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Pro-HEART – A Randomized Clinical Trial to Test the Effectiveness of a High Protein Diet Targeting Obese Individuals with Heart Failure: Rationale, Design and Baseline Characteristics

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Abstract

There is ample research to support the potential benefits of a high protein diet on clinical outcomes in overweight/obese, diabetic subjects. However, nutritional management of overweight/obese individuals with heart failure (HF) and type 2 diabetes mellitus (DM) or metabolic syndrome (MS) is poorly understood and few clinical guidelines related to nutritional approaches exist for this subgroup. This article describes the design, methods, and baseline characteristics of study participants enrolled in Pro-HEART, a randomized clinical trial to determine the short term and long term effects of a high protein diet (30% protein [~110 g/day],

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40% carbohydrates [150 g/day], 30% fat [~50 g/day]) versus a standard protein diet (15% protein [~55 g/day], 55% carbohydrates [~200 g/day], 30% fat [~50 g/day]) on body weight and adiposity, cardiac structure and function, functional status, lipid profile, glycemic control, and quality of life. Between August, 2009 and May, 2013, 61 individuals agreed to participate in the study; 52 (85%) - mean age 58.2 ± 9.8 years; 15.4% Blacks; 57.7% Whites; 19.2% Hispanics; 7.7% Asians; 73.1% male; weight 112.0 ± 22.6 kilograms- were randomized to a 3-month intensive weight management program of either a high protein or standard protein diet; data were collected at baseline, 3 months, and 15 months. This study has the potential to reveal significant details about the role of macronutrients in weight management of overweight/obese individuals with HF and DM or MS.

Keywords

Heart failure; Obesity; Nutrition; Clinical trial

1. Introduction

1.1 Heart Failure, Overweight/Obesity, and Diabetes

Heart failure (HF), overweight/obesity and type 2 diabetes mellitus (DM) are disease conditions associated with the progression of cardiovascular disease, functional disability, and diminished quality of life (QOL) [1]. When all three conditions co-exist, the pathophysiologic responses associated with each condition interact synergistically and result in higher morbidity and mortality [2–6]. In the United States, approximately 5M adults are affected by HF [7]; 97M by obesity [8]; and 15M by DM [9]; the number of individuals with all three conditions will continue to rise [2;3;5;10;11]. Therefore, interventions aimed at minimizing the pathophysiologic disturbances that occur in individuals with this deadly triad are warranted to potentially delay disease progression and improve clinical outcomes.

1.2 The Potential Benefits of Weight Loss

The potential benefits of voluntary weight loss in overweight/obese individuals with heart failure and DM can be deduced from data that support the deleterious effects of all three conditions on metabolic and neurohormonal profiles and the consequent hemodynamic abnormalities and diastolic and systolic dysfunction. A few small studies have shown the positive effects of voluntary weight loss on restoring left ventricular (LV) systolic function and regressing eccentric hypertrophy [5], improving functional status [12;13], and reducing cardiovascular risks [12]. Intentional weight loss also prevents many of the overweight/obesity-related risk factors for cardiovascular disease (i.e. insulin resistance and DM, dyslipidemia, hypertension, and inflammation). One study showed that substantial weight loss after gastroplasty in 14 morbidly obese individuals with HF resulted in improvements in functional status [14].

1.3 The Role of Nutrition in Managing Individuals with Heart Failure, Overweight/Obesity, and Diabetes Mellitus or Metabolic Syndrome

Given the evidence supporting the negative effects of visceral and ectopic adiposity on inflammatory and metabolic alterations and associated hemodynamic abnormalities and LV diastolic and systolic dysfunction, the potential role of nutrition in reducing risks and delaying disease progression is particularly relevant and timely [15–17]. However, nutritional management of overweight/obese individuals with HF and DM or metabolic syndrome (MS) is poorly understood and existing clinical guidelines provide little guidance related to nutritional approaches for this subgroup [18]. Further data particularly are needed regarding appropriate nutritional recommendations for this population.

Protein is essential in maintaining bodily functions (i.e. growth, tissue building, and maintenance) and lean body mass and is the major component of all biologically active molecules in the body. Proteins also function as enzymes, hormones, and antibodies, as well as transport and structural components [19]. Proteins are also associated with glucose control, insulin regulation, muscle building, regulation or increases in metabolism [20]. This article describes the design, methods, and baseline sample characteristics of Pro-HEART, a randomized clinical trial (RCT) examining the short term and long term effects of a high protein diet on body weight and adiposity and several clinical outcomes (cardiac structure and function, functional status, lipid profiles, glycemic control, QOL) in patients with HF and DM or MS.

2. Materials and Methods

2.1. Study design and research aims

The Pro-HEART trial is a 2-group, repeated measure, RCT conducted at two University of California campuses (Los Angeles and Irvine). The goal of the study is to explicate the role of high protein diets in delaying the progression of disease. The primary aim of the study is to determine if a high protein diet (30% protein [~110 g/day], 40% carbohydrates [150 g/day], 30% fat [~50 g/day]) is superior to a standard protein diet (15% protein [~55 g/day], 55% carbohydrates [~200 g/day], 30% fat [~50 g/day]) on the following primary outcomes: 1) adiposity (operationalized as weight, BMI, waist circumference, percent body fat and lean mass); 2) cardiac structure operationalized as LV end diastolic diameter (LVEDD); and 3) functional status (operationalized as peak V02 and six minute walk test). The secondary aims of the study are to test the effects of treatment group assignment on lipid profile, glycemic control, and QOL . The secondary outcome measures are: 1) lipid profiles (operationalized as total cholesterol, triglyceride, HDL-C, and LDL-C); 2) glycemic control (operationalized as fasting blood glucose); and 3) QOL (e.g. overall, physical, and emotional QOL). Figure 1 shows the relationship between the various variables involved in the hypothesis we are examining in this model of HF, obesity and DM (or MS).

