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Title Page

Effectiveness of a total meal replacement program (OPTIFAST® program) on weight loss: results from the OPTIWIN study.

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Study Importance Questions

What is already known about this subject?

- Behavioral weight loss using a calorie-restricted food-based diet can be effective for weight loss and is considered standard of care.
- Total meal replacement has been associated with greater short-term weight loss, but the effectiveness of this strategy for longer term weight loss has limited evidence.

What does this study add?

- This is the largest randomized controlled clinical trial of a total meal replacement treatment program in the U.S.
- This study demonstrates the effectiveness and safety of a total meal replacement program (OPTIFAST) for weight loss compared to a comprehensive behavioral intervention using a food-based diet through 52 weeks of treatment.

- Compared to the comprehensive food-based behavioral intervention, the OPTIFAST program significantly increased the magnitude of weight loss and the proportion of people who achieved clinically significant weight loss.

Abstract

Objective: To test the effectiveness of the OPTIFAST® program (OP), a total meal replacement dietary intervention, we compared it to a food-based (FB) dietary plan for weight loss.

Methods: We randomized 18-70y participants with BMI 30-55kg/m² to OP or FB dietary and lifestyle interventions for 26 weeks, followed by a weight maintenance phase. Outcomes were percent change in body weight (%WL) from baseline to weeks 26 and 52, associated changes in body composition (using dual energy x-ray absorptiometry), and adverse events. Primary analysis used repeated measures multivariable linear mixed models to compare outcomes between groups, in a modified intention-to-treat fashion (mITT).

Results: 273 (83% of randomized; 135 FMR, 138 FB) made up the mITT population. Mean age was 47.1±11.2y, 82% were female, and 71% non-Hispanic white; baseline BMI was 38.8±5.9kg/m². At 26 weeks, OP %WL was 12.4±0.6% vs 6.0±0.6% in FB (p< 0.001). At 52 weeks, OP %WL was 10.5±0.6% vs 5.5±0.6% in FB (p< 0.001). Fat mass loss was greater for OP; lean mass loss was proportional to total weight loss. There was no difference in serious adverse event rates between groups.

Conclusions: Compared to a FB approach, the OP was more effective with greater sustained weight loss.

Introduction

Weight loss requires an energy deficit, usually achieved by reducing the volume of food consumed through modifying portions, reducing certain macronutrients (e.g., lower fat or lower carbohydrate intake), or eliminating various food groups. However, irrespective of the strategy employed to modify intake, weight loss at 6-12 months with food-based diets averages 4-8% of initial body weight.[1-3]

Meal replacements (MR), typically formulated as pre-packaged shakes or bars, are another option for reducing energy intake. [4, 5] They help promote weight loss by eliminating choices, controlling portions, and providing satiation at lower calorie intakes. [6, 7] Total meal replacement (TMR), or the use of MR as the sole source of daily nutrition, has been studied as one option to enhance behavioral

weight loss. Several retrospective and prospective clinical trials through the 1990's showed significant initial weight loss with use of very low calorie (VLCD) diets, typically providing 400-600 kcal/day using TMR. However, the 1998 expert obesity panel convened by the National Heart, Lung, and Blood Institute did not recommend the use of VLCDs because of concerns that long-term weight losses, especially after cessation of the VLCD, were not significantly different from those achieved with standard low calorie diets.[8] At the time of the systematic review for the 2013 AHA/ACC/TOS Obesity Guidelines, there was insufficient high-quality evidence to support more than a limited recommendation for use of these types of dietary strategies. [3] While studies reviewed for the 2013 guidelines suggested that short-term TMR weight loss could be larger than achieved with food-based diets, the potential for weight regain after TMR still appeared high.[3] The studies of TMR reviewed in the 2013 guidelines, dating from 1998-2009, were generally short-term studies, often without follow up intervention beyond 3-6 months of initiation of TMR. [3]

The OPTIFAST® program (OP) is one example of a TMR weight loss intervention. Originally developed in the 1970's as a VLCD providing 420 kcal/day, the program has evolved to include comprehensive behavioral intervention and a higher calorie intake. This trial was designed to test the effectiveness of OP. The goal was to determine if OP was more effective than a food-based dietary plan (FB) and comprehensive behavioral intervention for weight loss at 26 and 52 weeks. We hypothesized that OP would lead to greater weight loss at 26 and 52 weeks and a greater proportion of patients achieving 5% and 10% weight loss, compared to FB. In this report, we present the main results of the OPTIWIN trial including weight change outcomes, changes in body composition, and adverse events.

