The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2008 VOL. 359 NO. 3

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

Iris Shai, R.D., Ph.D., Dan Schwarzfuchs, M.D., Yaakov Henkin, M.D., Danit R. Shahar, R.D., Ph.D., Shula Witkow, R.D., M.P.H., Ilana Greenberg, R.D., M.P.H., Rachel Golan, R.D., M.P.H., Drora Fraser, Ph.D., Arkady Bolotin, Ph.D., Hilel Vardi, M.Sc., Osnat Tangi-Rozental, B.A., Rachel Zuk-Ramot, R.N., Benjamin Sarusi, M.Sc., Dov Brickner, M.D., Ziva Schwartz, M.D., Einat Sheiner, M.D., Rachel Marko, M.Sc., Esther Katorza, M.Sc., Joachim Thiery, M.D., Georg Martin Fiedler, M.D., Matthias Blüher, M.D., Michael Stumvoll, M.D., and Meir J. Stampfer, M.D., Dr.P.H., for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group

ABSTRACT

BACKGROUND

Trials comparing the effectiveness and safety of weight-loss diets are frequently limited by short follow-up times and high dropout rates.

METHODS

In this 2-year trial, we randomly assigned 322 moderately obese subjects (mean age, 52 years; mean body-mass index [the weight in kilograms divided by the square of the height in meters], 31; male sex, 86%) to one of three diets: low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non–restricted-calorie.

RESULTS

The rate of adherence to a study diet was 95.4% at 1 year and 84.6% at 2 years. The Mediterranean-diet group consumed the largest amounts of dietary fiber and had the highest ratio of monounsaturated to saturated fat ($P<0.05$ for all comparisons among treatment groups). The low-carbohydrate group consumed the smallest amount of carbohydrates and the largest amounts of fat, protein, and cholesterol and had the highest percentage of participants with detectable urinary ketones ($P<0.05$ for all comparisons among treatment groups). The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group ($P<0.001$ for the interaction between diet group and time); among the 272 participants who completed the intervention, the mean weight losses were 3.3 kg, 4.6 kg, and 5.5 kg, respectively. The relative reduction in the ratio of total cholesterol to high-density lipoprotein cholesterol was 20% in the low-carbohydrate group and 12% in the low-fat group ($P=0.01$). Among the 36 subjects with diabetes, changes in fasting plasma glucose and insulin levels were more favorable among those assigned to the Mediterranean diet than among those assigned to the low-fat diet ($P<0.001$ for the interaction among diabetes and Mediterranean diet and time with respect to fasting glucose levels).

CONCLUSIONS

Mediterranean and low-carbohydrate diets may be effective alternatives to low-fat diets. The more favorable effects on lipids (with the low-carbohydrate diet) and on glycemic control (with the Mediterranean diet) suggest that personal preferences and metabolic considerations might inform individualized tailoring of dietary interventions. (ClinicalTrials.gov number, NCT00160108.)

From the S. Daniel Abraham Center for Health and Nutrition, Ben-Gurion University of the Negev, Beer-Sheva (I.S., D.R.S., S.W., I.G., R.G., D.F., A.B., H.V., O.T.-R.); the Nuclear Research Center Negev, Dimona (D.S., R.Z.-R., B.S., D.B., Z.S., E.S., R.M., E.K.); and the Department of Cardiology, Soroka University Medical Center, Beer-Sheva (Y.H.) — all in Israel; the Institute of Laboratory Medicine, University Hospital Leipzig (J.T., G.M.F.); and the Department of Medicine, University of Leipzig (M.B., M.S.) — both in Leipzig, Germany; and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and the Departments of Epidemiology and Nutrition, Harvard School of Public Health — all in Boston (M.J.S.). Address reprint requests to Dr. Shai at the S. Daniel Abraham International Center for Health and Nutrition, Department of Epidemiology and Health Systems Evaluation, Ben-Gurion University of the Negev, P.O. Box 653, Beer-Sheva 84105, Israel, or at irish@bgu.ac.il.

This article (10.1056/NEJMoa0708681) was updated on December 30, 2009, at NEJM.org.

N Engl J Med 2008;359:229-41.