To further characterize patients and obtain data on potential intervening variables, information on sociodemographic characteristics, Clinical History including Co-morbidity (using the Charlson Index) will also be collected along with measurements for the two biochemical tests used commonly as standard measures of HF disease severity and glycemic control, brain natriuretic peptides (BNP) and HbA1c , respectively, and serum creatinine and albumin levels (as tests to monitor patients at risk for renal failure or malnutrition during the study duration).

Participants in the 2 study arms participate in an intensive 3-month supervised dietary intervention and are seen by a registered dietician at 2, 4, 8, and 12 weeks. Weight, waist circumference, and percent body fat and lean mass are measured at each of these follow-up visits. After the intensive dietary intervention, participants are seen in clinic every 3 months for one year (6, 9, 12, and 15 months) to monitor weight maintenance and QOL. Data are obtained at three time points: 1) baseline, to assess and document status prior to the start of the dietary intervention; 2) 3 months, to measure effectiveness of dietary interventions immediately after the 3-month intensive weight loss phase (short-term outcome); and 3) 15 months to measure weight maintenance one year following completion of the dietary intervention (long-term outcome).

2.2. Eligibility

The study was designed to enroll overweight/obese patients with Class II to III HF with diabetes or MS. There were no cutoffs for enrollment based on ejection fraction. The

eligibility criteria are listed in Table 1. Participants need to be reasonably certain that they would be able to attend the follow-up visits with the registered dietician during the intensive 3-month dietary supervised sessions. Participants' primary care provider and/or cardiologists were notified prior to randomization of the patient's possible enrolment in the study; in rare instances, providers presented justification that precluded study participation (i.e. high likelihood of poor adherence, unstable medication regimen).

2.3. Recruitment and prescreening

The study protocol was approved by the appropriate Institutional Review Board (IRB) at the two major university-affiliated medical centers where the study was being conducted. Patient recruitment began in August 2009 using several strategies to increase the representativeness of the sample. A majority of the participants were identified through clinic schedules for the HF programs at the two medical centers and provider referrals (i.e. private offices or clinics of primary care providers). Flyers and study brochures were also placed in providers' clinic waiting rooms and other common places throughout both medical centers. A newspaper advertisement and general university-wide emails were sent using the electronic mail announcement system at both campuses at least twice a year. Participants' primary care providers authorized initial contact with the patient during routine clinic visits or by signing recruitment letters.

Participants were evaluated through a multi-stage screening process. The first stage of screening occurred either face to face for participants who were being seen in the clinic or by telephone for persons calling in response to advertisements. Individuals were asked a series of screening questions to determine basic eligibility. The second stage of the pre-screening occurred after potential participants signed the HIPAA consent to allow a member of the research team to access their medical records. When pre-screening eligibility criteria were met, primary care providers were notified and asked to provide confirmation of medical eligibility, prior to scheduling the baseline data collection visit.

2.4 Baseline assessment

Baseline assessments were conducted at the Clinical and Translational Research Centers on each campus; patient informed consents were obtained prior to initiation of any study activities. Participants were asked to complete an 8-hour overnight fast, and had their blood drawn for lipid and glucose levels, chemistry panel, complete blood count, inflammatory cytokines (e.g. TNF-alpha, , IL-8, IL-6,), and nutritional biomarkers (e.g. albumin levels, leptin, ghrelin, adeponectin). They were also asked to complete a battery of questionnaires for demographic and personal information, medical history, selected psychosocial data, and lifestyle behavior information during this visit. All completed questionnaires were reviewed by the staff for completeness; participants were asked to verify any missing data as needed.

Research staff assessed height, weight, waist circumference, and vital signs. Participants were weighed in clothing without shoes (to the nearest 0.1 kg) using a professional beam scale (model 402KLS; Health-o-Meter, Bridgeview, IL). Height was measured to the nearest 0.5 centimeter using a stadiometer. Waist circumference was obtained by applying the tape around the waist at the level of the narrowest part of the torso between the ribs and iliac crest, as recommended in the Anthropometric Standardization Reference Manual [21]. This standardized measurement was taken at the end of normal expiration and was measured to the nearest centimeter using an anthropometric tape measure. The tape was applied snugly around the body so it did not indent skin or compress subcutaneous tissue.

In addition, body composition was measured by having participants complete a whole-body scan with dual-energy X-ray absorptiometry (DXA), (Hologic 4500A, version 12.3;

Hologic, Inc., Waltham, MA, USA). Each subject was asked to lie in supine position on a table for approximately 5 minutes while the DXA fan beam scanner performed multiple fast speed transverse scans from head to toe with 1 centimeter intervals, with a scan area of 576 by 1968 millimeters and a sample interval of 1/32s. A rectilinear scanner was be used to detect density differences as the two levels of photon energy were projected through the subject. Data were collected in a maximum of 205 scan lines by 120 sample points (pixel size 4.8 × 9.6 mm). Bone, fat, and lean mass were derived according to computer algorithms (Hologic software) provided by the manufacturer. Percentage body fat was calculated as fat mass relative to body weight. Fat free mass was computed as the sum of lean mass and bone mineral content [22].

Participants also had a 2D and doppler echocardiographic (2D echo) test and, cardiopulmonary exercise (CPX) test to measure cardiac structure (LV end diastolic diameter) and function (LV ejection fraction) and functional status ($V0_2Max$), respectively. For the 2D echo subjects were asked to remain at rest and supine for the echo-derived measurements; images were obtained in the standard echocardiographic views of the LV (parasternal long- and short-axis and apical 4-chamber, 2-chamber, and long-axis views). The CPX was conducted using the symptom-limited bicycle exercise test with gas analysis [23]. All participants were tested using a 15-Watt ramp protocol. Participants were encouraged to exercise to exhaustion. Breath-to-breath on-line gas analysis was performed using a Med Graphics CPXID metabolic card (St. Paul, Minnesota). Incremental data including minute ventilation, VO_2, and carbon dioxide production were collected every 15 seconds; VO_2Max, anaerobic threshold, and the VO_2 ratio were calculated from these data.

