Clinical Studies
Meal Replacements for Weight Loss and Body Composition

References in support of Meal Replacements for weight loss and body composition include:

1. Bosello O, Cominacini L, Zocca I, et al. **Short- and long-term effect of hypocaloric diets containing proteins of different sources on plasma lipids and apoproteins of obese subjects.** *Ann Nutr Metab* 1988;32:206-214.

2. Jenkins, D. J. A., T. M. S. Wolever, G. Spiller, G. Buckley, Y. Lam, A. L. Jenkins, and R. G. Josse, **"Hypocholesterolemic Effect of Vegetable Protein in a Hypocaloric Diet**," Atherosclerosis, 78:99-107, 1989.

3. Heber D., Ashley JM, Wang HJ, Elashoff RM. **Clinical evaluation of a minimal intervention meal replacement regimen for weight reduction.** J Am Coll Nutr. 1994 Dec;13(6):608-14.

4. Peter Clifton. **"Assessing the evidence for weight loss strategies in people with and without type 2 diabetes.** World J Diabetes. Oct 15, 2017; 8(10): 440-454

5. Coleman CD1, Kiel JR1, Mitola AH2, Arterburn LM1. **Comparative effectiveness of a portion-controlled meal replacement program for weight loss in adults with and without diabetes/high blood sugar.** Nutr Diabetes. 2017 Jul 10;7(7):e284. doi: 10.1038/nutd.2017.32.

6. Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA. **A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss.** Obes Rev. 2019 Apr;20(4):569-587. doi: 10.1111/obr.12816. Epub 2019 Jan 24. Review.

7. Leo Treyzon, Steve Chen, Kurt Hong, Eric Yan, Catherine L Carpenter, Gail Thames, Susan Bowerman, He-Jing Wang, Robert Elashoff and Zhaopying Li, **A Controlled Trial of Protein Enrichment of Meal Replacements for Weight Reduction with Retention of Lean Body Mass** Nutrition Journal 2008, 7:23 doi:10.1186/1475-2891-7-23

8. Lee, J. Lee, W. K. Bae, J. K. Choi, H. J. Kim, B. Cho. **Efficacy of Low-Calorie, Partial Meal Replacement Diet Plans on Weight and Abdominal Fat In Obese Subjects With Metabolic Syndrome.** Int J Clin Pract, February 2009, 63, 2, 195–201

9. Flechtner-Mors M, Boehm BO, Wittmann R, Thoma U, Ditschuneit HH. **Enhanced Weight Loss with Protein-Enriched Meal Replacements in Subjects with the Metabolic Syndrome.** Diabetes Metab Res Rev. 2010; 26:393-405.

10. K.M. Gapparova, V.I. Pilipenko, Yu.G. Chekhonina, O.N. Grigoryan. **The Effect of Low-Calorie Diets with Inclusion of Protein Food Substitutes on the Anthropometric and Clinico-Biochemical Indices In Obese Patients** Dietology Issues, 2011, v. 1, №1, p.33-39

11. Ismael Campos-Nonato I, Hernández L, and Barquera S. **Effect of A High Protein Diet Versus Standard Protein Diet on Weight Loss and Biomarkers of Metabolic Syndrome: A Randomized Clinical Trial**. Obesity Facts 2017; 10:238-251

12. Gulati S, Misra A, Tiwari R, Sharma M, Pandey RM, Yadav CP. **Effect of High Protein Meal . Replacement on Weight And Cardiometabolic Profile in Overweight/Obese Asian Indians in North India**. British Journal of Nutrition 2017

13. Zhaoping Li, Leo Treyzon, Steve Chen, Eric Yan, Gail Thames, Catherine L Carpenter. **Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: An Outpatient Randomized Controlled Trial.** Nutrition Journal 2010, 9:72

14. Heymsfield SB1, van Mierlo CA, van der Knaap HC, Heo M, Frier HI**. Weight management using a meal replacement strategy: meta and pooling analysis from six studies.** Int J Obes Relat Metab Disord. 2003 May;27(5):537-49.

15. J. Bruce Redmon, MD, Susan K. Raatz, PHD, Kristell P. Reck, RD, Joyce E. Swanson, RD, Christine A. Kwong, RD, Qiao Fan, MS, William Thomas, PHD and John P. Bantle, MD. **One-Year Outcome of a Combination of Weight Loss Therapies for Subjects With Type 2 Diabetes**. Diabetes Care 2003 Sep; 26(9): 2505-2511. https://doi.org/10.2337/diacare.26.9.2505

1. ENDNOTE BACKGROUND

Bosello O, Cominacini L, Zocca I, et al. **Short- and long-term effect of hypcaloric diets containing proteins of different sources on plasma lipids and apoproteins of obese subjects.** *Ann Nutr Metab* 1988;32:206-214.

The Bossello study showed successful weight loss in obese subjects given a soy protein based low calorie meal replacement beverage versus a milk-based equivalent beverage.

Bosello et al. (1988) reported that in his population of obese hypercholesterolemic subjects, total cholesterol decreased in both groups but total triglycerides were reduced significantly ($p<.01$) in the group getting soy protein.

2. ENDNOTE BACKGROUND

Jenkins, D. J. A., T. M. S. Wolever, G. Spiller, G. Buckley, Y. Lam, A. L. Jenkins, and R. G. Josse, **"Hypocholesterolemic Effect of Vegetable Protein in a Hypocaloric Diet**," Atherosclerosis, 78:99-107, 1989.

The Jenkins study showed successful weight loss in obese subjects given a soy protein based low calorie meal replacement beverage versus a milk-based equivalent beverage.

Jenkins et al (1989) demonstrated that a very low-calorie soy-based meal replacement was as effective in promoting weight loss as a very low-calorie milk-based meal replacement.

3. ENDNOTE BACKGROUND

Heber D., Ashley JM, Wang HJ, Elashoff RM. **Clinical evaluation of a minimal intervention meal replacement regimen for weight reduction.** J Am Coll Nutr. 1994 Dec;13(6):608-14.

J Am Coll Nutr. 1994 Dec;13(6):608-14.

Clinical evaluation of a minimal intervention meal replacement regimen for weight reduction.

Heber D[1], Ashley JM, Wang HJ, Elashoff RM.
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Department of Medicine, UCLA School of Medicine 90024-1742.

Abstract

OBJECTIVE:

The purpose of this study was to evaluate a simplified weight loss program in which subjects were provided a widely available meal replacement product and its package insert information (Ultra Slim-Fast).

METHOD:

Weekly follow-up visits were carried out by non-physician personnel for weight measurement, distribution of product, and completion of a subjective questionnaire. No dietary counseling was provided. A total of 273 of 301 subjects (91%) completed 12 weeks of study. Men lost 50% (from 119 to 108% of ideal body weight) and women lost 35% (from 122 to 111% of ideal body weight) of excess body weight. Thirty-five patients who lost < 9 lbs in 12 weeks were considered non-adherent and were excluded from the next phase of the study during which 238 subjects were followed biweekly.

RESULTS:

Despite a $25/week payment for participation nearly 44% of subjects dropped out or were judged non-compliant prior to the end of the study. At 116 weeks, 133 (97 females, 36 males) of 238 subjects remained in the study (44% of the initial population), with average weight loss from baseline of 13.6 +/- 10.5 lb in females and 14.0 +/- 10.5 lb in males.

DISCUSSION:

The weight loss observed (approximately 10% of body weight) is significant and has been associated with important health benefits particularly for patients with hypertension and non-insulin dependent diabetes. The potential advantages of using meal replacements for mild obesity include wide availability to aid compliance, low cost and minimal professional intervention. PMID: 7706595 DOI: 10.1080/07315724.1994.10718456 [Indexed for MEDLINE]

4. ENDNOTE BACKGROUND

Peter Clifton. **"Assessing the evidence for weight loss strategies in people with and without type 2 diabetes.** World J Diabetes. Oct 15, 2017; 8(10): 440-454

World J Diabetes. 2017 Oct 15;8(10):440-454. doi: 10.4239/wjd.v8.i10.440.

Assessing the evidence for weight loss strategies in people with and without type 2 diabetes.

Clifton P[1].

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Division of Health Sciences, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5001, Australia. peter.clifton@unisa.edu.au.