The dramatic increase in obesity worldwide remains challenging and underscores the urgent need to test the effectiveness and safety of several widely used weight-loss diets.[1-3] Low-carbohydrate, high-protein, high-fat diets (referred to as low-carbohydrate diets) have been compared with low-fat, energy-restricted diets.[4-9] A meta-analysis of five trials with 447 participants[10] and a recent 1-year trial involving 311 obese women[4] suggested that a low-carbohydrate diet is a feasible alternative to a low-fat diet for producing weight loss and may have favorable metabolic effects. However, longer-term studies are lacking.[4,10] A Mediterranean diet with a moderate amount of fat and a high proportion of monounsaturated fat provides cardiovascular benefits.[11] A recent review citing several trials[12] included a few that suggested that the Mediterranean diet was beneficial for weight loss.[13,14] However, this positive effect has not been conclusively demonstrated.[15]

Common limitations of dietary trials include high attrition rates (15 to 50% within a year), small size, short duration, lack of assessment of adherence, and unequal intensity of intervention.[10,12,15-17] We conducted the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT) to compare the effectiveness and safety of three nutritional protocols: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; and a low-carbohydrate, non–restricted-calorie diet.

METHODS

ELIGIBILITY AND STUDY DESIGN

We conducted the trial between July 2005 and June 2007 in Dimona, Israel, in a workplace at a research center with an on-site medical clinic. Recruitment began in December 2004. The criteria for eligibility were an age of 40 to 65 years and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of at least 27, or the presence of type 2 diabetes (according to the American Diabetes Association criteria[18]) or coronary heart disease, regardless of age and BMI. Persons were excluded if they were pregnant or lactating, had a serum creatinine level of 2 mg per deciliter (177 μmol per liter) or more, had liver dysfunction (an increase by a factor of at least 2 above the upper limit of normal in alanine aminotransferase and aspartate aminotransferase levels), had gastrointestinal problems that would prevent them from following any of the test diets, had active cancer, or were participating in another diet trial.

The participants were randomly assigned within strata of sex, age (below or above the median), BMI (below or above the median), history of coronary heart disease (yes or no), history of type 2 diabetes (yes or no), and current use of statins (none, <1 year, or ≥1 year) with the use of Monte Carlo simulations. The participants received no financial compensation or gifts. The study was approved and monitored by the human subjects committee of Soroka Medical Center and Ben-Gurion University. Each participant provided written informed consent.

The members of each of the three diet groups were assigned to subgroups of 17 to 19 participants, with six subgroups for each group. Each diet group was assigned a registered dietitian who led all six subgroups of that group. The dietitians met with their groups in weeks 1, 3, 5, and 7 and thereafter at 6-week intervals, for a total of 18 sessions of 90 minutes each. We adapted the Israeli version (developed by the Maccabi Health Maintenance Organization) of the diabetes-prevention program[19] and developed additional themes for each diet group (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org). In order to maintain equal intensity of treatment, the workshop format and the quality of the materials were similar among the three diet groups, except for instructions and materials specific to each diet strategy. Six times during the 2-year intervention, another dietitian conducted 10-to-15-minute motivational telephone calls with participants who were having difficulty adhering to the diets and gave a summary of each call to the group dietitian. In addition, a group of spouses received education to strengthen their support of the participants (data not shown).

LOW-FAT DIET

The low-fat, restricted-calorie diet was based on American Heart Association[20] guidelines. We aimed at an energy intake of 1500 kcal per day for women and 1800 kcal per day for men, with 30% of calories from fat, 10% of calories from saturated fat, and an intake of 300 mg of cholesterol per day. The participants were counseled to consume low-fat grains, vegetables, fruits, and legumes and to limit their consumption of additional fats, sweets, and high-fat snacks.

MEDITERRANEAN DIET

The moderate-fat, restricted-calorie, Mediterranean diet was rich in vegetables and low in red meat, with poultry and fish replacing beef and lamb. We restricted energy intake to 1500 kcal per day for women and 1800 kcal per day for men, with a goal of no more than 35% of calories from fat; the main sources of added fat were 30 to 45 g of olive oil and a handful of nuts (five to seven nuts, <20 g) per day. The diet is based on the recommendations of Willett and Skerrett.[21]

LOW-CARBOHYDRATE DIET

The low-carbohydrate, non–restricted-calorie diet aimed to provide 20 g of carbohydrates per day for the 2-month induction phase and immediately after religious holidays, with a gradual increase to a maximum of 120 g per day to maintain the weight loss. The intakes of total calories, protein, and fat were not limited. However, the participants were counseled to choose vegetarian sources of fat and protein and to avoid trans fat. The diet was based on the Atkins diet (see Supplementary Appendix 2).[22]

NUTRITIONAL AND COLOR LABELING OF FOOD IN THE CAFETERIA

Lunch is typically the main meal in Israel. The self-service cafeteria in the workplace provided a varied menu and was the exclusive source of lunch for the participants. A dietitian worked closely with the kitchen staff to adjust specific food items to specific diet groups. Each food item was provided with a label showing the number of calories and the number of grams of carbohydrates, fat, and saturated fat, according to an analysis based on the Israeli nutritional database. Each food item was also labeled with a full circle (indicating "feel free to consume") or a half circle (indicating "consume in moderation"). The labels were color-coded according to diet group and were updated daily (see Supplementary Appendix 2).[23]