Methods

Setting and population

OPTIWIN was an open-label, multicenter, randomized controlled clinical trial. The 9 participating U.S. centers included private clinics (5) and academic medical centers (4). Participants had to be 18-70 years old, non-smokers, with a body mass index (BMI) of 30-55 kg/m². Key exclusions included recent weight loss or use of weight loss medications, previous bariatric surgery, organ failure, type 1 diabetes or hemoglobin A1c >10%, cardiovascular disease event or mental health hospitalization in the past 6 months, alcohol or drug dependence, positive screening for potential eating disorder, or poorly-controlled depression. Volunteers were screened by telephone to assess initial eligibility, followed by an

in-person visit to confirm eligibility and obtain written informed consent. Eligible individuals completed a 7-day run-in diet that included use of 1 serving of MR (OPTIFAST- Nestlé Health Science, Bridgewater, NJ) daily to assess tolerance to the product. The final screening visit was completed after the run-in to assess adherence to the run-in diet, self-monitoring tasks, and final eligibility. This study was overseen and approved by a central institutional review board (Quorum) after review by each site's institutional review board and registered on ClinicalTrials.gov (NCT02635698).

Treatment arms

OPTIFAST program

Participants randomized to OP were provided all MR at no cost. Participants with BMI <45 kg/m² were instructed to use 5 MR per day (800 kcal total) with 40% of calories as protein, 40% as carbohydrate, and 20% as fat. Participants with a BMI of 45-49.9 kg/m² received 6 MR/day (960 kcal); those with a BMI ≥50 kg/m² received 6 MR plus 1 meal daily of lean protein (3-4 ounces) and 1 non-starchy vegetable serving (1100-1200 kcal). Participants followed their prescription for 12 to 16 weeks based on provider discretion and patient preference, after which there was gradual reintroduction of food through week 26. After week 26, participants' calories were gradually increased to achieve weight stability. During this time, participants were advised to use 1-2 MR daily to facilitate weight loss maintenance.

The OPTIFAST protocol requires medical monitoring during the initiation of TMR. OP participants saw a clinician regularly to address health concerns and adjust medications, for a total of 11 medical monitoring visits during the first 26 weeks and 4 medical monitoring visits in weeks 27-52. Labs for medical monitoring, including either a basic or comprehensive metabolic panel, were obtained at weeks 2, 4, 6, 8, 10, 12, and 16. Participants had individual counseling with trained interventionists for a total of 16 individual counseling visits through the first 26 weeks and 11 individual counseling visits from week 27 through week 52.

Food-based program

The food-based program (FB) was a modified version of the Diabetes Prevention Program (DPP) intervention. [9-11] During active weight loss (0-26 weeks), FB participants were prescribed a calorie-restricted diet emphasizing lower fat intake (25-30% of total calories). They were advised to reduce calories by 500-750 kcal below estimated total energy expenditure, calculated based on resting

metabolic rate measured by indirect calorimetry (Microlife MedGem) plus an activity factor based on self-reported physical activity. To balance the incentive of free MR in the OP arm, FB participants received gift cards totaling \$800 to offset the cost of groceries during the active weight loss phase. They also had 2 medical monitoring visits and 7 individual counseling visits through week 26. During the maintenance phase (27-52 weeks), they had 2 medical monitoring visits and 5 individual counseling visits.

Comprehensive behavioral program

Both treatment groups had weekly 45-60 minute group behavioral sessions for the duration of the intervention. Group sessions were facilitated by trained professional interventionists using a standardized intervention manual. OP program sessions used the OPTIFAST Lifestyle Education Series content as the basis for the behavioral group sessions. The FB program used the DPP's Group Lifestyle Balance program. [9]

Both groups received prescriptions for physical activity that included a graduated target of 150-180 minutes/week of moderate to vigorous exercise. Participants were instructed to record daily food/beverage intake and minutes of exercise using written journals, which were reviewed weekly by the interventionist.

Study measures

Body weight was measured in light clothing on digital scales to the nearest 0.1 lb. Height was measured without shoes using a wall-mounted stadiometer to the nearest 0.5 cm. Body mass index was calculated as weight (kg) divided by height (m) squared. Waist circumference was measured using a spring-loaded tape measure (Gulick) 1 cm above the umbilicus. Two measures were averaged at each study visit. Body composition was measured using dual energy X-ray absorptiometry (DEXA). Physical activity was measured using a tri-axial accelerometer (Phillips Actiware®-CT) worn on the wrist for 7 days.

Adverse events (AEs) were ascertained at each clinic encounter or study visit using a standardized symptom checklist and questionnaire. Any new symptoms or medical problems were logged as AEs. The site medical provider reviewed each event and adjudicated the severity, relatedness, and classification. Because the FB group had fewer contacts with study personnel, the number of opportunities for

reporting AEs was higher for the OP group. To adjust the AE frequency for the number of contacts, rates of AEs were also reported as the number of events per contact.