Finally, functional status was measured with the 6-minute walk test. Timed walking tests differ from tests of maximal capacity because they employ submaximal workloads, allow participants to self-pace their performance, indicate functional capacity of daily living, and demonstrate a steady-state of VO_2 and carbon dioxide production [24]. The 6-minute walk test was conducted in a corridor beside the HF clinic, measured off in meters. A script was used by the research assistant to avoid possible coaching of participants.

Participants with elevated creatinine levels (≥ 1.5 mg/dL) were not eligible to continue in the study. All other individuals who completed the baseline assessment were eligible for randomization.

2.5 Randomization

Treatment assignments to high protein or standard protein diets were implemented by the study coordinator. A randomization algorithm provided by the study biostatistician was used to determine treatment assignments. Participants were equally allocated between treatment arms (by site) and permuted blocks with unequal block sizes on patient-level factors which included age (≥60 vs. < 60 years old), gender, ethnicity (White vs. non-White), and exercise capacity (≥ 10 ml/kg/min vs. < 10 ml/kg/min) to ensure balance across the two treatment groups.

2.6 Measurements

Table 3 shows the data collection schedule. Participants were asked to complete assessments that were similar to the baseline assessment at 3 months after completing the intensive dietary supervised phase of the study and 1 year thereafter (i.e., 15 months from baseline) to measure short-term and long-term outcomes, respectively. Participants were compensated for their time during each of these data collection visits.

2.7 The dietary intervention

Both of the diets used for the study are designed to be hypocaloric. Energy requirements (total energy needed in kilocalories per day) for each participant were calculated using their basal metabolic rate (resting energy expenditure) and lean body mass as determined by the DeltaTrac measurement (obtained by DXA scan at baseline). The goal of the meal plan was to provide a total calorie intake incorporating a 500–800 kilocalorie deficit per day to attain a weight loss of 0.5 to 1.0 kilogram per week, achieved gradually by reducing energy intake. Participants in both treatment arms received one of two standard structured energy-restricted meal plans (1200 or 1500 Kcal/day) based on their computed calorie deficit. The planned macronutrient profiles of the two diets are presented in Table 4.

Participants in both treatment arms were seen by the same dietician at regular intervals: baseline, 2, 4, 8, and 12 weeks and were provided with personalized nutrition counseling and support during each of these visits. If appropriate, spouses or significant family members or friends were asked to participate in the counseling sessions. Participants were also given a “Participant Handbook” which contained a list of resources (i.e. list of food items and serving sizes that have taken into account their food, lifestyle, and cultural preferences) and tools (i.e. weight chart, food checklists, and 3 Day Food Records [3DFR]). The registered dietician also reviewed completed dietary checklists and 3DFRs with each participant to clarify information, verify portion sizes, and obtain incomplete data. This review increased the completeness and accuracy of the 3DFR data. Both dietary interventions emphasized modification of eating behaviors for life-long health promotion.

Although the dietary component was the major focus of the intervention, all participants were also encouraged to exercise regularly to promote energy deficit and facilitate weight loss and maintenance. Initially, engaging in 20–30 minutes of physical activity, such as walking, swimming, jogging, or rowing three to five days per week was recommended for sedentary individuals. Subsequently, participants were instructed to increase physical activity to 30 to 60 minutes on most if not all days of the week to expend a total of 100–200 kcal [25]. Participants were asked to wear a pedometer that provided them with a tool to monitor their own physical activity levels and estimates of energy expenditure during the course of the study. Changes in levels of activity were monitored at each scheduled follow-up visit.

After 3 months (completion of the intensive weight loss phase), the dietician instructed participants in both groups to continue to follow the diets they were assigned to for weight maintenance. Some subjects continued to lose additional body fat over the duration of the study with continued caloric restriction. Participants were asked to come in to clinic every three months (6, 9, 12, and 15 months) during this one year maintenance phase. The follow-up visits during the weight maintenance phase of the study adhered to a formatted outline to 1) obtain and record participant weight; 2) identify causes of weight regain (if any); 3) review dietary patterns with an emphasis on problem areas; and 4) schedule the next follow-up visit. Every effort was made to encourage participants to remain in the study and attend follow-up clinic visits at these 3-month intervals for body weight assessment.

2.8 Dietary adherence

We recognize the importance of dietary adherence on outcomes and have integrated a few strategies into the study protocol to ensure optimum adherence to the dietary intervention: 1) establish a trusting relationship and engage participants in the study by discussing its potential contribution to HF care; 2) express appreciation for participation with cards and phone calls; 3) provide participants with easy access to investigators and research staff for any questions; 4) provide participants with culturally sensitive menu plans; 5) pay for

parking; 6) recognize potential barriers that will decrease dietary adherence and help participants identify solutions to avoid these barriers; and 7) enlist family support by encouraging them to attend the follow-up sessions.

Adherence with the dietary intervention was monitored using 3DFR prior to each of the scheduled follow-up visits during the intensive dietary intervention (2 weeks, 4 weeks, 8 weeks, and 12 weeks). The 3DFR asked for a detailed documentation of food eaten on three consecutive days (one weekend day and two weekdays). The main objective of having participants complete the 3DFR was to obtain a complete record of a participant's dietary intake during the given time period. This method provided an assessment of individual nutrient intake that is less subject to underreporting than other methods. We used the Nutrition Data System (NDS) software (NCC, University of Minnesota) to analyze the nutrient content of the diets [26]. The NDS software provided output for 126 nutrient and nutrient ratios from the food intake data. The database, which is updated twice yearly, contains ingredient information for over 19,000 foods including over 8000 brand name and many ethnic foods. There are data for over 160,000 food variants differing in preparation method or ingredients. The software provides the capability of inputting recipes from homemade foods allowing for accurate calculations of nutrients in these foods [26].