ELECTRONIC QUESTIONNAIRES AT BASELINE AND FOLLOW-UP

Adherence to the diets was evaluated by a validated food-frequency questionnaire[24] that included 127 food items and three portion-size pictures for 17 items.[25] A subgroup of participants completed two repeated 24-hour dietary recalls to verify absolute intake (data not shown). We used a validated questionnaire to assess physical activity.[26] At baseline and at 6, 12, and 24 months of follow-up, the questionnaires were self-administered electronically through the workplace intranet. The 15% of participants who requested aid in completing the questionnaires were assisted by the study nurse. The electronic questionnaire helped to ensure completeness of the data by prompting the participant when a question was not answered, and it permitted rapid automated reporting by the group dietitians.

OUTCOMES

The participants were weighed without shoes to the nearest 0.1 kg every month. With the use of a wall-mounted stadiometer, height was measured to the nearest millimeter at baseline for determination of BMI. Waist circumference was measured halfway between the last rib and the iliac crest. Blood pressure was measured every 3 months with the use of an automated system (Datascop Acutor 4) after 5 minutes of rest.

Blood samples were obtained by venipuncture at 8 a.m. after a 12-hour fast at baseline and at 6, 12, and 24 months and were stored at −80°C until an assay for lipids, inflammatory biomarkers, and insulin could be performed. Levels of fasting plasma glucose, glycated hemoglobin, and liver enzymes were measured in fresh samples. The level of glycated hemoglobin was determined with the use of Cobas Integra reagents and equipment. Serum levels of total cholesterol, high-density-lipoprotein (HDL) cholesterol, low-density-lipoprotein (LDL) cholesterol, and triglycerides were determined enzymatically with a Wako R-30 automatic analyzer, with coefficients of variation of 1.3% for cholesterol and 2.1% for triglycerides. Plasma insulin levels were measured with the use of an enzyme immunometric assay (Immulite automated analyzer, Diagnostic Products), with a coefficient of variation of 2.5%. Plasma levels of high-molecular-weight adiponectin were measured by an enzyme-linked immunosorbent assay (ELISA) (AdipoGen or Axxora), with a coefficient of variation of 4.8%. Plasma leptin levels were assessed by ELISA (Mediagnost), with a coefficient of variation of 2.4%. Plasma levels of high-sensitivity C-reactive protein were measured by ELISA (DiaMed), with a coefficient of variation of 1.9%. The clinic and laboratory staff members were unaware of the treatment assignments, and the study coordinators were unaware of all outcome data until the end of the intervention.

STATISTICAL ANALYSIS

For weight loss, the prespecified primary aim was the change in weight from baseline to 24 months. We used the Israeli food database[23] in the analysis of the results of the dietary questionnaires. We analyzed the dietary-composition data and biomarkers with the use of raw unadjusted means, without imputation of missing data. We compared the dietary-intake values between groups at each time point with the use of an analysis of variance in which all pairwise comparisons among the three diet groups were performed with the use of Tukey's Studentized range test. We transformed physical-activity scores into metabolic equivalents per week[27] according to the amount of time spent in various forms of exercise per week, with each activity weighted in terms of its level of intensity. For intention-to-treat analyses, we included all 322 participants and used the most recent values for weight and blood pressure. To evaluate the repeated measurements over time, we used generalized estimating equations for panel data analysis, also known as cross-sectional time-series analysis, with the use of the Stata software XTGEE command; this allowed us to account for the nonindependence of repeated measurements of the same bioindicator in the same participant over time. We used age, sex, time point, and diet group as explanatory variables in our models. To study changes over time and the effects of sex or the presence or absence of diabetes, we added appropriate interaction terms. We assessed the within-person changes from baseline in each diet group with the use of pairwise comparisons. We calculated the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following equation[28]: insulin (U/ml) × fasting glucose (mmol/liter) ÷ 22.5. For a mean (±SD) difference between groups of at least 2±10 kg of weight loss, with 100 participants per group and a type I error of 5%, the power to detect significant differences in weight loss is greater than 90%. We used SPSS software, version 15, and Stata software, version 9, for the statistical analysis.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

The baseline characteristics of the participants are shown in Table 1. The mean age was 52 years and the mean BMI was 31. Most participants (86%) were men. The overall rate of adherence (Fig. 1) was 95.4% at 12 months and 84.6% at 24 months; the 24-month adherence rates were 90.4% in the low-fat group, 85.3% in the Mediterranean-diet group, and 78.0% in the low-carbohydrate group ($P=0.04$ for the comparison among diet groups). During the study, there was little change in usage of medications, and there were no significant differences among groups in the amount of change; four participants initiated and three stopped cholesterol-lowering therapy. Twenty participants initiated blood-pressure treatment, five initiated medications for glycemic control, and one reduced the dosage of medications for glycemic control.

