 (72.1%)	0.829
Digoxin	30 (39.5%)	12 (36.4%)	18 (41.9%)	0.746
Pain medications	22 (28.9%)	11 (33.3%)	11 (25.6%)	0.475
Antidepressants	14 (18.4%)	6 (18.1%)	8 (18.6%)	0.951

ACE, angiotensin-converting enzyme; HF, heart failure; NYHA, New York Heart Association; SD, standard deviation.

high-protein and standard-protein diet eliminates much of the overweight and obesity-related effects, despite losing only 3.6% and 2.7% of their original baseline weights. Significant differences in body weight loss over 3 months have also been reported while contrasting high-protein diets with regular protein diets.[25,33,34]

We observed reduced TC and TG and systolic and diastolic BP levels on both diets, but these reductions were significantly higher in the high-protein group. High-protein diets have been shown to reduce the metabolic profile parameters after 3 months of energy restriction due to a comparatively higher protein content, which encourages a sustained level of satiety, sustainable energy intake, and increased fat oxidation.[34] Similar improvements in neurohormonal profiles and the consequent reduction in cardiovascular risk and diastolic and systolic dysfunction were reported with modest weight loss, equivalent to 5% of initial weight, and further improvement, which correlates with weight loss.[21] Further reductions in cardiometabolic risks may be attributable to improved atherogenic lipid profile following carbohydrate restriction.[4] The lack of changes in the LDL-C and HDL-C levels that were observed may be because improvements in these parameters are typically correlated with weight loss that has been maintained for more than 3 months.[35]

Our most notable findings have been a significant reduction in glycaemic control among participants in the high-protein-diet group. Similarly, in obese people with type 2 DM, insulin sensitivity improved rapidly in response to energy-deficit diets.[23] These results are likely due to glucose control, insulin regulation, muscle building, regulation, or increased metabolism associated with high-protein diets.[4,36] In addition, investigators have also shown that high-protein diets have acutely decreased post-prandial blood glucose and insulinaemia levels in individuals with DM,[37] contributing to more substantial reductions in glycaemic control observed in our research.

The establishment and maintenance of comparison in selected nutrients, without the conflicting effects of changes in other nutrients or weight changes, was a significant challenge. We tried to reduce variation by regular monitoring

DOI: 10.1002/ehf2.13213

Table 2 Baseline and 3 month outcomes ($N = 76$)

	High-protein group ($n = 33$)				Standard-protein group ($n = 43$)					
Variable	Baseline (mean ± SD)	3 month (mean ± SD)	Δ	%Δ	Baseline (mean ± SD)	3 month (mean ± SD)	Δ	%Δ	*P* (time)	*P* ($T \times G$)
Weight (lb)	105.5 ± 22.4	101.9 ± 21.7	−3.6	3.4	109.9 ± 19.3	106.9 ± 18.2	−3.0	2.7	0.000	0.383
Body mass index (kg/m^2)	36.2 ± 7.1	34.7 ± 6.9	−1.5	4.3	37.3 ± 5.4	36.3 ± 5.3	−1.0	2.8	0.000	0.067
Waist circumference (cm)	46.9 ± 6.2	45.0 ± 6.2	−1.9	4.0	47.9 ± 4.5	46.6 ± 4.3	−1.3	2.8	0.000	0.364
Total cholesterol (mg/dL)	160.2 ± 41.9	143.4 ± 33.2	−16.8	11.7	163.7 ± 39.3	162.8 ± 44.5	−0.9	0.6	0.017	0.031
LDL cholesterol (mg/dL)	85.5 ± 32.2	83.0 ± 33.1	−2.5	3.0	94.0 ± 32.4	92.9 ± 39.9	−1.1	1.2	0.552	0.811
HDL cholesterol (mg/dL)	37.9 ± 10.6	38.8 ± 9.5	0.9	2.3	40.0 ± 9.2	40.9 ± 8.2	0.9	2.2	0.094	0.926
Triglycerides (mg/dL)	163.2 ± 59.2	137.5 ± 54.8	−25.7	18.7	154.0 ± 65.1	148.3 ± 53.6	−5.7	3.8	0.001	0.032
HgbA1c (%)	7.2 ± 1.3	6.5 ± 1.0	−0.7	10.8	7.3 ± 1.8	7.2 ± 1.6	−0.1	1.4	0.000	0.002
Systolic BP (mmHg)	123.3 ± 12.8	112.5 ± 11.8	−10.8	9.6	116.8 ± 19.5	117.5 ± 15.7	0.7	0.9	0.001	0.000
Diastolic BP (mmHg)	72.8 ± 9.6	65.2 ± 8.1	−7.6	11.7	73.30 ± 1.0	70.1 ± 6.9	−3.2	4.6	0.000	0.040