A review of participants' 3DFRs during each of the follow-up visits allowed the dietician to identify variability in execution of the diet and determine whether the diet was being followed as planned. Early recognition of non-adherence to the assigned diet prompted the need for additional patient education aimed at improving treatment adherence, enhancing treatment integrity, and identifying and removing obstacles to fidelity with the assigned diet. Efforts to optimize adherence with completing the 3DFR included providing participants with detailed verbal and written instructions for dietary data collection and checking for accuracy and completeness of diaries during patient visits so that incomplete data could be rectified during each follow-up visit.

2.9. Medical follow-up and patient safety

The research team worked closely with the participants' primary care provider to monitor patient data from each of the follow-up visits including results of any procedures conducted during the study. Any patient complaints related to the dietary interventions or any significant changes in weight that potentially affected the patient's current treatment regimen were reported to the primary care provider and/or cardiologist to allow for an assessment of overall health and possible need to make adjustments in treatment plan (i.e. decrease dose of diuretics, statins, and oral hypoglycemic). Any adverse event (i.e. worsening renal function as evidenced by serum creatinine levels >1.5 mg/dl) during the course of the study were noted and reported to the primary care provider and/or cardiologist. If a determination was made that the adverse event was related to any procedures associated with the study protocol, the treating cardiologist made the decision to have the patient withdrawn from the study. At any point, immediate medical consultation was available for any participant who exhibited a life-threatening response while they were enrolled in the study. Any undesirable or unintentional event that occurred during the course of the study was recorded; the IRB was informed as soon as it was practical, but not more than 48 hours after the event.

2.10 Training and supervision of staff

The professional skills and training of the research staff and their ability to develop a relationship with study participants were central to the success of the intervention. To achieve this end, a special training session was developed and implemented for study personnel prior to the initiation of subject recruitment and enrollment. Several sessions were

included in this training and covered important topics, including: 1) An overview of the principles of nutrition and weight management; 2) Understanding the study protocol; 3) Guidelines for conducting the follow-up visits; 4) Guidelines for using the participant worksheets; and 5) Ethics for conducting research in human subjects. Trainees were tested on their knowledge of the content. The investigators conducted site visits to ensure that the registered dieticians at the two sites used a standardized approach to managing the sessions with participants. This included weighing the patient, receiving, reviewing, and keeping track records, discussing successes and difficulties in meeting the study goals, reviewing the last session, presenting the new topic, setting goals, and developing action plans.

2.11. Sample size

The proposed sample size was calculated using nQuery Advisor 6.01 and included 90 individuals who met the established inclusion criteria. The sample size was based on effect sizes obtained from the research team's preliminary work, Table 2 [27]. Effect sizes for this calculation were based on the differences in the outcome between baseline and 3-month follow up, that is, the first follow-up measurement. 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 here, at a significance level of 0.05. Also, in order to correct for multiple comparisons, we used a modified (conservative) alpha to estimate our sample size. Adjusted alpha =.05/14 = .004 (based on Bonferroni's correction). Furthermore, we estimated the sample size based on the number of covariates included in the model and the corresponding effect sizes. Using these calculations, a sample of approximately 31 participants per group in the experimental and control groups (n = 62) would produce significant results for all outcomes of interest with a minimum power of 80%. To account for a dropout rate of approximately 30%, the sample size was increased to 45 participants in each group (n = 90).

2.10. Data analysis

Data will be analyzed using SAS 9.1 for Windows. To examine the equality of the 2 groups, baseline sociodemographic and clinical variables will be compared using chi-square or t-tests depending on the level of measurement. Randomization should ensure equal distribution between the 2 groups of potentially confounding characteristics. However, age, gender, ethnicity, NYHA functional class, and statin use at baseline will be used as factors or covariates as appropriate in subsequent analyses. Likewise, data will also be analyzed separately by weight loss schedule and clinical parameters. Descriptive statistics (mean ± SD and median with interquartile range) will be reported to characterize changes in weight, BMI, waist circumference, percent body fat and lean mass, LVEDD, peak VO2, 6-minute walk test, total cholesterol, triglycerides, HDL-C, LDL-C, fasting blood sugar, and overall, physical, and emotional QOL. The statistical analysis will be based on the outcomes, percent change in weight over the study period and absolute change in QOL metrics. The general method entails an initial analysis that will employ the t-test (or Wilcoxon rank sum test if non-normality is observed) to compare the outcomes between the two groups. Next, univariate linear regression models will be constructed for each outcome examining the effects of gender, age, ethnicity, NYHA class, as well as any variables observed to be different between the two groups at baseline [28]. In addition, to search for interaction terms to add to subsequent multiple regression models, we will use tree-structured regression models (CART), a procedure that iteratively searches for cut-points in the predictor variables to determine factors that predict the outcomes. CART models can often suggest interactions between predictor variables that are themselves important predictors due to the structure of the final model Subsequent analyses of the outcomes on the differences between time points (baseline to 3 months, baseline to 15 months, 3 months to 15 months), will involve multiple linear regression, in which the primary predictor variable is group (high

protein vs. standard protein), and any of the factors found to be significant in the univariate regressions are entered into the model as additional covariates.

Longitudinal data analysis using mixed models will be performed on each outcome using generalized linear equations. This analysis will model changes in the outcome variable(s) over time (baseline, 3 months, and 15 months) between the two groups. One of the primary motivations for using mixed linear model is that it allows us to incorporate the temporal correlation in within-subject, repeated measures into the model. In particular, to account for this inherent within-subject correlation in response over time, we will consider an autoregressive covariate matrix, which assumes that the correlations between measurements are decreasing over successive time points for each patient. Comparisons will be made, using this model, between different time points within each group, as well as between the two groups. In order to determine whether high protein diets are beneficial in overweight/obese individuals with HF, we will track the amount of weight loss in both groups; it is anticipated that weight loss will occur in both groups. We will do multiple regressions on the other outcomes after adjusting for weight loss in addition to any known variables affecting our findings (e.g. age, gender, functional status) as well as changes in other important time-dependent variables (i.e. medications and treatment regimens, activity levels) and include them in our mixed model. This method will be able to identify at which point, if any, the break in improvement between the two groups occur with any of the analyses. This approach will apply to all hypotheses, since in each, the outcome is a continuous variable. We will explore possible transformation to ensure appropriate normality. Furthermore, appropriate covariates for each outcome will be included in the regression analyses. For example, when analyzing cardiac structure (primary aim 2), covariates such as presence of LV systolic dysfunction will be included. Similarly, in examining lipid profiles (secondary aim 2), we will include statin drug use as a covariate.