DIETARY INTAKE, ENERGY EXPENDITURE, AND URINARY KETONES

At baseline, there were no significant differences in the composition of the diets consumed by participants assigned to the low-fat, Mediterranean, and low-carbohydrate diets. Daily energy intake, as assessed by the food-frequency questionnaire, decreased significantly at 6, 12, and 24 months in all diet groups as compared with baseline ($P<0.001$); there were no significant differences among the groups in the amount of decrease (Table 2). The low-carbohydrate group had a lower intake of carbohydrates ($P<0.001$) and higher intakes of protein ($P<0.001$), total fat ($P<0.001$), saturated fat ($P<0.001$), and total cholesterol ($P=0.04$) than the other groups. The Mediterranean-diet group had a higher ratio of monounsaturated to saturated fat than the other groups ($P<0.001$) and a higher intake of dietary fiber than the low-carbohydrate group ($P=0.002$). The low-fat group had a lower intake of saturated fat than the low-carbohydrate group ($P=0.02$). The amount of physical activity increased significantly from baseline in all groups, with no significant difference among groups in the amount of increase. The proportion of participants with detectable urinary ketones at 24 months was higher in the low-carbohydrate group (8.3%) than in the low-fat group (4.8%) or the Mediterranean-diet group (2.8%) ($P=0.04$).

WEIGHT LOSS

A phase of maximum weight loss occurred from 1 to 6 months and a maintenance phase from 7 to 24 months. All groups lost weight, but the reductions were greater in the low-carbohydrate and the Mediterranean-diet groups ($P<0.001$ for the inter-

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Low-Fat Diet (N=104)	Mediterranean Diet (N=109)	Low-Carbohydrate Diet (N=109)	All (N=322)
Age — yr	51±7	53±6	52±7	52±7
Male sex — no. (%)	89 (86)	89 (82)	99 (91)	277 (86)
Current smoker — no. (%)	19 (18)	16 (15)	16 (15)	51 (16)
Weight — kg	91.3±12.3	91.1±13.6	91.8±14.3	91.4±13.4
BMI	30.6±3.2	31.2±4.1	30.8±3.5	30.9±3.6
Blood pressure — mm Hg†				
Systolic	129.6±13.2	133.1±14.1	130.8±15.1	131.3±14.5
Diastolic	79.1±9.1	80.6±9.2	79.4±9.1	79.7±9.2
Waist circumference — cm‡	105.3±9.2	106.2±9.1	106.3±9.1	105.9±9.1
Type 2 diabetes — no. (%)	12 (12)	15 (14)	19 (17)	46 (14)
Coronary heart disease — no. (%)	38 (37)	46 (42)	34 (31)	118 (37)
Blood biomarkers				
Serum LDL cholesterol — mg/dl	117.0±35.6	122.8±34.4	117.2±34.5	119.0±34.8
Serum HDL cholesterol — mg/dl	38.6±9.6	39.4±9.4	37.5±8.7	38.5±9.2
Serum triglycerides — mg/dl	156.5±62.4	173.6±67.7	181.7±116.9	170.8±90.0
Serum non-HDL cholesterol — mg/dl	154.2±37.9	163.3±35.8	161.3±36.0	159.6±36.7
Ratio of total cholesterol to HDL cholesterol	5.2±1.4	5.4±1.6	5.6±1.7	5.4±1.6
Fasting plasma insulin — μU/ml	13.3±6.8	14.6±8.0	14.1±10.2	14.0±8.5
Fasting plasma glucose — mg/dl	86.9±26.0	94.3±38.1	92.6±28.5	91.3±31.5
HOMA-IR	2.9±1.8	3.6±2.9	3.2±2.9	3.2±2.6
Plasma high-sensitivity C-reactive protein — mg/liter	3.6±2.9	4.6±3.4	4.5±3.3	4.2±3.2
Plasma high-molecular-weight adiponectin — mg/dl	7.3±2.6	7.3±2.8	7.3±3.1	7.3±2.8
Plasma leptin — mg/dl	12.0±9.6	14.2±13.2	11.2±8.1	12.5±10.5
Plasma bilirubin — mg/dl	0.74±0.34	0.79±0.35	0.77±0.36	0.77±0.34
Plasma alkaline phosphatase — U/liter	71.4±18.0	74.2±20.1	71.6±17.7	72.4±18.6
Plasma alanine aminotransferase — U/liter	28.2±14.2	27.7±12.6	28.3±11.2	28.1±12.7
Medications in current use				
Lipid-lowering therapy — no. (%)	28 (27)	29 (27)	27 (25)	84 (26)
Antihypertensive therapy — no. (%)	23 (22)	37 (34)	36 (33)	96 (30)
Hormone-replacement therapy — no. (%)	0	3 (3)	4 (4)	7 (2)
Oral glycemic-control medications — no. (%)	6 (6)	7 (6)	13 (12)	26 (8)
Insulin treatment — no. (%)	2 (2)	0	2 (2)	4 (1)