Abstract

This review will examine topical issues in weight loss and weight maintenance in people with and without diabetes. A high protein, low glycemic index diet would appear to be best for 12-mo weight maintenance in people without type 2 diabetes. This dietary pattern is currently being explored in a large prevention of diabetes intervention. Intermittent energy restriction is useful but no better than daily energy restriction but there needs to be larger and longer term trials performed. There appears to be no evidence that intermittent fasting or intermittent severe energy restriction has a metabolic benefit beyond the weight loss produced and does not spare lean mass compared with daily energy restriction. Meal replacements are useful and can produce weight loss similar to or better than food restriction alone. Very low calorie diets can produce weight loss of 11-16 kg at 12 mo with persistent weight loss of 1-2 kg at 4-6 years with a very wide variation in long term results. Long term medication or meal replacement support can produce more sustained weight loss. In type 2 diabetes very low carbohydrate diets are strongly recommended by some groups but the long term evidence is very limited and no published trial is longer than 12 mo. Although obesity is strongly genetically based the microbiome may play a small role but human evidence is currently very limited.

KEYWORDS:

Alternate day fasting; Glycemic index; Intermittent energy restriction; Low fat diets; Protein; Very low calorie diet; Very low carbohydrate diet

PMID: 29085571

PMCID: PMC5648990

DOI: 10.4239/wjd.v8.i10.440 **Free PMC Article**

5. ENDNOTE BACKGROUND

Coleman CD1, Kiel JR1, Mitola AH2, Arterburn LM1. **Comparative effectiveness of a portion-controlled meal replacement program for weight loss in adults with and without diabetes/high blood sugar.** Nutr Diabetes. 2017 Jul 10;7(7):e284. doi: 10.1038/nutd.2017.32.

Nutr Diabetes. 2017 Jul 10;7(7):e284. doi: 10.1038/nutd.2017.32.

Comparative effectiveness of a portion-controlled meal replacement program for weight loss in adults with and without diabetes/high blood sugar.

Coleman CD[1], Kiel JR[1], Mitola AH[2], Arterburn LM[1].

Author information

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2 Independent Consultant, Clifton Park, NY, USA.

Abstract

BACKGROUND:

Individuals with type 2 diabetes (DM2) may be less successful at achieving therapeutic weight loss than their counterparts without diabetes. This study compares weight loss in a cohort of adults with DM2 or high blood sugar (D/HBS) to a cohort of adults without D/HBS. All were overweight/obese and following a reduced or low-calorie commercial weight-loss program incorporating meal replacements (MRs) and one-on-one behavioral support.

SUBJECTS/METHODS:

Demographic, weight, body composition, anthropometric, pulse and blood pressure data were collected as part of systematic retrospective chart review studies. Differences between cohorts by D/HBS status were analyzed using Mann-Whitney U-tests and mixed model regression.

RESULTS:

A total of 816 charts were included (125 with self-reported D/HBS). The cohort with D/HBS had more males (40.8 vs 25.6%), higher BMI (39.0 vs 36.3 kg m^{-2}) and was older (56 vs 48 years). Among clients continuing on program, the cohorts with and without D/HBS lost, on average, 5.6 vs 5.8 kg (NS) (5.0 vs 5.6%; P=0.005) of baseline weight at 4 weeks, 11.0 vs 11.6 kg (NS) (9.9 vs 11.1%; P=0.027) at 12 weeks and 16.3 vs 17.1 kg (13.9 vs 15.7%; NS) at 24 weeks, respectively. In a mixed model regression controlling for baseline weight, gender and meal plan, and an intention-to-treat analysis, there was no significant difference

in weight loss between the cohorts at any time point. Over 70% in both cohorts lost ⩾5% of their baseline weight by the final visit on their originally assigned meal plan. Both cohorts had significant reductions from baseline in body fat, blood pressure, pulse and abdominal circumference.

CONCLUSION:

Adults who were overweight/obese and with D/HBS following a commercial weight-loss program incorporating MRs and one-on-one behavioral support achieved therapeutic weight loss. The program was equally effective for weight loss and reductions in cardiometabolic risk factors among adults with and without D/HBS.

PMID: 28692020

PMCID: PMC5549252

DOI: 10.1038/nutd.2017.32 [Indexed for MEDLINE] **Free PMC Article**

6. ENDNOTE BACKGROUND

Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA. **A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss.** Obes Rev. 2019 Apr;20(4):569-587. doi: 10.1111/obr.12816. Epub 2019 Jan 24. Review.

From a 2019 review of meal replacement:
A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss.
Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA.
Obes Rev. 2019 Apr;20(4):569-587. doi: 10.1111/obr.12816. Epub 2019 Jan 24. Review.

Mean weight change at 1 year favoured the MR group relative to the control group in each comparison. In those comparisons where we conducted meta-analysis, in people assigned to a diet incorporating MR, mean difference was -1.44 kg (-2.48 to -0.39 kg; I^2 = 38%) compared with alternative kinds of diets. In those assigned to a MR diet along with support, mean difference was -2.22 kg (-3.99 to -0.45, I^2 = 81%) compared with other diets with support and -3.87 kg (-7.34 to -0.40; I^2 = 60%) compared with other kinds of diet without support. In those assigned a MR diet with an enhanced level of support, mean difference was -6.13 kg (-7.35 to -4.91, I^2 = 19%) compared with alternative diets and regular support. Programmes incorporating meal replacements led to greater weight loss at 1 year than comparator weight loss programmes and should be considered as a valid option for management of overweight and obesity in community and health care settings.

7. ENDNOTE BACKGROUND

Leo Treyzon, Steve Chen, Kurt Hong, Eric Yan, Catherine L Carpenter, Gail Thames, Susan Bowerman, He-Jing Wang, Robert Elashoff and Zhaopying Li, **A Controlled Trial of Protein Enrichment of Meal Replacements for Weight Reduction with Retention of Lean Body Mass**
Nutrition Journal 2008, 7:23 doi:10.1186/1475-2891-7-23

Herbalife Nutrition Institute

CURRENT PUBLICATIONS ON FORMULA 1

Introduction

This summary of published clinical studies on the use of Herbalife Formula 1 for weight management is provided as an educational service by the Herbalife Nutrition Institute. These studies were conducted using Herbalife Formula 1 in university-affliliated research centers in countries around the world: including the United States of America, Korea, Germany, Russia, China, Taiwan, Mexico, and India.

Reducing the risk of age-related chronic diseases such as diabetes and heart disease through weight management and a healthy active lifestyle are key missions of the Herbalife Nutrition Institute's. It is hoped that this summary of completed and published clinical studies will help the public and scientific community to appreciate the extensive evidence of the effects of Formula 1 on Weight Management shown through these clinical studies.

David Heber, MD, PhD, FACP, FASN,

Chairman Herbalife Nutrition Institute

A Controlled Trial of Protein Enrichment of Meal Replacements for Weight Reduction with Retention of Lean Body Mass

Leo Treyzon, Steve Chen, Kurt Hong, Eric Yan, Catherine L Carpenter,Gail Thames, Susan Bowerman, He-Jing Wang, Robert Elashoff and Zhaopying Li

Nutrition Journal 2008, 7:23 doi:10.1186/1475-2891-7-23

High protein diets have been shown to improve satiety and retention of lean body mass. This study was designed to determine effects of Formula 1 used as a protein-enriched meal replacement with added protein (Personalized Protein Powder) on weight loss and lean body mass retention by comparison to a control carbohydrate-enriched meal replacement placebo with the same number of calories. In addition, customized diet plans were developed to achieve high protein (30% of total

calories) or standard protein intakes (15% of total calories) including foods and the meal replacements. Eighty-five subjects completed the study conducted at the University of California, Los Angeles. As expected, since the calories in both groups were the same, there were no differences in weight loss at 12 weeks (-4.19 ± 0.5 kg for the high protein group and -3.72 ± 0.7 kg for standard protein group, $p > 0.1$). However, the subjects in the high protein group (HP) lost significantly more fat weight than the standard protein (SP) group (HP = -1.65 ± 0.63 kg; SP = -0.64 ± 0.79 kg, $P = 0.05$) as estimated by bioelectrical impedance analysis.

Impact: Subjects lost more fat weight on the higher protein intake using Formula 1 as a meal replacement. See figure to the left.