2.11. Handling missing values

Missing data in a RCT similar to Pro-HEART is common, generally resulting when participants drop out of the study or when participants miss an assessment. Checks will be made to compare the baseline data on complete and incomplete cases to decide whether it may be assumed that data are missing at random. In addition, we will use multivariate imputation techniques to estimate the missing values and then perform the analysis on the completed sample [29;30]. The imputation techniques will be based on a multivariate extension of the linear mixed model described by Laird and Ware (1982) [31] using software developed by Schafer (1998) [32] to accommodate multiple outcomes. These methods accommodate specific missing outcomes. However, unlike conventional methods for handling univariate outcomes in linear mixed models, the methods also make use of information from observed outcomes that are sometimes available at those same time points, which have the potential to improve the precision of estimation. Missing data on dichotomous outcomes will be multiply imputed using log-linear models for incomplete categorical data with a model selection procedure that allows significant interaction terms to enter the models [33]. Reported results will be based on multiple imputation inferences. We will then combine the findings, calculating the estimated variations in the outcomes across iterations. Other software programs may be used depending on the procedures needed. The final results will be compared to the analyses based on the complete cases only and the final reports will be based on a synthesis of both sets of analyses.

2.12. Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB), comprised of two physicians not involved in the study, two researchers with expertise in dietary and/or exercise interventions and HF management, and a biostatistician, meets bi-annually to review data and serious adverse

events. Data are unblinded as necessary when adverse events are discussed. However, confidentiality of individual participant data is maintained, as only patient study record numbers and not the names themselves will be reviewed. The only criterion for termination of the study is a significant increase in adverse events (p=0.05) or trend toward an increase in adverse events in either one of the two treatment groups. All adverse events will be reported to the DSMB and both IRBs within 5 days. Any serious adverse events will be reported within 48 hours.

3. Results

3.1. Recruitment

Participants were recruited and enrolled starting August 2009. Figure 2 shows a flow diagram which details overall recruitment and enrollment. A total of 1266 patients with a BMI ≥ 27 kg/m^2 were prescreened, but only 96 (8%) individuals met all inclusion criteria. Of the total of eligible individuals, 61 (63.5%) provided informed consent to participate in the study; the remaining 36.5% did not want to participate in the study due to several reasons (e.g. lack of time, not interested, lived to far from medical center, etc.). Fifty-two (85.2%) of the individuals who signed informed consent actually completed the baseline visit and were randomized either the high protein diet (n = 20) or the standard protein diet (n = 32). Of the 52 participants who completed the baseline visit, 33 (63.5%) and 12 (23.1%) completed the 3-month and the 15-month follow-up visit, respectively.

3.2. Baseline characteristics of participants

Baseline demographic and clinical characteristics between the two groups were comparable (Table 5). Participants range in age from 27 to 78 and were on the average 58.2 ± 5.9 years old. They were predominantly male (73%), white (58%), married (29%), college graduates and above (40%), and retired (23%). On average, participants were moderately obese (weight, 112.0 ± 22.6 kilograms, BMI 37.5 ± 6.5 kg/m^2) and had a mean VO_2Max of 12.45 ± 4.0 ml/kg/min, 6-minute walk distance 1270.9 ± 383.1 meters, and LV ejection fraction of 36.7 ± 12.7%. In addition, participants had a relatively high disease burden as reflected by the Charlson Index (2.78 ± 2.35) and reported relatively poor QOL based on multiple QOL measures.

4. Discussion

Cardiac dysfunction, metabolic derangements, neurohormonal activation, and poor QOL that characterize HF, overweight/obesity, and DM or MS are complex and contribute to worse clinical outcomes and are expected to continue to worsen as the prevalence of all three conditions continue to rise in epidemic proportions [34]. Therefore, interventions aimed at minimizing the pathophysiologic disturbances that occur in individuals with this deadly triad are warranted to potentially delay disease progression and improve clinical outcomes.

The potential benefits of voluntary weight loss in individuals with HF, obesity, and DM or MS can be deduced from data that support the deleterious effects of all three conditions on metabolic and neurohormonal profiles. Intentional weight loss may improve or prevent many of the obesity-related risk factors for cardiovascular disease (i.e. insulin resistance and DM, dyslipidemia, hypertension, and inflammation). Moreover, these metabolic benefits are often found after only modest weight loss, equivalent to 5% of initial weight and with further improvement which parallels continued weight loss [35;36]. Weight loss of 5–10% can decrease the risk of complications most commonly associated with obesity, including reduced blood pressure, improved glycemic control, and improved lipid levels in

overweight/obese individuals [37]. Reduction of 5–10% of body weight may also improve hemodynamic abnormalities; regression of LV hypertrophy and improvement in LV diastolic filling occurs in persons with impaired LV systolic function [14].

Insulin sensitivity also improved rapidly in response to an energy-deficit diet. In individuals with obesity and type 2 DM, a 5% weight loss at the end of 1 year of dietary therapy decreased fasting blood glucose, insulin, glycated hemoglobin (HbA_{1c}) concentrations, and doses of hypoglycemic therapy [1]. Weight loss was also associated with lower serum LDL-C and triglyceride concentrations, whereas increased levels of HDL-C were observed when weight loss was sustained. The beneficial effects on serum lipids were related to the percentage of weight lost; weight regain resulted in a relapse in serum lipid concentrations [38]. A sustained weight loss of ≥5% was needed to maintain lower serum triglyceride concentrations; whereas serum total and LDL-C reverted toward baseline if a ≥10% weight loss was not maintained [39]. Recent studies have also shown that weight loss can reduce cardiac lipotoxity and abnormal glucose metabolism that occur in the myocardial cells in response to obesity [40–43]. The clinical effects of weight loss in obese individuals with DM have generally been positive and support potential rationale for implementing appropriate weight-management strategies in overweight/obese persons with HF and DM or MS.