* Plus–minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for bilirubin to micromoles per liter, multiply by 17.1. BMI denotes body-mass index, HDL high-density lipoprotein, HOMA-IR homeostasis model assessment of insulin resistance, and LDL low-density lipoprotein.
† Data were available from 297 participants.
‡ Data were available from 302 participants.

action between diet group and time) than in the low-fat group (Fig. 2). The overall weight changes among the 322 participants at 24 months were –2.9±4.2 kg for the low-fat group, –4.4±6.0 kg for the Mediterranean-diet group, and –4.7±6.5 kg for the low-carbohydrate group. Among the 277 male participants, the mean 24-month weight changes were –3.4 kg (95% confidence interval [CI], –4.3 to –2.5) for the low-fat group, –4.0 kg (95% CI, –5.1 to –3.0) for the Mediterranean-diet

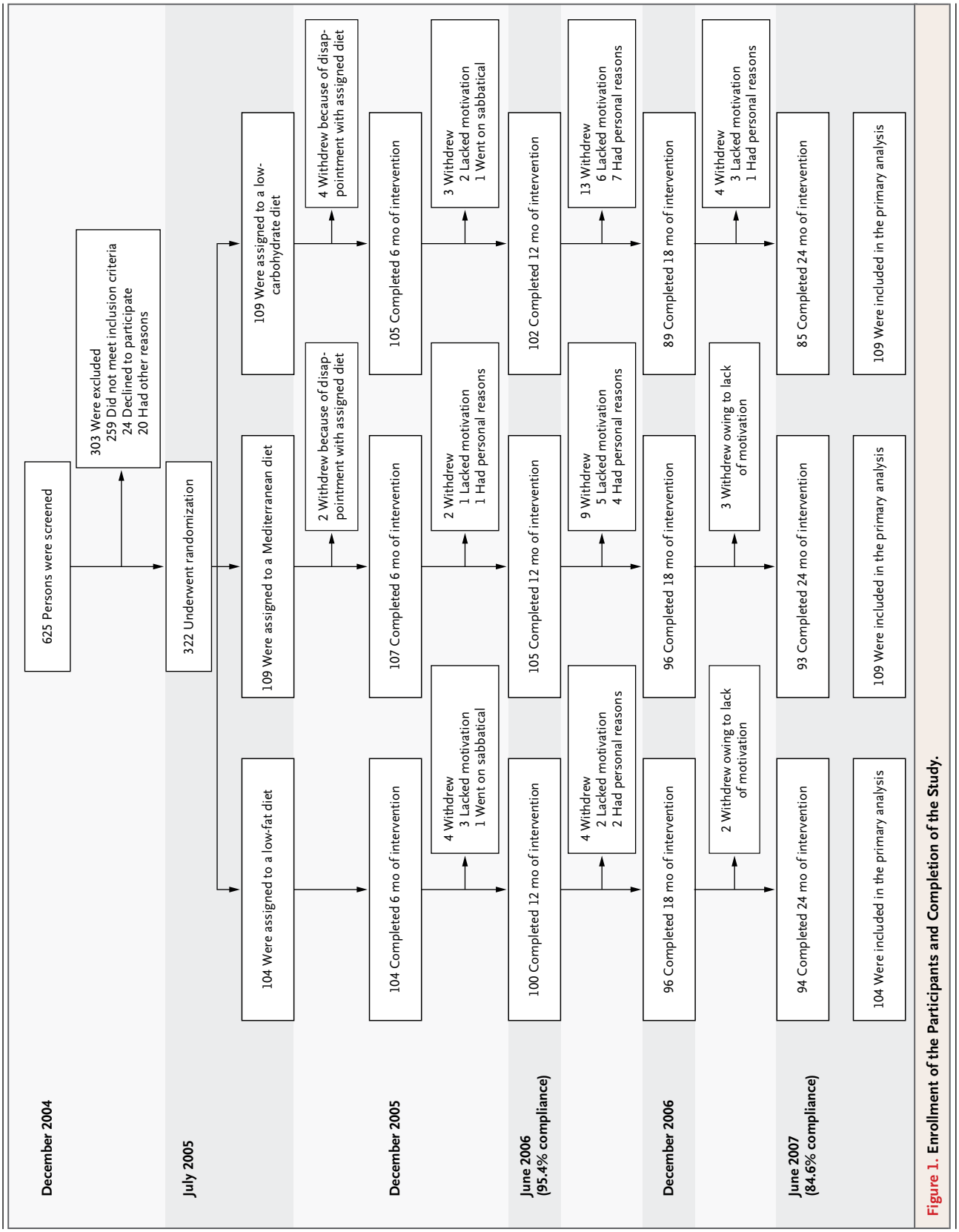

Figure 1. Enrollment of the Participants and Completion of the Study.

group, and −4.9 kg (95% CI, −6.2 to −3.6) for the low-carbohydrate group. Among the 45 women, the mean 24-month weight changes were −0.1 kg (95% CI, −2.2 to 1.9) for the low-fat group, −6.2 kg (95% CI, −10.2 to −1.9) for the Mediterranean-diet group, and −2.4 kg (95% CI, −6.9 to 2.2) for the low-carbohydrate group (P<0.001 for the interaction between diet group and sex). The mean weight changes among the 272 participants who completed 24 months of intervention were −3.3±4.1 kg in the low-fat group, −4.6±6.0 kg in the Mediterranean-diet group, and −5.5±7.0 kg in the low-carbohydrate group (P=0.03 for the comparison between the low-fat and the low-carbohydrate groups at 24 months). The mean (±SD) changes in BMI were −1.0±1.4 in the low-fat group, −1.5±2.2 in the Mediterranean-diet group, and −1.5±2.1 in the low-carbohydrate group (P=0.05 for the comparison among groups).

All groups had significant decreases in waist circumference and blood pressure, but the differences among the groups were not significant. The waist circumference decreased by a mean of 2.8±4.3 cm in the low-fat group, 3.5±5.1 cm in the Mediterranean-diet group, and 3.8±5.2 cm in the low-carbohydrate group (P=0.33 for the comparison among groups). Systolic blood pressure fell by 4.3±11.8 mm Hg in the low-fat group, 5.5±14.3 mm Hg in the Mediterranean-diet group, and 3.9±12.8 mm Hg in the low-carbohydrate group (P=0.64 for the comparison among groups). The corresponding decreases in diastolic pressure were 0.9±8.1, 2.2±9.5, and 0.8±8.7 mm Hg (P=0.43 for the comparison among groups).