Analysis

Sample size was calculated primarily to show effectiveness of the OP compared to FB on percent weight change at 52 weeks. To obtain 90% statistical power based on a 2-sided test assuming $\alpha=0.05$, 113 participants per study group were required to detect a mean difference in weight change of 5% with an estimated standard deviation of 11.5%. With an estimated drop-out rate of 30%, we planned to recruit 300 participants to provide 150 participants per study group.

The co-primary outcomes were percent change in body weight from baseline to weeks 26 and 52, tested using a hierarchical procedure. First, we planned to test the week 26 outcome. If this analysis was statistically significant ($p<0.05$), then the week 52 endpoint would be tested at the $\alpha=0.05$ level of significance. However, if the week 26 analysis was not statistically significant, then the week 52 analysis would be exploratory rather than confirmatory.

The primary analysis population was a Modified Intention-To-Treat (mITT) population, consisting of randomized subjects known to have started the study program and have at least one post-baseline assessment of body weight. For the primary analysis, we used a repeated measures model with both random and fixed effects to compare the percent weight change between the OP and FB groups. The linear mixed model included a random intercept for subject, fixed visit effect, fixed treatment effect, and fixed baseline body weight effect and a treatment-by-visit interaction term. The model also included age, race, sex, site, diabetes status, and gender as covariates. The final model was fit using the SAS PROC MIXED procedure using the RANDOM and LSMEANS statements. A sensitivity analysis employed multiple imputation (MI) for missing body weight values at scheduled post-baseline visits (weeks 12, 26, 40 and 52) in the mITT population. Imputation was performed separately (imputations= 50) for each treatment group using the SAS PROC MI procedure. Primary outcomes were then calculated from the imputed datasets. For secondary outcomes including body composition and adverse event frequency, continuous measures were compared using standard t-tests while categorical measures were compared using Chi-square tests.

Results

Study population

We screened 463 participants and confirmed eligibility on 330 participants (164 randomized to OP and 166 randomized to FB). There were 57 participants who either declined further participation in the study after learning their randomization assignment (9-OP; 16-FB) or discontinued participation without a follow up weight (20-OP; 12-FB); these participants were demographically similar to the mITT population except they were younger (42.5 years, $p=0.006$) and reported less weight loss on average with prior attempts (0.1 kg, $p<0.001$). The remaining 273 participants (135-OP; 138-FB) made up the mITT study population (82.7% of randomized participants; Figure 1-CONSORT). In the mITT study population, there were 19 participants in the OP group (14.1%) and 25 (18.1%) in the FB group who discontinued participation. Participants were typically middle aged (47.1 ± 11.2 y), predominately female (82%) and white (71%) (Table 1). Fifty-two percent had prediabetes or diabetes, 33% were being treated for hypertension, and 21% for dyslipidemia. OP and FB participants attended 53.5% and 46.2% of weekly group behavioral sessions, respectively.

Weight Loss Outcomes

Both treatment groups lost weight at 26 and 52 weeks (Figure 2). Percent weight loss at 26 weeks was $12.4\pm 0.6\%$ in OP compared to $6.0\pm 0.6\%$ in FB (difference $6.4\pm 0.9\%$, $p<0.001$). At 52 weeks, percent weight loss was $10.5\pm 0.6\%$ for OP versus $5.5\pm 0.6\%$ in FB (difference $4.9\pm 0.9\%$, $p<0.001$) (Figure 2). Sensitivity analyses showed similar estimates for percent weight loss. Using MI to handle missing data showed a weight loss of $12.1\pm 0.6\%$ and $10.1\pm 0.7\%$ for OP at 26 and 52 weeks, respectively. Comparatively, FB had weight loss of $6.0\pm 0.6\%$ and $5.5\pm 0.7\%$ at 26 and 52 weeks. All differences between OP and FB remained significant at $p<0.001$.

At week 52, higher proportions of OP participants achieved 5% (63.7%) and 10% weight loss (43.7%) compared to FB (42% and 21.7%, respectively) ($p<0.001$). (Figure 3) The percentage of people who lost 15% or more of their initial weight was more than double in OP than FB (30% vs. 12%, $p<0.001$). We also examined the proportion of participants who were non-responders to assigned treatments, defined by a failure to lose $\geq 3\%$ of their initial body weight. At week 26, 15.6% of OP and 39.1% of FB participants were non-responders. By week 52, 23.7% of OP participants were non-responders versus 43.5% of FB participants.

Changes in body composition

Changes in body composition outcomes are shown in table 2. Changes in waist circumference paralleled weight loss in both treatment groups; however, there were greater reductions for the OP group compared to FB at both 26 and 52 weeks. Changes in body composition measured by DEXA followed a similar pattern. By week 52, mean total fat mass was decreased by 9.7 ± 10.4 kg for OP participants. The mean reduction in total fat mass for FB participants was 3.5 ± 6.6 kg at 52 weeks. Both treatment groups also had decreases in lean mass; the absolute difference was statistically significant, however, the proportion of weight loss from lean mass at 52 weeks was similar (23% for OP; 25.5% for FB). There was no difference in change in total bone mineral density by treatment group.