8. ENDNOTE BACKGROUND

Lee, J. Lee, W. K. Bae, J. K. Choi, H. J. Kim, B. Cho. **Efficacy of Low-Calorie, Partial Meal Replacement Diet Plans on Weight and Abdominal Fat In Obese Subjects With Metabolic Syndrome.** Int J Clin Pract, February 2009, 63, 2, 195–201

Efficacy of Low-Calorie, Partial Meal Replacement Diet Plans on Weight and Abdominal Fat In Obese Subjects With Metabolic Syndrome: A Double-Blind, Randomized Controlled Trial of Two Diet Plans – One High in Protein and One Nutritionally Balanced

Lee, J. Lee, W. K. Bae, J. K. Choi, H. J. Kim, B. Cho

Int J Clin Pract, February 2009, 63, 2, 195–201

This study conducted in South Korea at the National Seoul University was designed to evaluate the efficacy of two low-calorie diets with partial meal replacement plans–a high-protein plan (HP) and a conventional protein (SP) plan–on reducing obesity in obese subjects with metabolic syndrome. In a 12-week, double-blind study, 75 participants were randomly assigned to either the high protein (HP) or conventional protein (SP) plan. The overall mean weight losses were similar at 5 kg in the HP-plan group and 4.9 kg in the SP-plan group as expected since the number of recommended calories were the same. Truncal fat mass decreased 1.6 kg in the HP-plan group and 1.5 kg in the SP-plan group as measured by Dual Energy X-Ray Absorptiometry. Whole body fat mass decreased 2.5 kg in the HP-plan group and 2.3 kg in the SP-plan group. Between-group losses did not differ significantly for truncal or whole body fat mass in the analysis of all subjects. However, when the subjects who followed the diet plans with 70% or greater fidelity were analyzed, truncal and whole body fat mass decreased more in the HP-plan group than in the SP-plan group (-3.5 kg vs -.2.2 kg) as did abdominal fat (-1.9 kg vs -1.5 kg respectively). These differences in total and abdominal fat between groups were statistically significant ($p < 0.05$).

Impact: Both low-calorie partial meal replacement diets plans – the high-protein and the conventional – were safe and had a similar effect on weight, but the high protein diet was more effective in reducing body fat and abdominal fat in obese subjects with Metabolic Syndrome among subjects with greater than 70 percent compliance with the plan.

9. ENDNOTE BACKGROUND

Flechtner-Mors M, Boehm BO, Wittmann R, Thoma U, Ditschuneit HH. **Enhanced Weight Loss with Protein-Enriched Meal Replacements in Subjects with the Metabolic Syndrome.** Diabetes Metab Res Rev. 2010; 26:393-405.

Enhanced Weight Loss with Protein-Enriched Meal Replacements in Subjects with the Metabolic Syndrome

Flechtner-Mors M, Boehm BO, Wittmann R, Thoma U, Ditschuneit HH.

Diabetes Metab Res Rev. 2010; 26:393-405.

This study was conducted at the University of Ulm in Germany to compare the effects of two partial meal replacement diet plans using either high or standard protein prescription in obese subjects with the Metabolic Syndrome, a common group of risk factors for chronic disease based on the levels of blood fats, sugar, blood pressure, and waist circumference. Obese subjects with Metabolic Syndrome received instructions for an energy-restricted diet with a calorie deficit of 500 kcal/day and were randomly assigned to either high-protein (1.34 g/kg body weight) or conventional protein (0.8 g/kg body weight) diets for 12 months. Protein-enriched meal replacements were used to enrich one arm of the diet with protein throughout the study. In all, 67% of the participants completed the 1-year study.

Subjects following the high-protein diet lost more body weight and more fat mass compared with those on the conventional protein diet, whereas the loss of lean mass was similar in both diet groups indicating that the higher protein helped to maintain lean mass better than the standard protein diet. Blood test measures associated with the metabolic syndrome improved in both diet groups. Improvements were greater in subjects in the high protein group. After 12 months of treatment, 64.5% of the subjects in the high-protein diet group and 34.8% of the subjects in the conventional diet group no longer met three or more of the criteria for having the metabolic syndrome.

Impact: Individuals with the metabolic syndrome achieved significant weight loss while preserving fat-free mass when treated with an energy-restricted, high-protein diet that included nutrient-dense meal replacements (Formula 1 and Personalized Protein Powder), as compared with the results for conventional protein intake. An intervention with a protein-enriched diet demonstrated advantages for the management of the metabolic syndrome which is common in middle-aged individuals globally and increases the risk for diabetes and heart disease.

10. ENDNOTE BACKGROUND

K.M. Gapparova, V.I. Pilipenko, Yu.G. Chekhonina, O.N. Grigoryan
The Effect of Low-Calorie Diets with Inclusion of Protein Food Substitutes on the Anthropometric and Clinico-Biochemical Indices In Obese Patients
Dietology Issues, 2011, v. 1, №1, p.33-39

The Effect of Low-Calorie Diets with Inclusion of Protein Food Substitutes on the Anthropometric and Clinico-Biochemical Indices In Obese Patients

K.M. Gapparova, V.I. Pilipenko, Yu.G. Chekhonina, O.N. Grigoryan

Dietology Issues, 2011, v. 1, №1, p.33-39

This study was conducted in the Scientific Research Institute of Nutrition at the Russian Academy of Medical Sciences in Moscow in order to assess the tolerance and effectiveness of low-calorie protein-modified diets a randomized controlled study was carried out on three groups of patients with obesity and overweight (30 patients in each group) aged from 21 to 60 years. The study was conducted in two phases, each lasted 3 months. The patients were divided into three groups, each consisting of 30 persons. During the 6-month observation period, two groups of patients received variants of a low-calorie diet with various protein contents by including Formula 1 and Protein Powder in their diet to substitute for two meals in the first three month period and one meal in the second three month period. The patients in the third group (control group) received a standard low-calorie diet with no meal replacements.

In the process of diet therapy, the dynamics of the indices of body composition, lipidograms, carbohydrate metabolism and also changes of the feeling of hunger and satiation were assessed. In the groups of patients receiving protein food substitutes in the diet, a significant reduction of body mass, predominantly at the expense of fatty component, was noted. In the reference group, decrease of fatty mass was accompanied by reduction of lean body mass. In two studied groups of patients with inclusion of protein food substitutes into the diet, on the background of the optimal dynamics of the feeling of hunger and satiation a tendency to normalization of the indices of lipidograms and carbohydrate metabolism was noted as compared with the group that received the standard low-calorie diet.

Impact: The results of the study support the use of Formula 1 high-protein food substitute in long-term programs of body mass reduction with the aim to enhance the effectiveness of low-calorie diets and to improve the quality of life in patients with overweight and obesity.

11. ENDNOTE BACKGROUND

Ismael Campos-Nonato I, Hernández L, and Barquera S. **Effect of A High Protein Diet Versus Standard Protein Diet on Weight Loss and Biomarkers of Metabolic Syndrome: A Randomized Clinical Trial**. Obesity Facts 2017; 10:238-251

Effect of A High Protein Diet Versus Standard Protein Diet on Weight Loss and Biomarkers of Metabolic Syndrome: A Randomized Clinical Trial

Ismael Campos-Nonato I, Hernández L, and Barquera S.

Obesity Facts 2017; 10:238-251

This study was conducted at the Center for Research in Nutrition and Health. Mexican National Institute of Public Health in Cuernavaca Mexico in order to determine the effect of increased protein intake using Formula 1 as part of a meal replacement program on weight loss in Mexican adults with Metabolic Syndrome. The prevalence of metabolic syndrome is approximately 25% of the worldwide adult population and 49.8% in Mexicans. 118 adults meeting criteria for Metabolic Syndrome were randomized to prescribed hypocaloric diets (500kcal less than resting metabolism providing either 0.8 g/kg body weight proteimn (SP group) or 1.34 g/kg body weight (HP group) protein for 6 months. 105 subjects (51 for SP and 54 for HP) completed the trial. Overall weight loss was 5.1±3.6 kg in the SP group compared to 7.0±3.7 kg in the in the HP group. Decreased waist circumference was noted in both groups (HP= -8.8±2.6 percent and SP= -6.5±2.6 percent). In the subgroup judged to be adherent more than 75% of the time with the prescribed diets, there was a significant difference in mean weight loss between the HP and SP groups (HPD -9.5% vs. SPD -5.8%) In a study in free-living subjects reduced compliance may have obscured the effects of the higher protein plan on satiety and weight loss.

Impact: This was the first study conducted in Mexico that investigated the impact of partial diet replacement with protein-enriched meal in individuals with metabolic syndrome, although there have been similar studies in overweight and obese adults conducted in other countries. Formula 1 meal replacements improved adherence to the diet by offering a simple and healthy alternative meal option that resulted in improvements in biomarkers of Metabolic Syndrome in both the high and standard protein groups.