LIPID PROFILES

Changes in lipid profiles during the weight-loss and maintenance phases are shown in Figure 3. HDL cholesterol (Fig. 3A) increased during the weight-loss and maintenance phases in all groups, with the greatest increase in the low-carbohydrate group (8.4 mg per deciliter [0.22 mmol per liter], P<0.01 for the interaction between diet group and time), as compared with the low-fat group (6.3 mg per deciliter [0.16 mmol per liter]). Triglyceride levels (Fig. 3B) decreased significantly in the low-carbohydrate group (23.7 mg per deciliter [0.27 mmol per liter], P=0.03 for the interaction between diet group and time), as compared with the low-fat group (2.7 mg per deciliter [0.03 mmol per liter]). LDL cholesterol levels (Fig. 3C) did not change significantly within groups, and there were no significant differences between the groups in the amount of change. Overall, the ratio of total cholesterol to HDL cholesterol (Fig. 3D) decreased during both the weight-loss and the maintenance phases. The low-carbohydrate group had the greatest improvement, with a relative decrease of 20% (P=0.01 for the interaction between diet group and time), as compared with a decrease of 12% in the low-fat group.

HIGH-SENSITIVITY C-REACTIVE PROTEIN, HIGH-MOLECULAR-WEIGHT ADIPONECTIN, AND LEPTIN

The level of high-sensitivity C-reactive protein decreased significantly (P<0.05) only in the Mediterranean-diet group (21%) and the low-carbohydrate group (29%), during both the weight-loss and the maintenance phases, with no significant differences among the groups in the amount of decrease (Fig. 4A). During both the weight-loss and the maintenance phases, the level of high-molecular-weight adiponectin (Fig. 4B) increased significantly (P<0.05) in all diet groups, with no significant differences among the groups in the amount of increase. Circulating leptin, which reflects body-fat mass, decreased significantly (P<0.05) in all diet groups, with no significant differences among the groups in the amount of decrease; the decrease in leptin paralleled the decrease in body weight during the two phases (Fig. 4C). The interaction between the effects of low-carbohydrate diet and sex on the reduction of leptin (P=0.04), as compared with the low-fat diet, reflects the greater effect of the low-carbohydrate diet among men.