Adverse events

Mild or moderate adverse events (AE) were reported by 76.8% of OP participants and 62.7% of FB (Table 3). Serious AEs were reported by 4.5% (7/155) of OP and 3.3% (5/150) of FB participants. Serious AEs in OP included knee pain, seventh cranial nerve paralysis, cholelithiasis, a third degree burn, abdominal pain, pyelonephritis associated with acute liver failure, and pancreatitis associated with cholelithiasis. In FB, serious AEs included post-concussion syndrome following a motor vehicle accident, pneumonia, vascular surgery to repair a ruptured arterial vessel with subsequent death, depression with suicidal ideation, and a wound abscess. Discontinuation rates were not statistically different between groups (29.3% OP; 31.9% FB; $p=0.60$). Main reasons for discontinuation were subject request to no longer participate in the program (11.0% OP; 18.7% FB) or lost to follow-up (11.0% OP; 9.6% FB). There were a total of 695 AEs reported by OP participants and 356 AEs reported by FB participants. When adjusted for the number of contacts where participants reported symptoms or other potential AEs, the number of AEs per contact was 0.17 for OP and 0.24 for FB ($p=0.014$).

Discussion

This clinical trial compared two behavioral weight loss strategies—the OPTIFAST program versus a modified version of the DPP. Participants in the OP treatment arm lost 10.5% of their initial weight by 52 weeks, representing a near doubling of the effect on body weight seen with FB. A larger proportion of participants lost 5, 10, or 15% of their body weight with OP, and a greater percentage of people responded with at least 3% weight loss to OP. The OP participants had greater losses of fat mass, and OP was well tolerated and safe. Overall, the OP proved to be a more effective treatment than FB.

Previous trials of interventions using TMR, typically in the form of VLCD, suggested that short-term weight loss was much greater than no treatment controls or low-calorie diets. However, once the TMR was discontinued, weight regain led to only modest differences between the treatment arms with longer follow up. [3, 12] In a meta-analysis of 6 randomized trials comparing VLCD to low-calorie diets with at least 1 year of follow up, weight loss was $6.4 \pm 2.7\%$ greater for VLCD used on average for 12.7 weeks. However, longer-term weight loss (mean follow up 1.9 ± 1.6 years) was not significantly different between the groups (VLCD 1.3% greater weight loss, $p > 0.2$). [12] The 2013 AHA/ACC/TOS Obesity Guidelines included 4 VLCD trials that met the inclusion criteria for the systematic review. Weight losses from 14-17 weeks ranged from 14.2-21.1 kg; during observational follow up, weight regain was 3.1-3.7 kg through 38 weeks. In 2 of the trials that tested weight loss maintenance interventions, weight regain was 5.9-9.7 kg through 33 months.[3]

In OPTIWIN, OP achieved greater weight loss through 12 months, experiencing less of the weight regain previously seen in TMR interventions. One difference from prior trials that may account for sustained weight loss after TMR in our study is the presence of an active weight loss maintenance strategy, including continued behavioral therapy coupled with recommendations to use 1-2 MR per day. Continuation of behavioral treatment is recognized as a critical component for improving maintenance of weight loss; however, ongoing modification of calorie intake to achieve energy balance in a weight-reduced state continues to be a major challenge for weight loss maintenance. Following TMR with ongoing use of MR for weight loss maintenance may be advantageous because of the characteristics of MR associated with lower energy intake (e.g., portion control, low calorie, reduced choice) and because of changes in an individual's subjective cravings and desire for food, objectively supported by contemporaneous changes in the brain regions on fMRI responsible for regulation of food intake and reward. [6]

Two prior studies lend some support to the idea that continued treatment and use of MR can be important for ongoing maintenance of lost weight. Vazquez et al showed in a randomized trial of adults who lost at least 5% of their weight in 6 months using diet alone that use of 1 MR as a substitute for dinner was effective for maintaining weight loss over the next 6 months (83.9% of participants) compared to diet alone (58.1%).[13] The importance of continuing active treatment can be highlighted by comparing results from a study by Argas et al where OPTIFAST was used to induce weight loss, and those who achieved 5% weight loss were randomized to 1 of 4 maintenance strategies involving use of

regular or pre-packaged foods. After 12 weeks of TMR, participants achieved approximately 15 kg of weight loss.[14] Behavioral intervention continued for 9 months after the TMR phase, and weight loss for all treatment groups was 12.1 to 15 kg, suggesting continued maintenance of weight loss. However, after discontinuation of the behavioral treatment, significant weight regain was noted at 18 months post-randomization in all groups.[14]

Nutritional differences in OPTIWIN may have affected weight loss maintenance as well. The OP caloric prescription has increased over time. Previously all patients would be initiated on 420 kcal/day. Currently, the lowest recommended calorie prescription is 800 kcal/day with allowances for additional calories for higher initial body weight. The OP diet also provided a higher percentage of calories from protein compared to the FB diet. The higher percentage of calories from protein may have contributed to the observed maintenance of weight loss, as higher protein intakes have been associated with greater satiation leading to better weight loss maintenance [15]. Additional research is needed to quantify how much these dietary factors influence weight loss maintenance and the durability of weight loss differences beyond 12 months, as this is relatively early in the weight maintenance process.