Individuals with advanced HF are at risk for hypermetabolism and hypercatabolic states characterized by loss of lean tissue, bone, and muscle mass. The term “cardiac cachexia” has been coined to describe this state of catabolism of protein-based tissue [44]. The literature is replete with data to support the obesity paradox or reverse epidemiology of HF, in which individuals with increased body mass demonstrated better outcomes [2]. Investigators suggest that improved outcomes might be related to higher metabolic reserves in the presence of catabolic HF among moderately obese individuals, which augments physiologic adaptation to metabolic or neurohormonal stressors. This evidence has prompted researchers and clinicians to be prudent in recommending weight reduction in individuals with advanced HF [15].

Several investigators have examined the nutritional intake of individuals with chronic HF and have provided data to help researchers and clinicians understand the effects of micronutrients (i.e. calcium, folic acid, manganese, riboflavin, thiamine, zinc) on HF outcomes [15;16;45]. However, to the best of our knowledge, no studies to date have examined the role of dietary composition or macronutrient levels (carbohydrates, proteins, and fats) on patient outcomes. Thus, our knowledge regarding nutritional recommendations for individuals with HF is limited and no specific guidelines currently exist [15].

ProHEART is the first study to measure the effects of a high protein diet on adiposity, cardiac structure and function, and functional status in overweight/obese individuals with HF and DM or MS. Although a high protein diet has been shown to reduce cardiovascular risk and improve clinical outcomes in diabetic adults, it has never been tested in the projected population. Protein is essential in maintaining bodily functions (i.e. growth, tissue building, and maintenance) and lean body mass and is the major component of all biologically active molecules in the body. Proteins also function as enzymes, hormones, and antibodies, as well as transport and structural components [19]. Proteins are also associated with glucose control, insulin regulation, muscle building, regulation or increases in metabolism [20].

Data obtained from the study will effectively broaden the existing knowledge base on nutrition, dietary interventions, and HF. Data from the study will provide researchers and clinicians with a better understanding of the biobehavioral underpinnings associated with

obesity, high protein diets, and weight loss outcomes. This information will provide evidence for rational recommendations for nutritional management and possibly weight loss modalities that can be integrated in HF management and treatment guidelines. Our findings will potentially increase our understanding of factors that influence or negate success with weight loss or weight maintenance programs (i.e. patient adherence, presence of family support, effectiveness of weight loss tools and usefulness of educational and counseling approaches) and provide data to refine existing interventions or develop new multidisciplinary approaches for promoting weight loss and better health in individuals with HF, overweight/obesity, and DM or MS. Data from the current study may help us identify individuals who may not benefit from a high protein diet or a dietary intervention including overweight/obese individuals at risk for cardiac cachexia who exhibit symptoms and pathophysiologic impairments (i.e. impaired metabolism, altered immune function, muscle wasting) associated with protein depletion. Although it is difficult to identify the specific benefits and cost effectiveness of nutrition services compared with other treatment modalities, data from the current study can provide clinicians and researchers with information related to the delivery of nutrition-related services that have the potential to reduce frequent hospitalizations and delay the progression of disease and disability ascribed to deviations from diet in overweight/obese individuals with HF and DM or MS.

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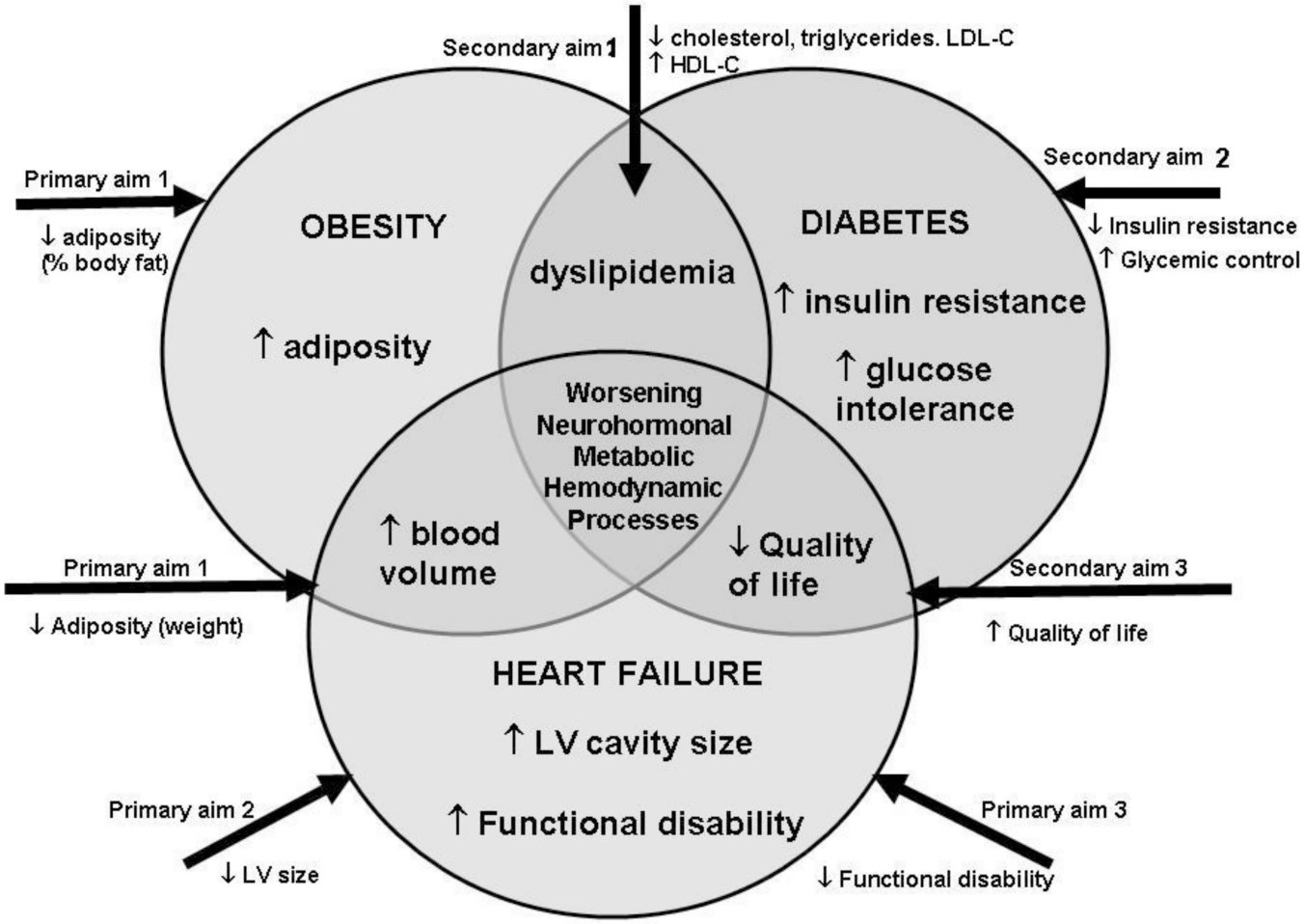