FASTING PLASMA GLUCOSE, HOMA-IR, AND GLYCATED HEMOGLOBIN

Among the 36 participants with diabetes (Fig. 4D), only those in the Mediterranean-diet group had a decrease in fasting plasma glucose levels (32.8 mg per deciliter); this change was significantly different from the increase in plasma glucose levels among participants with diabetes in the low-fat group (P<0.001 for the interaction between diet group and time). There was no significant change in plasma glucose level among the participants without diabetes (P<0.001 for the interaction among diabetes and Mediterranean diet and time). In contrast, insulin levels (Fig. 4E) decreased significantly in participants with diabetes and in those without diabetes in all diet groups, with no significant differences among groups in the

amount of decrease. Among the participants with diabetes, the decrease in HOMA-IR at 24 months (Fig. 4F) was significantly greater in those assigned to the Mediterranean diet than in those assigned to the low-fat diet (2.3 and 0.3, respectively; P=0.02; P=0.04 for the interaction among diabetes and Mediterranean diet and time). Among the participants with diabetes, the proportion of glycated hemoglobin at 24 months decreased by 0.4±1.3% in the low-fat group, 0.5±1.1% in the Mediterranean-diet group, and 0.9±0.8% in the low-carbohydrate group. The changes were signifi-

Table 2. Changes in Dietary Intake, Energy Expenditure, and Urinary Ketones during 2 Years of Intervention.*

Variable	Low-Fat Diet	Mediterranean Diet	Low-Carbohydrate Diet	P Value†
Energy change from baseline (kcal/day)				
6 mo	−458.3±1412.9	−254.6±740.6	−560.8±1568.3	0.22
12 mo	−559.1±1764.8	−321.7±802.4	−591.1±1472.9	0.33
24 mo	−572.6±1638.0	−371.9±864.2	−550.0±1453.9	0.55
Carbohydrate				
% of energy				
Baseline	51.8±8.1	51.5±8.3	50.8±8.4	0.63
6 mo	50.4±6.9	49.8±8.0	41.4±9.3‡	<0.001
12 mo	50.5±6.8	50.0±7.7	41.6±8.8‡	<0.001
24 mo	50.7±5.7	50.2±8.6	40.4±7.1‡	<0.001
Change from baseline (g/day)				
6 mo	−69.1±191.7	−39.6±98.1	−123.6±223.5‡	0.003
12 mo	−83.4±215.8	−49.0±112.3	−127.7±216.3‡	0.01
24 mo	−82.8±202.0	−50.5±126.1	−129.8±212.6‡	0.02
Protein				
% of energy				
Baseline	18.2±3.3	18.4±3.8	18.7±3.8	0.61
6 mo	19.6±3.7	18.9±3.6	21.6±3.5‡	<0.001
12 mo	19.4±3.4	18.9±3.6	21.5±4.0‡	<0.001
24 mo	19.0±3.2	18.8±3.5	21.8±3.9‡	<0.001
Change from baseline (g/day)				
6 mo	−12.8±58.7	−10.2±47.7	−10.2±69.7	0.99
12 mo	−16.7±84.9	−12.2±47.6	−11.8±69.3	0.86
24 mo	−19.8±75.0	−17.5±48.1	−6.9±66.6	0.38
Total fat				
% of energy				
Baseline	31.4±4.7	31.7±4.9	32.1±5.5	0.65
6 mo	30.7±4.0	33.2±5.1	38.8±6.9‡	<0.001
12 mo	30.8±4.2	32.9±5.1	38.5±6.5‡	<0.001
24 mo	30.0±3.9	33.1±5.5	39.1±5.5§	<0.001
Change from baseline (g/day)				
6 mo	−14.7±55.6	−5.8±30.8	−3.6±58.2	0.23
12 mo	−18.0±68.1	−8.3±33.1	−4.8±57.7	0.21
24 mo	−18.9±66.4	−10.5±33.2	−1.7±51.2	0.10

Table 2. (Continued.)