12. ENDNOTE BACKGROUND

Gulati S, Misra A, Tiwari R, Sharma M, Pandey RM, Yadav CP. **Effect of High Protein Meal . Replacement on Weight And Cardiometabolic Profile in Overweight/Obese Asian Indians in North India**. British Journal of Nutrition 2017

Effect of High Protein Meal Replacement on Weight And Cardiometabolic Profile in Overweight/Obese Asian Indians in North India

Gulati S, Misra A, Tiwari R, Sharma M, Pandey RM, Yadav CP

British Journal of Nutrition 2017

This study was conducted at the Fortis C-DOC Center for Excellence for Diabetes, Metabolic Disease and Endocrinology, and the All India Institute of Medical Sciences in New Delhi, India evaluate the impact of high protein meal replacement (HPMR) on weight, and metabolic, lipids and inflammatory parameters in overweight/obese Asian Indians. Diets consumed by Asian Indians are high in refined carbohydrates, saturated and trans-fats, salt, sugar and low in fiber, omega 3 polyunsaturated fatty acids and protein. There is a lower intake of protein in Asian Indians (10.8% in rural and 10.9% in urban population) vs. north Americans in USA (nearly 16%). A total of 122 overweight/obese men and women were prescribed a high protein meal replacement plan or control diet after a 2 weeks stabilization. One hundred subjects completed the study and demonstrated a fat mass loss of 3.4 Kg with high protein Formula 1 based diet as compared to 0.7 Kg in the control diet. A 2.8 cm reduction in waist circumference with the high protein meal replacement diet as compared to the control diet.

Impact: This study demonstrated for the first time in Asian Indians that a high protein meal replacement diet using Formula 1 resulted in significant weight loss, reduction in waist circumferenc, body fat mass, and numerous biomarkers of Metabolic Syndrome. These findings are of practical and clinical significance keeping in mind the body composition and nutritional state of Asian Indians, and their high risk of Metabolic Syndrome.

13. ENDNOTE BACKGROUND

Zhaoping Li, Leo Treyzon, Steve Chen, Eric Yan, Gail Thames, Catherine L Carpenter. **Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: An Outpatient Randomized Controlled Trial.** Nutrition Journal 2010, 9:72

Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: An Outpatient Randomized Controlled Trial
Zhaoping Li, Leo Treyzon, Steve Chen, Eric Yan, Gail Thames, Catherine L Carpenter
Nutrition Journal 2010, 9:72

In order to address the concern that recommending protein-enriched meal replacements as part of a weight management program could lead to changes in biomarkers of liver or renal function and reductions in bone density, this study was designed as a placebo-controlled clinical trial utilizing two meal plans providing the same number of calories utilizing either a high protein-enriched (HP) or a standard protein (SP) meal replacement in an outpatient weight loss program at the University of California, Los Angeles. 100 obese men and women over 30 years of age with a body mass index (BMI) between 27 and 40 kg/m2 were randomized to one of two weight loss meal plans with the same number of calories 1). HP group: providing 2.2 g protein/kg of lean body mass (LBM)/day or 2). SP group: providing 1.1 g protein/kg LBM/day. Meal replacement (MR) was used twice daily (one meal, one snack) for 3 months and then once a day for 9 months. Body weight, lipid profiles, liver function, renal function and bone density were measured at baseline and 12 months.

Seventy subjects completed the study. Both groups lost weight (HP -4.29 ± 5.90 kg vs. SP -4.66 ± 6.91 kg, $p < 0.01$) and as expected, since both diet plans recommended the same number of calories per day, there was no difference in weight loss observed between the groups at one year. There was no significant change noted in liver function in either group over one year as measured by the levels of the enzymes Alanine transaminase (ALT) or Aspartate transaminase (AST). There were no differences in gallbladder function over one year as determined from the levels of bilirubin and alkaline phosphatase. There were no differences in renal function over one year determined from the levels of serum creatinine, blood urea nitrogen, 24 hour urine creatinine clearance, and calcium excretion. There were no changes in bone mineral density measured by Dual Energy X-ray Absorptiometry (DEXA) in either group over one year.

Impact: Both the HP and SP diets were well tolerated, resulted in expected weight loss, were sustainable, and did not result in any adverse effects. There were no changes of liver function, renal function or bone mineral density over one year in either group using Formula 1.

14. ENDNOTE BACKGROUND

Heymsfield SB1, van Mierlo CA, van der Knaap HC, Heo M, Frier HI. **Weight management using a meal replacement strategy: meta and pooling analysis from six studies.** Int J Obes Relat Metab Disord. 2003 May;27(5):537-49.

Int J Obes Relat Metab Disord. 2003 May;27(5):537-49.

Weight management using a meal replacement strategy: meta and pooling analysis from six studies.

Heymsfield SB[1], van Mierlo CA, van der Knaap HC, Heo M, Frier HI.
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Abstract

OBJECTIVE:

Although used by millions of overweight and obese consumers, there has not been a systematic assessment on the safety and effectiveness of a meal replacement strategy for weight management. The aim of this study was to review, by use of a meta- and pooling analysis, the existing literature on the safety and effectiveness of a partial meal replacement (PMR) plan using one or two vitamin/mineral fortified meal replacements as well as regular foods for long-term weight management.

DESIGN:

A PMR plan was defined as a program that prescribes a low calorie (>800<or=1600 kcal/day) diet whereby one or two meals are replaced by commercially available, energy-reduced product(s) that are vitamin and mineral fortified, and includes at least one meal of regular foods. Randomized, controlled PMR interventions of at least 3 months duration, with subjects 18 y of age or older and a BMI>or=25 kg/m(2), were evaluated. Studies with self-reported weight and height were excluded. Searches in Medline, Embase, and the Cochrane Clinical Trials Register from 1960 to January 2001 and from reference lists identified 30 potential studies for analysis. Of these, six met all of the inclusion criteria and used liquid meal replacement products with the associated plan. Overweight and obese subjects were randomized to the PMR plan or a conventional reduced calorie diet (RCD) plan. The prescribed calorie intake was the same for both groups. Authors of the six publications were contacted and asked to supply primary data for analysis. Primary data from the six studies were used for both meta- and pooling analyses.

RESULTS:

Subjects prescribed either the PMR or RCD treatment plans lost significant amounts of weight at both the 3-month and 1-year evaluation time points. All methods of analysis indicated a significantly greater weight loss in subjects receiving the PMR plan compared to the RCD group. Depending on the analysis and follow-up duration, the PMR group lost approximately 7-8% body weight and the RCD group lost approximately 3-7% body weight. A random effects meta-analysis estimate indicated a 2.54 kg (P<0.01) and 2.43 kg (P=0.14) greater weight loss in the PMR group for the 3-month and 1-y periods, respectively. A pooling analysis of completers showed a greater weight loss in the PMR group of 2.54 kg (P<0.01) and 2.63 kg (P<0.01) during the same time period. Risk factors of disease associated with excess weight improved with weight loss in both groups at the two time points. The degree of improvement was also dependent on baseline risk factor levels. The dropout rate for PMR and RCD groups was equivalent at 3 months and significantly less in the PMR group at 1 y. No reported adverse events were attributable to either weight loss regimen.

CONCLUSION:

This first systematic evaluation of randomized controlled trials utilizing PMR plans for weight management suggests that these types of interventions can safely and effectively produce significant sustainable weight loss and improve weight-related risk factors of disease.

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15. ENDNOTE BACKGROUND

J. Bruce Redmon, MD, Susan K. Raatz, PHD, Kristell P. Reck, RD, Joyce E. Swanson, RD, Christine A. Kwong, RD, Qiao Fan, MS, William Thomas, PHD and John P. Bantle, MD. **One-Year Outcome of a Combination of Weight Loss Therapies for Subjects With Type 2 Diabetes**. Diabetes Care 2003 Sep; 26(9): 2505-2511. https://doi.org/10.2337/diacare.26.9.2505

American Diabetes Association

Diabetes Care

One-Year Outcome of a Combination of Weight Loss Therapies for Subjects With Type 2 Diabetes

A randomized trial

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A RANDOMIZED TRIAL

Abstract

OBJECTIVE—The purpose of this study was to evaluate the effects of a combination weight loss program using intermittent low-calorie diets, energy-controlled meal replacement products, and sibutramine on weight loss, diabetes control, and cardiovascular risk factors in overweight or obese subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Overweight or obese individuals with type 2 diabetes treated with diet or oral medication were randomly assigned to either a standard therapy or combination therapy group. Both groups received a standardized program to facilitate weight loss. The combination therapy group also received 10–15 mg sibutramine daily, low-calorie diets using meal replacement products for 1 week every 2 months, and between low-calorie diet weeks, once daily use of meal replacement product and snack bars to replace one usual meal and snack. Primary outcome measures were changes in body weight, glycemic control, plasma lipids, blood pressure, pulse, and body composition at 1 year.