Figure 1. Study Conceptual Model: Illustrating the Hypothesized Effects of a HP Diet*

* The figure depicts the hypothesized effects of a HP diet on selected variables as reflected in the study aims. It does not necessarily portray the complete pathophysiologic changes that occur with HF, obesity, and DM.

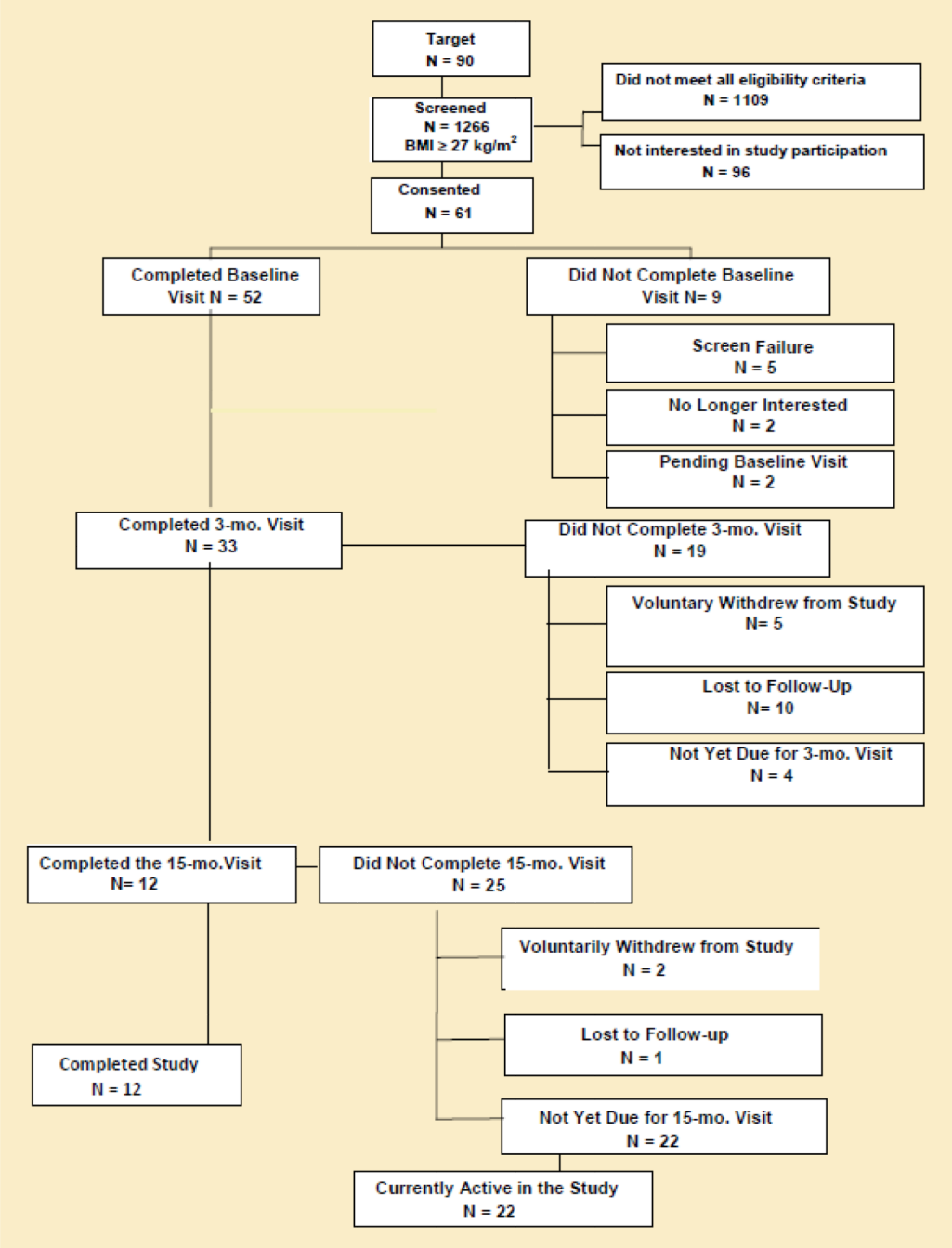

Figure 2. Study Flow Chart

Table 1

Inclusion and exclusion criteria for Pro-HEART intervention

Inclusion Criteria:

- Chronic HF, New York Heart Association functional class II and III[1]
- Body mass index (BMI) ≥ 27 kg/m2
- History of DM or documented impaired fasting glucose (IFG) of 100–125 mg/dl

  or

  History of metabolic syndrome (must meet 3 of the 4 criteria for metabolic syndrome)
  - Abdominal Obesity (waist circumference: men > 103 cm (>40 inches), women > 88 cm (>35 inches)
  - Triglycerides > 150 mg/dL (or currently receiving medications to lower or control hyperlipidemia)
  - HDL Cholesterol: men < 40 mg/dL or women < 50 mg/dL (or currently receiving medications to lower or control hyperlipidemia).
  - Blood Pressure: Systolic > 130 and/or Diastolic > 85 (or currently receiving medications to lower or control blood pressure).
- Optimization of medical therapy (stable for 3 months)