BP, blood pressure; HDL, high-density lipoprotein; HgbA1c, glycosylated haemoglobin; LDL, low-density lipoprotein; SD, standard deviation.

and support to overcome inconsistent adherence to the prescribed diet, which arises in behavioural intervention trials designed to achieve contrast in diets. We observed that being flexible and responsive to patients' dietary needs and preferences allowed them to adhere to their prescribed diet. Translating the two dietary interventions into traditional clinical settings may be challenging because of time and resource constraints. A vital component of the two dietary interventions was a biweekly one-on-one consultation with a registered dietician to help identify non-adherence with the prescribed diet and guidance to overcome challenges. Until intervention programmes are widely available in the community, healthcare providers and other medical care team members may play an essential role in educating patients about their dietary consumption. Patients should be provided with tools to help support patients with behavioural and dietary changes at no cost.

Given the evidence that visceral and ectopic adiposities adversely affect inflammatory and metabolic changes, haemodynamic disorders, and left ventricular diastolic and systolic dysfunction, nutrition's potential role in reducing cardiometabolic risks and slowing disease progression is particularly relevant and timely.[29,32,38] To our knowledge, our study is the first to investigate the impact of macronutrients on HF outcomes in overweight and obese patients with HF and DM. Both hypocaloric diets showed progressive weight loss throughout the 12 week dietary intervention, culminating in decreases in inflammatory and metabolic disorders linked with worse clinical outcomes in this population. However, patients with higher daily protein consumption showed more significant improvements. Protein's role in glucose control, insulin regulation, and weight and visceral fat reduction requires further research into the effects of protein level's activity on body functions, including improved satiety hormone secretion, muscle building, and modulation or increased metabolism. Likewise, a more extensive study is warranted to explore the effect of high-protein diets on cardiometabolic risks, which could contribute to a deeper understanding of the obesity paradox and the various conflicting and sometimes contradictory mechanisms that exist.[10] Nevertheless, our findings provide healthcare providers with data on dietary alternatives for overweight and obese patients with HF and DM integrated into the existing clinical practice guidelines.

While the achievement of high adherence and low attrition rates was a strength of the research, the complexity of the intervention, with a high level of professional support, could restrict the generalizability of wide-scale community adoption. Additional research exploring the obstacles and barriers to weight loss is warranted to better understand and endorse weight loss strategies in this subgroup of patients. A further limitation to the study is that although the two groups were successfully stratified with respect to age, gender, and exercise capacity, further stratification was lacking, and possible confounders such presence of reduced vs. preserved ejection fraction, New York Heart Association class, and socio-economic status were not taken into account. Future initiatives need to integrate these research outcomes into cost-effective community-based delivery models. As participants were predominantly Caucasians, future studies should investigate the effectiveness of a high-protein diet in individuals of diverse ethnicities.

Conclusions

In this 3 month randomized controlled trial, both energy-restricted diets resulted in weight and visceral fat reductions in overweight and obese patients with HF and DM. These findings encourage both patients and providers to feel that weight loss is not achievable in this population due to

their limited exercise capability. More significantly, the high-protein diet over the 3 months resulted in more substantial changes in glycaemic control, TC and TG levels, and BP than the standard-protein diet. These findings indicate that a high-protein diet could be more effective in reducing this population's cardiometabolic risk and maybe a more realistic, feasible, and sustainable goal for a dietary intervention than weight loss. Additional more extensive clinical trials of longer duration should be considered.

Conflict of interest

None declared.

Funding

This work was supported by funding from the National Heart, Lung, and Blood Institute (1R01HL093466). The project described was also supported by the National Institutes of Health/National Center for Research Resources and the National Center for Advancing Translational Sciences (NIH/NCRR/NCATS), through the University of California Irvine Institute for Clinical and Translational Science Grant Number UL1TR000153 and by NIH/NCRR/NCATS, University of California, Los Angeles Clinical and Translational Science Institute Grant Number UL1TR000124. The content is solely the authors' responsibility and does not necessarily represent the official views of the funding agencies listed.

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