RESULTS—At 1 year, combination therapy, compared with standard therapy, resulted in significantly more weight loss (−7.3 ± 1.3 kg vs. −0.8 ± 0.9 kg, $P < 0.001$) and reduction in HbA_{1c} (−0.6 ± 0.3 vs. 0.0 ± 0.2%, $P = 0.05$). Combination therapy resulted in reduced requirement for diabetes medications and decreased fat mass and lean body mass. A 5-kg decrease in weight at 1 year was associated with a decrease of 0.4% in HbA_{1c} ($P = 0.006$). Changes in fasting glucose, lipids, pulse, and blood pressure did not differ between groups.

CONCLUSIONS—This combination weight loss program resulted in greater weight loss and improved diabetes control compared with a standard weight loss program in overweight or obese subjects with type 2 diabetes.

Type 2 diabetes is estimated to afflict ~12% of people between the ages of 40 and 74 years in the U.S. (1). This high prevalence of type 2 diabetes, combined with its substantial human and economic burden, makes it one of our most important public health problems. Among those individuals with type 2 diabetes, as many as 80% are overweight or obese (2). Weight loss may be the single most important therapeutic objective for such individuals

(2). Short-term studies lasting 6 months or less have demonstrated that weight loss in overweight or obese type 2 diabetic subjects is associated with decreased insulin resistance, substantial improvements in measures of glycemic control, reduced lipemia, and reduced blood pressure (3–5). However, long-term data substantiating that these improvements can be maintained are limited. The most recent American Diabetes Association nutrition recommendations concluded, “optimal strategies for preventing and treating obesity long term have yet to be defined” (6).
Examination of long-term options to promote weight loss in people with type 2 diabetes suggested that standard weight reduction diets were not effective (6). Very low-calorie diets produced substantial initial weight loss but it was difficult to maintain the weight loss long term (7). Although weight loss medications might be helpful, the available evidence is limited. Fenfluramine and phentermine produced significant weight loss and reduction in HbA_{1c} in type 2 diabetic subjects (8), but fenfluramine was removed from the market in the U.S. because of its association with valvular heart disease. Orlistat treatment of type 2 diabetic subjects for 1 year produced weight loss of 6.2% of starting weight but a decrement in HbA_{1c} of only 0.5% compared with placebo (9). Similarly, sibutramine treatment of type 2 diabetic subjects for 24 weeks produced weight loss of 4.5% of starting weight but had only a modest effect on HbA_{1c} (10).

Other approaches to weight loss that might be effective but have not been adequately tested in type 2 diabetic subjects include meal replacements and repetitive use of low-calorie diets.

Ditschuneit et al. (11) used energy-controlled meal replacements for two meals and two snacks daily for 3 months and then for one meal and one snack daily for an additional 24 months in obese subjects. After 27 months, weight loss was 11.3% of starting weight for subjects following the meal replacement program.

Williams et al. (12) compared a standard diet to very low-calorie diets used either 1 day per week or 5 consecutive days every 5 weeks in type 2 diabetic subjects. After 15 weeks, the 1-day-per-week and the 5-days-per-5-weeks very low-calorie diet groups lost 9.6 and 10.4 kg, respectively, compared with weight loss of 5.4 kg in the standard diet group.

We hypothesized that efficacy might be increased if several weight loss approaches were combined. Accordingly, we initiated a clinical trial combining intermittent low-calorie diets, energy-controlled meal replacements, and sibutramine to treat overweight and obese type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS

Sixty-one overweight or obese type 2 diabetic subjects were enrolled in the study. After giving informed consent, each potential subject underwent a history, physical examination, screening laboratory tests, urinalysis, and electrocardiogram. Eligibility criteria were age 30–70 years, diagnosis of type 2 diabetes with HbA_{1c} 7.0–10.0%, BMI 27–50 kg/m^2, stable weight for the previous 3 months, and constant doses of any oral diabetes, hypertension, and lipid medications for at least 1 month. Exclusionary criteria included current use or use in the previous 6 months of insulin, prior use of sibutramine, use of any weight loss product or participation in any formal weight loss program in the previous month, significant abnormality on screening tests, history of heart disease or stroke, prior bariatric surgery, lactose intolerance, and any chronic disease or therapy that would make adherence to the study protocol difficult. The University of Minnesota Institutional Review Board approved the study.

Study protocol

Subjects were evaluated in the University of Minnesota General Clinical Research Center, and eligible subjects were randomly assigned to either a standard therapy or combination therapy group by a single study coordinator using a random allocation schedule provided by the study statistician. The study coordinator was blinded to the randomization schedule. Randomization was stratified by sex.

Subjects in both groups received individual counseling by a registered dietitian. At baseline, each subject's basal energy requirement was calculated, and resting energy expenditure was measured. Using these data and an estimate of the subject's typical activity level, the dietitian prescribed an individualized diet that would promote a 500–1,000 kcal reduction in daily energy. Subjects also received an individualized exercise prescription that included, at a minimum, walking for 30 min three times weekly in addition to

usual activity. All subjects received an educational program of dietary, exercise, and behavioral strategies to facilitate weight loss using a commercially available dietary and lifestyle modification resource (13). Subjects in the combination therapy group received the following additional interventions: *1*) 10 mg sibutramine daily with the option to increase to 15 mg daily after 6 months if BMI remained >27 kg/m^2; *2*) low-calorie diets providing 900–1,300 kcal per day made up exclusively of meal replacement products (meal shakes or meal bars, 220 kcal/serving, four to six servings daily) for 7 consecutive days every 2 months; and *3*) between low-calorie diet weeks, use of one meal replacement product and one snack bar daily (120 kcal/snack bar) to replace one usual meal and snack and thereby facilitate achievement of the goal of a 500- to 1,000-kcal-per-day reduction in energy intake. Meal replacement products and snack bars were provided by Slim Fast Foods Company. Follow-up visits took place at 1 month, 2 months, and every 2 months thereafter. Subjects in the combination therapy group were also seen after each low-calorie diet week for measurement of weight, pulse, and blood pressure.

At baseline and each follow-up visit, body weight, height, blood pressure, and heart rate were measured, and blood samples for fasting glucose, lipids, and HbA_{1c} were obtained. Body composition was assessed at baseline, 2, 6, and 12 months. Diabetes, hypertension, and lipid medications were adjusted, added, or stopped according to a preestablished protocol. Diabetes medication was initiated or increased if there were symptoms attributable to hyperglycemia or if HbA_{1c} was >10.0%. Diabetes medication was reduced or discontinued if symptomatic hypoglycemia occurred more than twice per week or home blood glucose values were frequently <80 mg/dl.

Analytical techniques

Fasting plasma glucose, HbA_{1c}, fasting plasma total cholesterol, HDL cholesterol, and triglycerides were determined in the Biochemistry Laboratory of Fairview-University Medical Center. LDL cholesterol was calculated from the formula: LDL cholesterol = total cholesterol − (HDL cholesterol + triglycerides/5). LDL cholesterol was not calculated if fasting plasma triglycerides exceeded 400 mg/dl. Plasma glucose was determined by a glucose oxidase method. $HbA_{1c}$was determined by high-pressure liquid chromatography using a Diamet Glycosylated Hemoglobin Analyzer (Bio-Rad Laboratories, Hercules, CA). Body composition was assessed by total body dual-energy X-ray absorptiometry using a Lunar Prodigy (software version 2.15; General Electric Corporation, Madison, WI). Resting energy expenditure

was measured using a DeltaTrac II Metabolic Monitor (Sensormedics, Yorba Linda, CA). Body weight was measured on an electronic scale with subjects wearing light clothing and no shoes. Height was measured with a stadiometer. Blood pressure and pulse were measured by automated blood pressure cuff after subjects were seated for 5 min. Three readings were obtained, and the average of the last two was recorded.

Statistical analysis

Data from subjects who returned for their initial follow-up visit after randomization were analyzed on an intention-to-treat basis. Data from subjects who discontinued study participation before 12 months were included through their last study visit. Baseline data and 12-month changes from baseline data were compared between treatment groups using Student's *t* test for two independent samples. A χ^2 test was used to compare categorical data. The relationship between weight loss and change in HbA_{1c} was examined by least squares linear regression. All data are presented as mean ± SEM unless otherwise stated. *P* values ≤0.05 were considered significant. With 30 subjects in each treatment group, the study had a 90% power of detecting a difference of 6.2 kg in mean weight loss between the two groups at the α = 0.05 level.