This is the largest randomized controlled trial of TMR in the US, which allowed us to recruit a broad population of individuals with obesity. The length of intervention and generalizable study population help to address the acceptability of TMR as part of a behavioral weight loss strategy. In our study population, attrition was approximately 25% (229/305 participants who started intervention). However, the discontinuation rate was similar for OP and FB, suggesting a TMR strategy is an acceptable strategy for those actively seeking to lose weight. The rate of AEs was slightly lower for the OP group, indicating that the increased weight loss from TMR may not result in more safety concerns. A suitable contemporary comparison to OPTIWIN is the DiRECT trial from the U.K. [16] In this 12-month intervention, individuals with type 2 diabetes and BMI 27-45 kg/m² were assigned to TMR (n=149) or standard of care (n=149) to assess impact on diabetes remission. At 1 year, the intervention group had a mean weight change of -10.0 ± 8.0 kg and a net of control weight loss of 8.8 kg (95% CI, 10.3 to 7.3). The DiRECT trial had a similar rate of discontinuations from active treatment (21%) and serious adverse events (4% of participants) as OPTIWIN. [16]

The clinical impact on weight of the OP intervention relative to FB requires some consideration of cost-effectiveness. As a result of analyzing interventions like the DPP, we know that high intensity lifestyle

interventions to promote weight loss can be cost effective. In years 1-3, the DPP lifestyle intervention was associated with the most direct medical care cost per participant (\$2,780) compared to metformin (\$2,542) and placebo (\$79).[17] However, prevention of new onset diabetes in individuals with impaired glucose tolerance led to gains in quality adjusted life years at a significantly lower cost than with the use of metformin or placebo. [18] The near doubling of effect on body weight for OP was achieved at a higher overall cost than FB due to the additional medical monitoring and individual counseling. While we did not directly study cost effectiveness in this analysis, we are aware of other research that suggests the potential for this type of intervention to be cost effective. Rothberg et al reported clinical outcomes and per-member per-month (PMPM) costs for University of Michigan (UM) Weight Management Program participants (n=153) compared to other insurance-covered lifestyle interventions or no treatment.[19] The UM program utilized a treatment protocol similar to the OP, including total meal replacement as part of the initial dietary intervention. On average, participants in the UM program decreased their BMI from 40.4±5.3 to 36.2±6.1 kg/m² in 12 months of follow up. The UM program was associated with an adjusted PMPM cost increase of only 4% compared to a 10% increase for Weight Watchers, 16% for a walking program, and 29% for those not participating in any program. The cost per unit BMI reduction was \$146-148 less for the TMR program compared to Weight Watchers and the walking programs. Similarly, a recent study using event-driven decision analysis models suggested that OP over a 3 year period would be cost saving compared to liraglutide or naltrexone/bupropion in individuals with class I-II obesity.[20] Ultimately, additional research is needed to understand the health economic impact in the OPTIWIN trial.

The results of this trial should be interpreted within the context of the limitations of the study design. This study was designed as a test of the OP, not just the use of a MR; as such, conclusions about effectiveness are limited to the program, which included a comprehensive high intensity behavioral intervention with a weight maintenance strategy. Future studies could isolate the effect of MR by matching calorie prescriptions between TMR and a food-based diet.

The frequency of individual clinical visits was higher for OP, and this could bias results in favor of OP. The high frequency of contact is a feature of the OP, and because the contact protocols were not equal between groups, we cannot make specific inferences about the individual effect of the TMR diet on the observed outcomes. The higher frequency of contact also led to ascertainment bias for AEs, potentially increasing the frequency of AEs reported for the OP group. Alternatively, in some cases more frequent

visits may have actually prevented potential AEs in the OP group, whereas the FB group had more time to develop AEs between visits. When adjusted for the frequency of contact, we observed a lower rate of AEs for the OP group. However, it is possible that the absolute rate of AEs would be higher in the OP group even if ascertainment had been equal between groups.

Lastly, even though the FB group received a stipend to defray the cost of food, it may not have completely matched the perceived value of the MR as done in the OP. This could have affected engagement in favor of the OP.