Exclusion Criteria:

- Age ≤18 years old
- History of clinically significant illness including acute myocardial infarction or sustained ventricular arrhythmia in the prior 3 months or current liver, respiratory, and/or gastrointestinal disease and malignancy
- Pregnancy or lactation
- Serum creatinine level > 1.5 mg/dl
- Currently participating in a supervised weight loss program
- Physician refusal to permit patient participation in the study
- Weight loss of >6% in the last 6 months
- Gout or a history of gout

[1] Patients with systolic and/or diastolic dysfunction will qualify for the study; there are no eligibility criteria specific to HF etiology (e.g. ischemic, idiopathic)

Table 2

Effect sizes for outcome variables (α=0.05, 80% power)

Variable	Difference in mean	Common S.D.	Effect Size	N per Group
Body fat, %	1.432	1.92	0.745	31
Lean mass, gm	0.870	0.10	3.346	3
Body mass index	1.400	1.12	2.311	5
Waist circumference	−3.860	1.57	2.459	4
LVEDD	−2.40	3.17	0.757	29
Peak VO2	3.41	0.97	3.515	3
6-minute walk test	299.54	60.00	4.341	3
Fasting blood glucose	−22.00	6.70	3.283	4
Total cholesterol	−15.20	9.00	1.689	7
Triglycerides	−48.00	25.50	1.882	6
HDL-C	15.00	2.09	7.177	2
LDL-C	−4.25	1.9	2.237	5
QOL, overall	−7.90	9.50	0.832	24
QOL, physical	−7.80	8.89	0.877	22

Table 3

Data collection scheme for primary and secondary outcome measures

	Baseline	12 Weeks	60 Weeks
PRIMARY OUTCOME VARIABLES			
Body size and composition (adiposity) Weight, body mass index, waist circumference, percent body fat and lean mass	X	X	X
Cardiac Structure Echocardiogram (left ventricular end diastolic diameter)	X	X	X
Functional Status Cardiopulmonary exercise test & 6-minute walk test	X	X	X
SECONDARY OUTCOME VARIABLES			
Lipid Profiles Total cholesterol, triglycerides, LDL-C, HDL-C	X	X	X
Glycemic Control and insulin resistance HbAlc, Fasting blood sugar, Homeostasis Model Assessment	X	X	X
QOL Measurement Minnesota Living with Heart Failure Questionnaire	X	X	X
ADDITIONAL VARIABLES			
Sociodemographic Characteristics Sociodemographic Form	X		
Clinical History Clinical History/Co-Morbidity Form	X		
Biochemical analyses BNP, serum creatinine, serum albumin, CRP	X	X	X

Table 4

Macronutrient intake by dietary treatment group

	High Protein		Standard Protein	
	1200 kcal/day	**1500 kcal/day**	**1200 kcal/day**	**1500 kcal/day**
Carbohydrates, % energy (gm.)	40 (120)	40(150)	55 (165)	55 (200)
Protein, % energy (gm.)	30 (90)	30(110)	15(45)	15(55)
Fat, % energy (gm.)	30 (40)	30 (50)	30 (40)	30 (50)

Table 5

Demographics and clinical measures at baseline

Variable		High Protein Group (n=20)	Standard Protein Group (n=32)	P
Age	(mean ± SD)	59.8 ± 8.7	57.3 ± 10.5	0.374
Gender	Male, n (%)	13 (65.0)	25(78.1)	0.299
	Female, n (%)	7 (35.0)	7(21.9)	
Race	Whites, n (%)	12(60.0)	18(56.2)	0.950
	Blacks, n (%)	3(15.0)	5(15.6)	
	Hispanics, n (%)	4 (20.0)	6(18.8)	
	Asian, n (%)	1 (5.0)	3 (9.4)	
Marital Status	Married, n (%)	10 (50.0)	19 (59.0)	0.438
	Not Married, n (%)	10 (50.0)	13(41.0)	
Education	≤ High School, n (%)	4 (20.0)	7(21.9)	0.708
	Some College, n (%)	8 (40.0)	12(37.5)	
	College and above, n (%)	8 (40.0)	13 (40.6)	
Clinical Variables	Weight (kg) (mean ± SD)	113.1 ± 24.7	111.7 ± 20.6	0.819
	BMI (kg/m^2) (mean ± SD)	37.30 ± 8.3	37.6 ± 5.5	0.858
	Waist Circumference (cm) (mean ± SD)	118.1 ± 11.7	122.2 ± 12.4	0.246
	Total % Fat (mean ± SD)	37.6 ± 7.6	36.8 ± 7.0	0.693
	Total Cholesterol (mg/dL) (mean ± SD)	150.0 ± 46.1	162.2 ± 39.1	0.25
	HDL (mg/dL) (mean ± SD)	40.6 ± 14.9	40.8 ± 10.2	0.943
	LDL (mg/dL) (mean ± SD)	83.1 ± 29.1	94.7 ± 35.8	0.169
	Triglycerides (mg/dL) (mean ± SD)	133.1 ± 59.8	153.5 ± 87.2	0.530
	Glucose (mg/dL) (mean ± SD)	131.1 ± 55.2	139.2 ± 66.9	0.649
	HbAlC (g/dL) (mean ± SD)	11.1 ± 3.9	9.6 ± 3.8	0.187
	VO_2 max mg/kg/min (mean ± SD)	12.1 ± 2.7	12.7 ± 4.6	0.640
	6 minute walk (m) (mean ± SD)	1222.7 ± 451.4	1300 ± 337.9	0.479
	Left ventricular ejection fraction (mean ± SD)	39.6 ± 14.1	34.9 ± 11.6	0.189