Excluded data

One subject in the standard therapy group had fasting plasma triglycerides at baseline >2,000 mg/dl, so this value was excluded as an outlier from both baseline and 12-month change comparisons. One subject from the combination therapy group was excluded from the linear regression estimate because the subject's weight loss was more than twice as large as any other subject and would have led to extrapolating the regression line. This subject's weight decreased by 20 kg and HbA_{1c} decreased by 0.8%.

RESULTS

Sixty-one subjects were enrolled and randomly assigned to treatment groups. Two subjects in the standard therapy group withdrew from the study before their first follow-up visit and were excluded from further analysis. The intention-to-treat population was therefore comprised of 29 subjects in the standard therapy group and 30 subjects in the combination therapy group.

Five subjects (two in the standard therapy group and three in the combination therapy group) discontinued study participation before 1 year. Reasons for discontinuation were inability to keep study visits (two subjects), desire to start a commercial weight loss program (two subjects), and personal reasons (one subject). Thus, 54 subjects (92%) completed 12 months of study participation.

There were no significant differences between the two treatment groups in baseline demographic, clinical, or metabolic parameters (**Table 1**). The majority of subjects in both groups were taking one or more oral diabetes medications at baseline, and the pattern of diabetes medication use was not different between the two groups (**Table 1**). The numbers of subjects taking hypertension and lipid medications at baseline were not different between groups (data not shown).

Changes in medications

At 1 year, diabetes medications had been changed in 28 subjects. Sixteen subjects in the standard therapy group (59%) and 4 subjects in the combination therapy group (15%) were taking more diabetes medications, whereas 1 subject in the standard therapy group (4%) and 7 subjects in the combination therapy group (26%) were taking less diabetes medications ($P \leq 0.01$). Hypertension medications were increased in six subjects in each group and decreased in two subjects in the combination therapy group ($P = 0.35$). Lipid medications were increased in four subjects and decreased in one subject in each group.

Weight loss

Weight loss is shown in **Fig. 1** and **Table 2**. At 12 months, weight loss in the standard therapy group was 0.8 ± 0.9 kg and in the combination therapy group was 7.3 ± 1.3 kg ($P < 0.001$) (0.8 ± 0.8 vs. 6.4 ± 1.1% as percent of initial weight). Approximately 60% of the total weight loss incurred by the combination therapy group occurred during the initial low-calorie diet week and the ensuing 7 weeks leading up to the second low-calorie diet week (**Fig. 1**). At 1 year, the mean weight loss of 7.3 kg in the combination therapy group resulted from a net weight loss of 7.7 kg during the 6 low-calorie diet weeks and a net weight gain of 0.4 kg during the six intervening periods. Decreases in BMI, fat mass, and lean body mass at 1 year were all significantly greater in the combination therapy group than in the standard

therapy group (Table 2). In the combination therapy group, 63% of the weight loss at 1 year was due to loss of fat mass.

Glycemic end points

HbA_{1c} decreased 0.6 ± 0.3% in the combination therapy group but was unchanged in the standard therapy group (P = 0.05) (Fig. 2 and Table 2). Absolute HbA_{1c} values at 1 year were 8.2 ± 0.2 and 7.5 ± 0.3% in the standard therapy and combination therapy groups, respectively. At 1 year, 4 of 27 subjects (15%) in the standard therapy group and 11 of 27 subjects (41%) in the combination therapy group had HbA_{1c} values <7.0% (P = 0.19).
As noted above, more subjects in the standard therapy group had increases in diabetes medications, whereas more subjects in the combination therapy group had decreases in diabetes medications. These treatment modifications would tend to decrease the differences between the groups with respect to changes in glycemic control. We used two approaches to control for the confounding effect of medication changes. *1*) We reanalyzed the changes in HbA_{1c} after excluding values obtained after a change in diabetes medication occurred (i.e., the last HbA_{1c} value obtained before any change in diabetes medications was carried forward to the end of the study). *2*) The HbA_{1c} value obtained at 1 year was increased by 0.5% if there had been an increase in diabetes medication from baseline and decreased by 0.5% if there had been a decrease in diabetes medication from baseline. Using the first method, the changes in HbA_{1c} from baseline were +0.3 ± 0.2 and −0.5 ± 0.2% for the standard therapy and combination therapy groups, respectively (P = 0.007). Using the second method, the changes were +0.3 ± 0.2 and −0.7 ± 0.3% for the standard therapy and combination therapy groups, respectively (P = 0.009).
To examine the relationship between long-term weight loss and change in HbA_{1c}, each subject's 12-month weight change was plotted against the corresponding 12-month change in HbA_{1c}. To avoid the confounding effect of diabetes medication changes, we restricted the analysis to 25 subjects (10 subjects in the standard therapy group and 15 subjects in the combination therapy group) whose diabetes medications were not changed from baseline. For the observed range of weight changes (−10 to +4 kg), there was a significant positive linear association between change in weight at 1 year and change in HbA_{1c} (r = 0.53, P = 0.006) (Fig. 3). A 5-kg decrease in weight at 1 year was associated with a decrease of 0.4% in HbA_{1c}. Expressing weight loss as percent of initial weight, our model would predict that a 5% weight loss would result in a 0.4% decrease in HbA_{1c}. As described in research design

and methods, one subject in the combination therapy group with very large weight loss of 20 kg was excluded from this analysis to avoid extrapolating the regression line.

Other end points

Changes in blood pressure, pulse rate, and fasting plasma lipids did not differ between the two groups at 1 year (**Table 2**). The combination therapy group did experience a decrement in fasting plasma triglycerides relative to the standard therapy group, which approached statistical significance (**Table 2**). At the completion of 1 year, 6 subjects in the combination therapy group were on an increased dose of hypertension medications, and 21 subjects were on the same or reduced dose compared with baseline. There was no difference between these two subgroups at baseline with respect to weight, sex distribution, HbA_{1c}, or initial blood pressure. Subjects in the combination therapy group who had an increase in hypertension medications lost less weight on average compared with the subjects who had no change or a decrease in hypertension medications, although the difference was not statistically significant (4.8 ± 2 vs. 8.0 ± 2 kg, $P = 0.22$).

Adverse effects

There were no serious adverse events related to the study treatments. Dry mouth and constipation were reported by some subjects on initiation of combination therapy, but these symptoms were not severe and did not require discontinuation of therapy. One subject discontinued sibutramine because of insomnia and one because of nervousness. One subject started an antidepressant and sibutramine was discontinued. Of the remaining 24 subjects taking sibutramine at 1 year, the daily dose was 10 mg in 4 subjects and 15 mg in 20 subjects. Some subjects in the combination therapy group experienced mild hypoglycemia during low-calorie diet weeks and required temporary reductions in diabetes medications. No episodes of serious hypoglycemia occurred in either group.

CONCLUSIONS

The goal of our study was to determine whether a weight loss program combining *1*) intermittent low-calorie diets composed of meal replacements only, *2*) use of meal replacements to replace one meal and snack once a day

between intermittent low-calorie diet periods, and *3*) the weight loss medication sibutramine would result in long-term weight loss and improved glycemic control in overweight and obese people with type 2 diabetes. Our strategy was to aggressively pursue weight loss 1 week every 2 months with a low-calorie diet composed of inexpensive and readily available commercial products. Between low-calorie diets, we tried to achieve slower weight loss or, at a minimum, weight maintenance by asking subjects to use meal replacement products and low calorie snacks once daily to replace one usual meal and snack. Sibutramine at a dose of 10–15 mg once daily was given to increase satiety and facilitate reduced energy intake.

After 1 year, subjects randomized to this combination therapy demonstrated significantly greater weight loss, a decrement in HbA_{1c}, and a decreased requirement for diabetes medications when compared with a control group of subjects who received a standard weight loss program. In the combination therapy group, weight loss was 7.3 kg or 6.4% of baseline weight, HbA_{1c} decreased 0.6%, 41% of subjects had HbA_{1c} values <7.0%, and 26% of subjects were taking reduced doses of diabetes medications. Of the weight lost, >60% came from fat mass.

Weight loss in the combination therapy group did not result in reductions in blood pressure or plasma lipids, although the combination therapy group demonstrated a reduction in triglyceride levels that approached statistical significance. We did not see increases in blood pressure or pulse as have been reported in some trials using sibutramine (**14**). It is possible that any effect of weight loss to reduce blood pressure was offset by an effect of sibutramine to increase blood pressure. In the combination therapy group, subjects who required an increase in hypertension medications during the study tended to have less weight loss compared with those subjects who had no change or a decrease in hypertension medications, although the difference did not reach statistical significance. Weight loss in the combination therapy group produced significantly greater reductions in fat mass than occurred with standard therapy.