Conclusion

This multicenter clinical trial using the OP demonstrated that a comprehensive behavioral weight loss intervention with TMR led to greater clinically significant weight loss at 26 and 52 weeks compared to a well-established food-based behavioral intervention. It also showed the feasibility of such an intervention for motivated individuals.

Table 1. Summary of demographic and baseline characteristics according to treatment groups

	OPTIFAST Program (N=135)	Food-Based Program (N=138)	Total (N=273)	p-value
Age in years, mean (SD)	47.1 (11.2)	47.2 (11.3)	47.1 (11.2)	0.88
Sex, n (%)				
Male	19 (14.1%)	29 (21.0%)	48 (18%)	0.13
Female	116 (85.9%)	109 (79.0%)	225 (82%)	
Race				
Caucasian	100 (74.1%)	95 (68.8%)	195 (71%)	0.10
African American	22 (16.3%)	37 (26.8%)	59 (22%)	
Asian/Pacific Islander	4 (3.0%)	2 (1.4%)	6 (2%)	
Hispanic	5 (3.7%)	4 (2.9%)	9 (3%)	
Other	4 (3.0%)	0 (0%)	4 (1%)	
Baseline characteristics				

	OPTIFAST Program (N=135)	Food-Based Program (N=138)	Total (N=273)	p-value
Weight in kg, Mean (SD)	106.8 (20.8)	109.9 (23.2)	108.4 (22.1)	0.26
BMI in kg/m ² , Mean (SD)	38.4 (5.5)	39.2 (6.2)	38.8 (5.9)	0.26
BMI Categorization, n (%)				
Overweight (25-29.9 kg/m ²)	0 (0%)	3 (2.2%)	3 (1%)	0.13
Obesity Class I (30.0-34.9 kg/m ²)	44 (32.6%)	38 (27.5%)	82 (30%)	
Obesity Class II (35-39.9 kg/m ²)	43 (31.9%)	36 (26.1%)	79 (29%)	
Obesity Class III (≥ 40 kg/m ²)	48 (35.6%)	61 (44.2%)	109 (40%)	
Type 2 Diabetes diagnosis, n (%)	13 (9.6)	20 (14.5)	33 (12.1%)	0.22
Pre-Diabetes diagnosis, n (%)	57 (42.2)	49 (35.5)	106 (38.8%)	0.26
Number of Previous Weight Loss Attempts, Mean (SD)	5.5 (8.3)	7.0 (9.2)	6.3 (8.8)	0.19
Typical Weight Loss with Previous Weight Loss Attempts in kg, Mean (SD)	2.1 (5.3)	2.4 (6.6)	2.2 (6.0)	0.67
Used Diabetes medications ¹	14 (10%)	19 (14%)	33 (12%)	0.39
Used Hypertension medications ¹	46 (34%)	43 (31%)	89 (33%)	0.61
Used Lipid-modifying medications ¹	29 (21%)	29 (21%)	58 (21%)	0.92

Note: Continuous variables compared using standard t-test. Categorical variables compared using Chi-square test with the exception of race which uses a Fisher's Exact Test due to small cell counts.

¹ Medication use includes use prior to study with continuation during study or medication use that started during study and either continued throughout study or ended before study completion

Table 2. Change in body composition outcomes from baseline

Outcome	OPTIFAST Program (N=135)	Food-Based Program (N=138)	p-value
	Mean (SD)		
Waist circumference, cm			
Baseline	116.6 (14.0)	119.5 (15.2)	0.10
Change at 26 weeks	-12.0 (16.0)	-7.7 (8.3)	0.011

Change at 52 weeks	-11.9 (12.1)	-7.2 (9.3)	0.0011
Total body fat mass (kg)			
Baseline	49.8 (11.8)	49.7 (11.7)	0.96
Change at 26 weeks	-11.3 (7.5)	-4.4 (5.9)	<0.0001
Change at 52 weeks	-9.7 (10.4)	-3.5 (6.6)	<0.0001
Total body lean mass (kg)			
Baseline	51.6 (9.6)	53.5 (12.1)	0.15
Change at 26 weeks	-2.3 (2.8)	-1.1 (3.3)	0.008
Change at 52 weeks	-2.9 (5.8)	-1.2 (5.9)	0.043
Bone mineral density, total (g/cm²)			
Baseline	1.2 (0.1)	1.3 (0.1)	0.026
Change at 26 weeks	-0.01 (0.04)	-0.006 (0.03)	0.28
Change at 52 weeks	-0.01 (0.04)	-0.01 (0.03)	0.95

Note: Change from baseline is defined as [Post-baseline value - baseline value]. Differences compared using standard t-test

Table 3. Adverse events (AE) affecting more than 5% of either treatment group and key blood measures, by treatment group

	OPTIFAST Program AEs (N=155)		Food-Based Program AEs (N=150)	
	N	%	N	%
AE affecting ≥ 5%				
Alanine aminotransferase increased	16	10.3%	6	4.0%
Alopecia	9	5.8%	1	0.67%
Arthralgia	7	4.5%	9	6.0%
Aspartate aminotransferase increased	10	6.5%	2	1.3%
Back pain	8	5.2%	9	6.0%
Blood uric acid increased	8	5.2%	4	2.7%
C-reactive protein increased	9	5.8%	6	4.0%
Constipation	29	18.7%	4	2.7%

Diarrhea	17	11.0%	6	4.0%
Dizziness	26	16.8%	3	2.0%
Fatigue	16	10.3%	1	0.67%
Headache	27	17.4%	7	4.7%
Influenza	7	4.5%	8	5.3%
Low density lipoprotein increased	15	9.7%	9	6.0%
Nasopharyngitis	18	11.6%	14	9.3%
Nausea	18	11.6%	3	2.0%
Sinusitis	11	7.1%	9	6.0%
Upper respiratory tract infection	8	5.2%	4	2.7%
Key Blood Measures				
Hypokalemia	1	0.6%	1	0.7%
Hyperkalemia	0	0	2	1.3%
Hyponatremia	1	0.6%	0	0
Elevated blood urea nitrogen	4	2.6%	1	0.7%
Elevated serum creatinine	2	1.3%	0	0

NOTE: Adverse events reported in population of patients who were randomized and started the assigned intervention (N = 305)

Figure 1. CONSORT diagram

Figure 2. Relative weight change by treatment group at 26 weeks and 52 weeks

NOTE: Percent weight change values are calculated from a least square means from a linear mixed model. The linear mixed model contains a random intercept subject effect, fixed visit effect, fixed treatment effect, fixed baseline body weight effect, a treatment-by-visit interaction term and covariates including age, race, sex, site, and reported baseline diabetes status.

Figure 3. Proportion of participants who lost at least 5, 10, or 15% of initial body weight at weeks 26 and 52

* - significantly different from Food-Based group at $p < 0.001$.

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Figure 1.