Shortcomings of our study include the study duration, the confounding effect of medication changes, and the absence of a blinded protocol. However, only a few randomized, prospective studies of weight loss treatments in people with type 2 diabetes have lasted as long as ours (**8**,**9**,**15**–**17**), and the efficacy of weight loss treatments beyond 1 year has not been established. In our study, weight loss achieved over the first 6 months of the study was thereafter maintained by offsetting effects of rapid weight loss during

repetitive low-calorie diet weeks and slower weight regain during the 7 weeks between low-calorie diets.

The confounding effect of medication changes during a 1-year study was difficult to avoid. We followed predetermined protocols for making changes in diabetes, hypertension, and lipid medications. Using these protocols, diabetes medications were decreased more often in the combination therapy group and increased more often in the standard therapy group. This probably caused us to underestimate the effect of weight loss on improvement in diabetes control in the combination therapy group. Adjusting by either of two methods for changes in diabetes medication resulted in a difference in adjusted HbA_{1c} values between the two groups at 1 year of ~1.0%.

It was not possible to blind study participants or investigators to the study interventions because of the use of low-calorie diets and meal replacements in one group only. Subjects in both treatment groups in our study were seen every 2 months. In addition, members of the combination therapy group were seen for a brief visit after every low-calorie diet week. While intensive lifestyle programs can produce greater weight loss than that observed in our standard therapy group (7), such programs are time consuming and expensive and may not be practical for widespread application. Our combination therapy intervention was not so intensive as to be impractical in an outpatient setting. The intervention was simple for subjects to understand and implement. Individuals at risk for hypoglycemia during low-calorie diet weeks were easily identified, and preemptory reductions in appropriate diabetes medications were made during the low-calorie diet week, after which subjects resumed their usual regimen. Other studies have demonstrated the feasibility of implementing a weight loss program in traditional outpatient settings using meal replacement products (18,19).

Due to the design of our intervention, it was not possible to determine which component of combination therapy was most important in producing and sustaining weight loss. Presumably, all three components (intermittent low-calorie diets, meal replacements, and sibutramine) contributed to weight loss. At least four short-term trials have evaluated the effect of sibutramine alone in obese people with type 2 diabetes (10,20–22). All four trials found sibutramine produced greater weight loss than placebo; however, in only one trial was there a significant improvement in HbA_{1c} (21).

Food provision and structured meal plans have been shown to facilitate greater weight loss than interventions that provide instruction in calorie goals, exercise, and behavioral therapy but do not provide meals or

structured meal plans (23). Several mechanisms have been suggested to account for this difference, including more regular and better eating patterns, better control of portion sizes, and greater adherence to energy goals because of greater accuracy in calorie estimation (23). Nonetheless, in a 1-year study of people with type 2 diabetes, no significant difference in weight loss or glycemia was observed when an intervention using liquid meal replacements was compared with an energy-restricted diet (24).

The relationship between weight loss and improvement in glycemia in type 2 diabetic subjects has not been clearly defined. Caloric restriction and weight loss produce rapid improvements in glycemia, which are mitigated with the passage of time, even when weight loss is maintained (4,8,15). Possible explanations for this include acute effects of caloric restriction on glycemia, which lessen as caloric intake returns toward baseline, and confounding effects of medication changes in studies extending more than a few weeks or months. When we attempted to adjust for the effect of changes in diabetes medication using two different approaches, the effect of the study intervention to improve diabetes control became even stronger. Few studies have quantified the effect of sustained weight loss on glycemic control (15). Based on analysis of 25 subjects in our study who had no change in diabetes medications over the course of 1 year, a 5-kg (11 lb) or 5% weight loss at 1 year would be expected to result in a 0.4% decrease in HbA_{1c}. This is a modest but clinically significant improvement in diabetes control for a weight loss intervention, which is probably achievable by many people with type 2 diabetes.

In summary, overweight or obese people with type 2 diabetes randomized to a weight loss intervention that combined intermittent low-calorie diets, daily meal replacements, and the medication sibutramine achieved greater decreases in weight, body fat, and HbA_{1c} at 1 year than a similar group of subjects who received a standard weight loss program. The intervention used was simple and easy for subjects to understand and implement. These results suggest that weight loss programs that achieve and maintain even modest degrees of weight loss for at least 1 year can have clinically beneficial effects for overweight or obese people with type 2 diabetes.

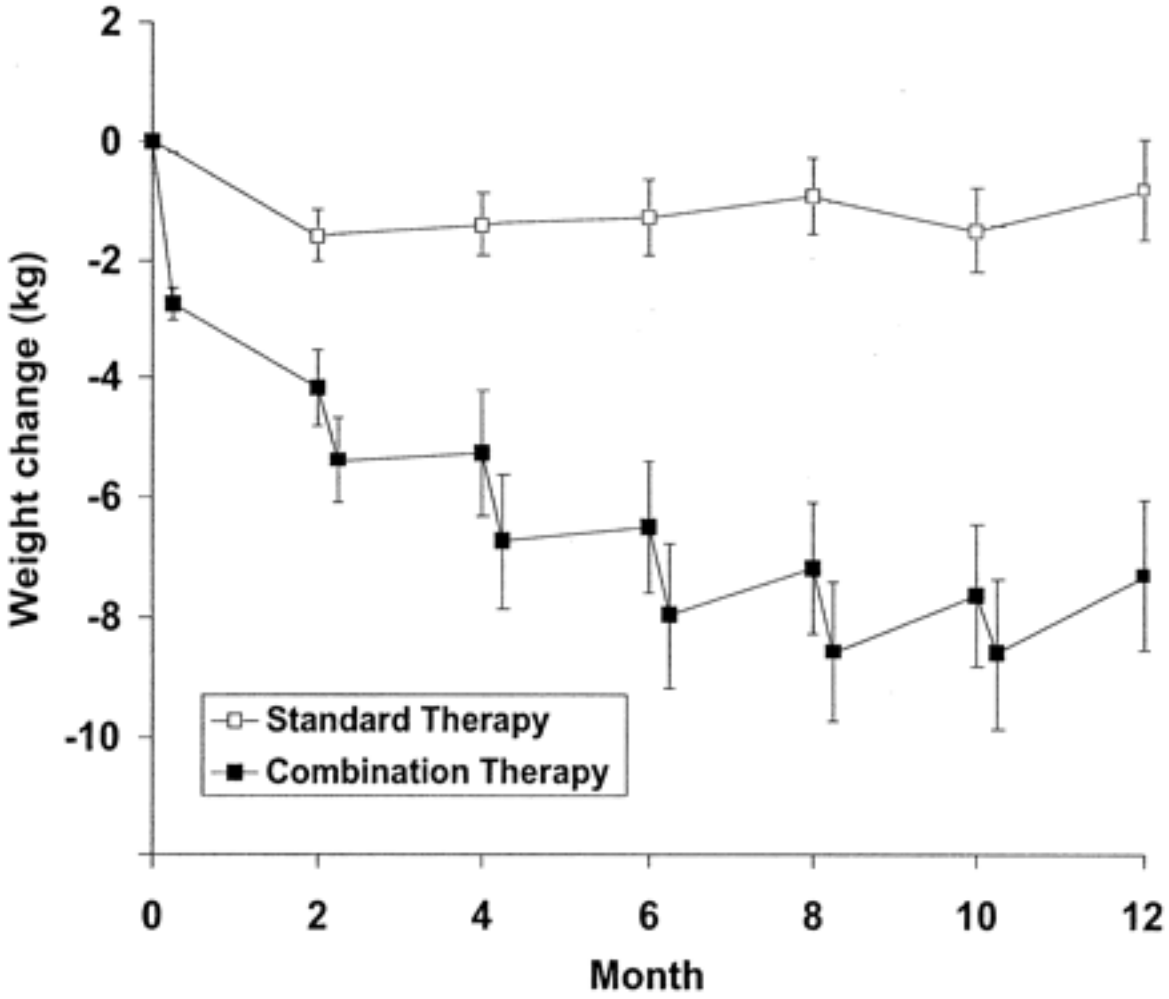

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Figure 1—

Mean ± SEM change in weight from baseline in standard therapy and combination therapy groups.