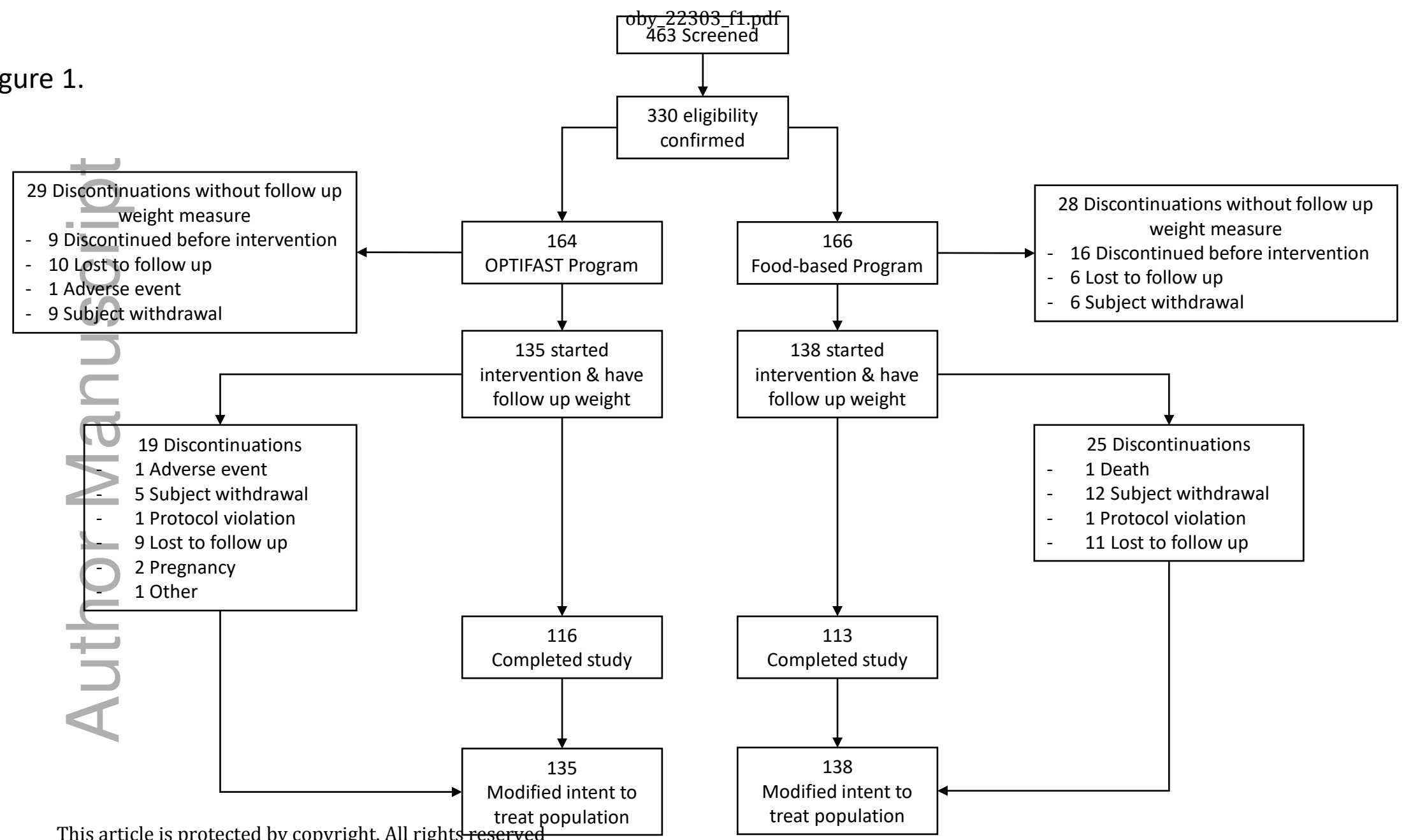


Figure 2.

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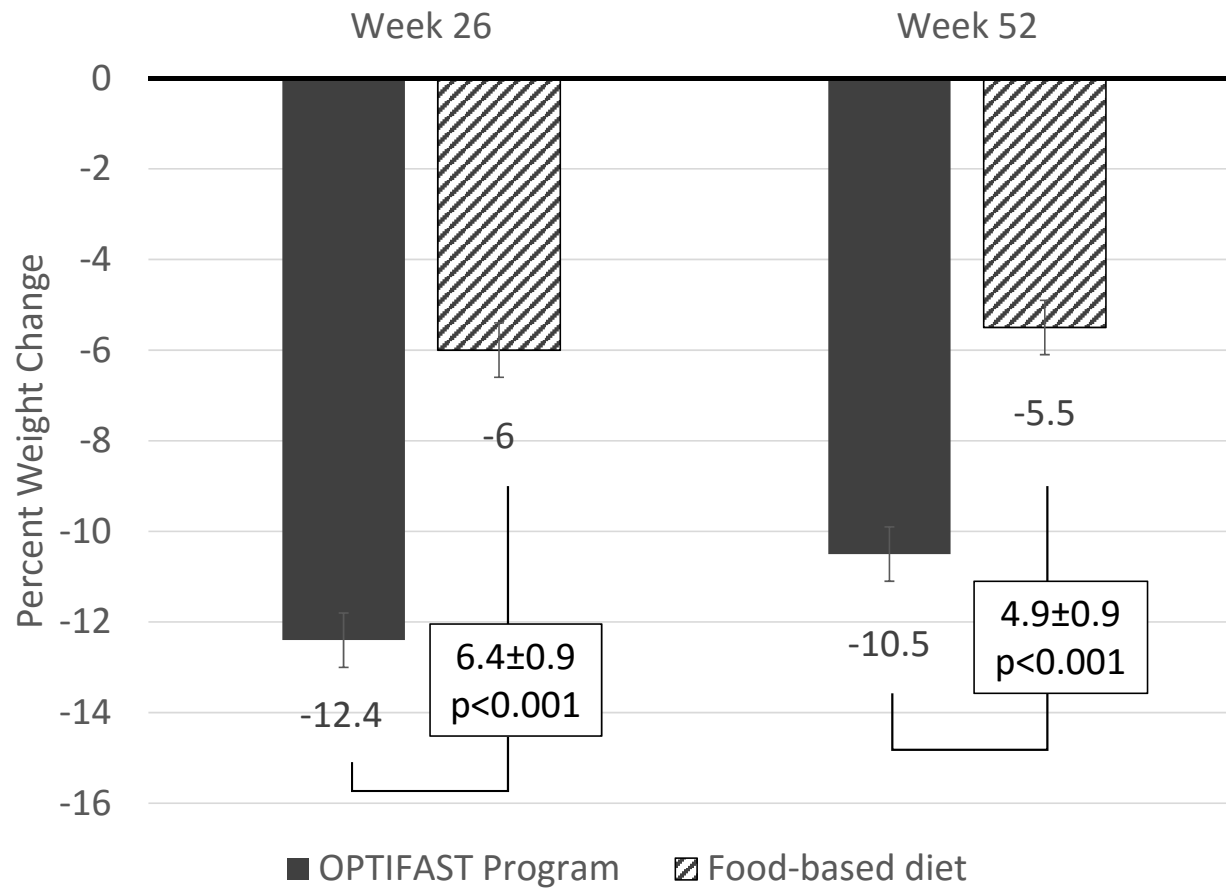


Figure 3.