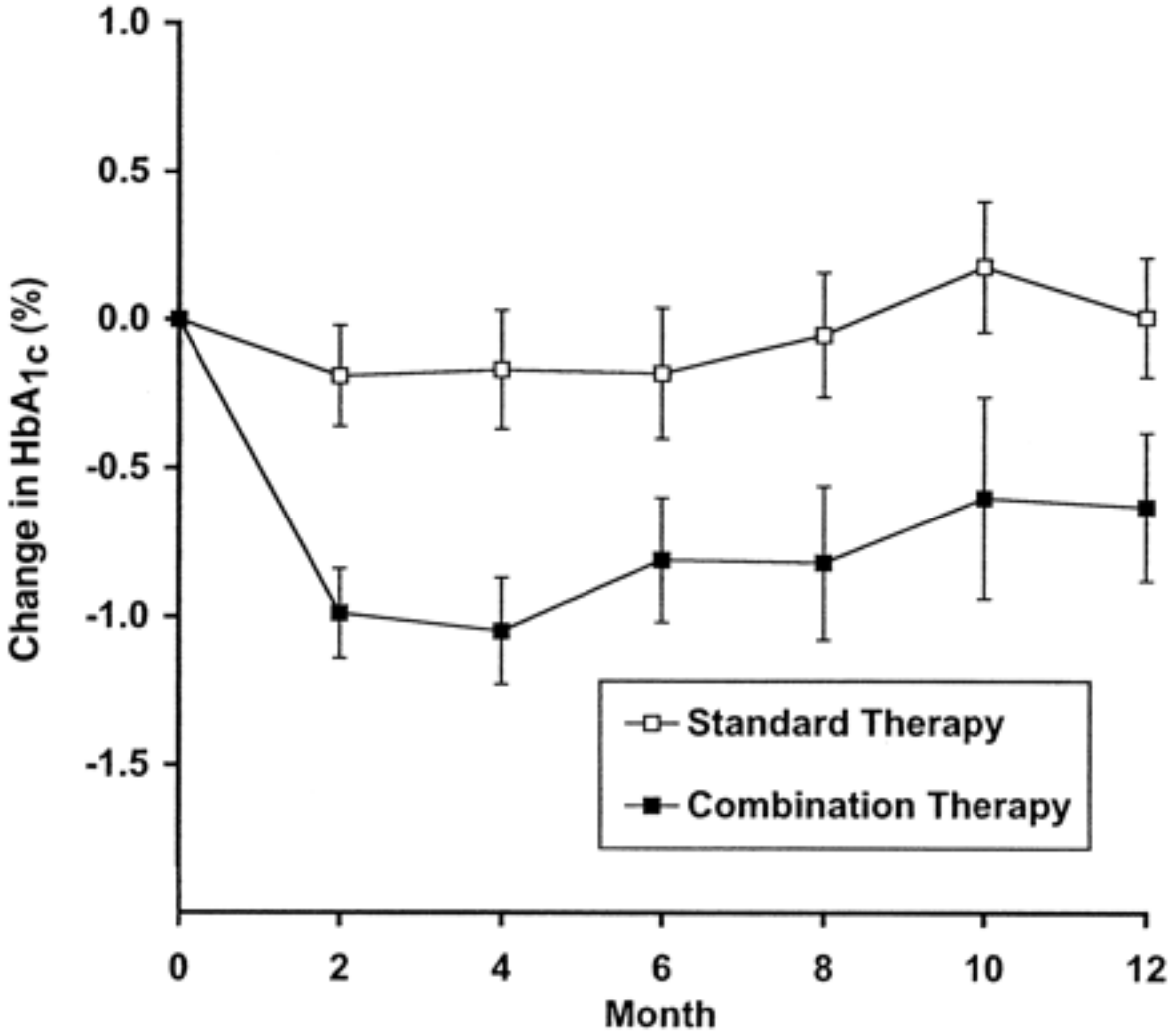

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Figure 2—

Mean ± SEM change in HbA_{1c} from baseline in standard therapy and combination therapy groups.

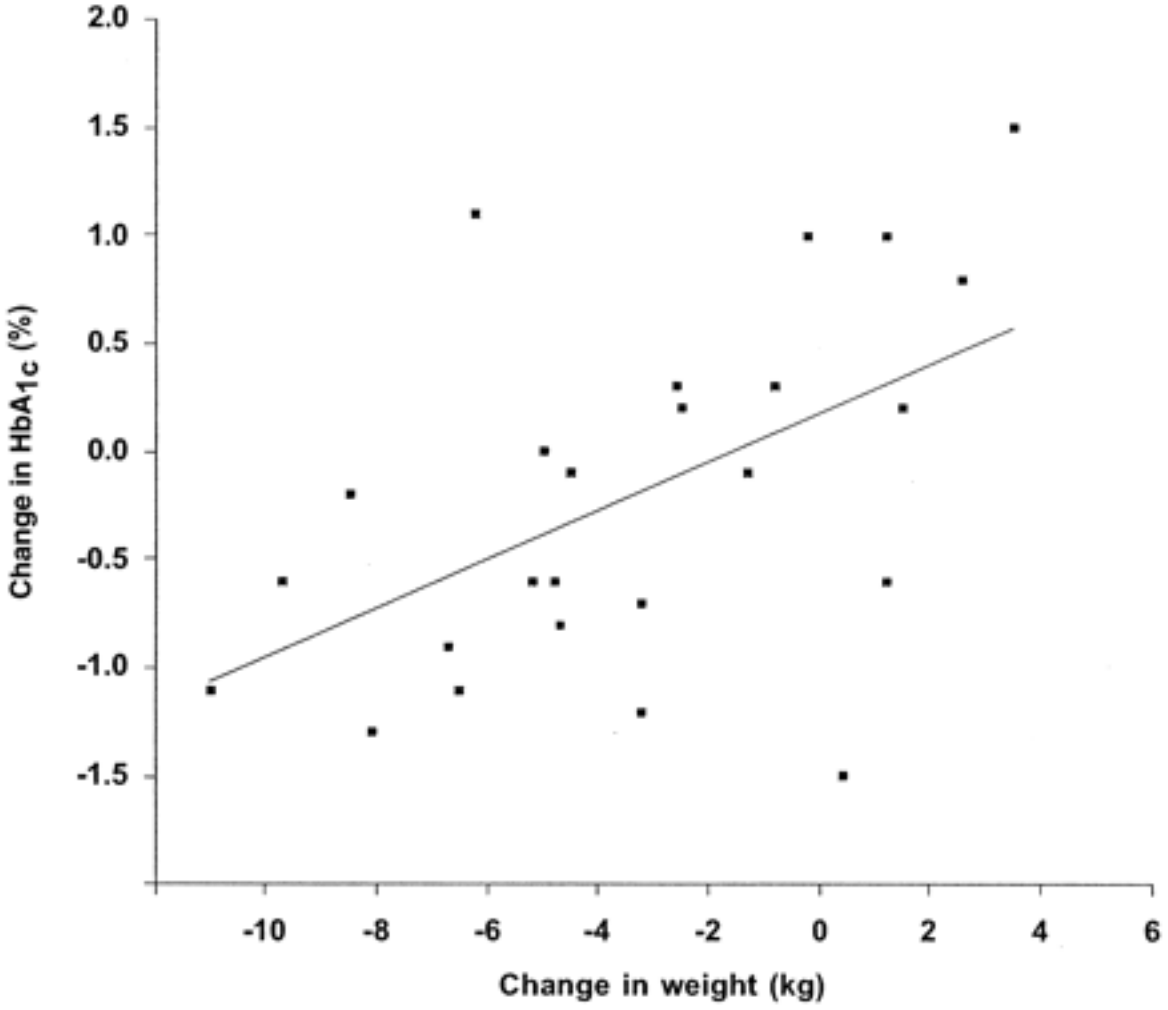

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Figure 3—

Plot of change in weight versus change in HbA_{1c} at 1 year for 25 subjects (10 subjects in the standard therapy group and 15 subjects in the combination therapy group) whose diabetes medications did not change from baseline. The fitted regression equation was (HbA_{1c} change) = 0.11(weight change in kg) + 0.18 (r = 0.53, P = 0.006). One subject was excluded whose weight change was −20 kg and change in HbA_{1c} was −0.8%.

- View inline
- View popup

Table 1—

Baseline demographic and clinical data

- View inline

- View popup

Table 2—
Comparison of endpoints at 1 year expressed as changes from baseline

Acknowledgments

This study was supported by National Institutes of Health Grant M01-RR-00400 from the Division of Research Resources and grants from Abbott Laboratories and Slim Fast Nutrition Institute.

We acknowledge the valuable assistance of the staff of the University of Minnesota General Clinical Research Center.

Footnotes

- The study was designed by the investigators and approved by the sponsors. The conduct of the study, collection of data, analysis of data, interpretation of data, and preparation of the manuscript were solely the responsibility of the investigators.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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- DIABETES CARE

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