Variable	Low-Fat Diet	Mediterranean Diet	Low-Carbohydrate Diet	P Value†
Saturated fat				
% of energy				
Baseline	9.7±2.4	9.7±2.4	9.9±2.3	0.84
6 mo	9.6±1.9	9.7±2.5	12.2±3.9‡	<0.001
12 mo	9.8±2.1	9.6±2.1	12.5±3.8‡	<0.001
24 mo	9.6±1.8	9.6±2.2	12.3±3.2‡	<0.001
Change from baseline (g/day)				
6 mo	−4.8±17.0	−3.0±11.4	0.28±18.7	0.07
12 mo	−5.3±21.3	−3.8±11.5	0.78±19.5§	0.04
24 mo	−6.2±21.4	−4.6±11.3	0.56±15.7§	0.02
Change in monounsaturated:saturated fat ratio from baseline				
6 mo	0.00±0.18	0.09±0.21¶	−0.02±0.23	0.001
12 mo	−0.02±0.18	0.08±0.19¶	−0.05±0.22	<0.001
24 mo	0.02±0.21	0.11±0.20¶	−0.01±0.21	<0.001
Change in dietary cholesterol from baseline (mg/day)				
6 mo	−71.8±312.2	−66.7±243.4	11.7±283.2	0.06
12 mo	−87.4±377.0	−78.8±239.8	1.76±325.3	0.09
24 mo	−94.2±373.5	−94.6±254.6	6.51±262.9‡	0.04
Change in dietary fiber from baseline (g/day)				
6 mo	−2.3±17.4	1.2±12.6	−7.4±22.0‖	0.002
12 mo	−4.3±19.0	0.22±12.9	−8.3±21.6‖	0.004
24 mo	−4.7±18.8	0.29±13.8	−10.0±21.7‖	0.002
Level of physical activity (MET/wk)				
Baseline	15.8±22.6	11.3±15.7	14.0±29.4	0.37
6 mo	17.5±23.1	14.2±19.3	18.7±32.0	0.41
12 mo	20.0±23.6	16.1±18.0	18.8±32.5	0.55
24 mo	21.4±26.7	15.6±18.9	16.3±18.9	0.18
Detectable urinary ketone bodies (% of participants)				
Baseline	2.9	1.8	4.6	0.10
24 mo	4.8	2.8	8.3	0.04

* Plus–minus values are means ±SD.

† P values for differences among the three diet groups were calculated by analysis of variance, except for urinary ketone values, for which the chi-square test was used. When the difference among the groups was significant (P<0.05), all pairwise comparisons between groups were tested for significance with the use of Tukey's Studentized range test. The Mediterranean-diet group consumed the largest amounts of dietary fiber and had the highest ratio of monounsaturated to saturated fat (P<0.05 for all comparisons among treatment groups). The low-carbohydrate group consumed the smallest amount of carbohydrates and the largest amounts of fat, protein, and cholesterol; the percentage of participants with detectable urinary ketones was also highest in this group (P<0.05 for all comparisons among treatment groups). The amount of decrease in intake of calories was similar among the diet groups.

‡ The value for the low-carbohydrate group is significantly different from the value for the low-fat group or the Mediterranean-diet group (P<0.05).

§ The value for the low-carbohydrate group is significantly different from the value for the low-fat group (P<0.05).

¶ The value for the Mediterranean-diet group is significantly different from the value for the low-fat group or the low-carbohydrate group (P<0.05).

‖ The value for the low-carbohydrate group is significantly different from the value for the Mediterranean-diet group (P<0.05).

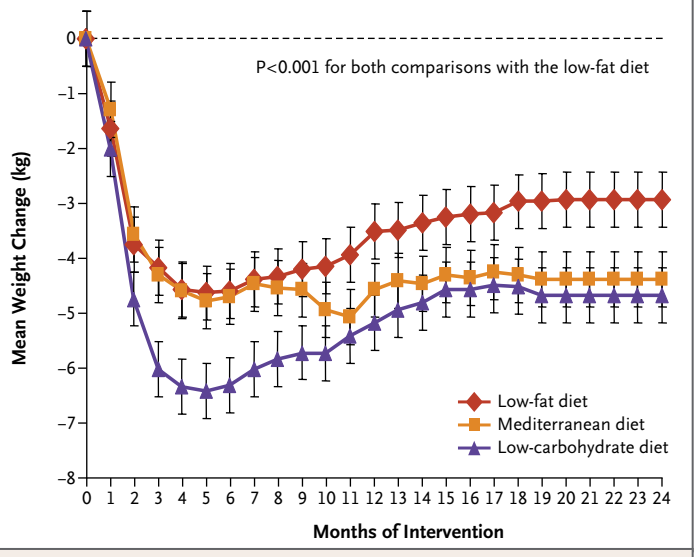

Figure 2. Weight Changes during 2 Years According to Diet Group.
Vertical bars indicate standard errors. To statistically evaluate the changes in weight measurements over time, generalized estimating equations were used, with the low-fat group as the reference group. The explanatory variables were age, sex, time point, and diet group.

cant ($P<0.05$) only in the low-carbohydrate group ($P=0.45$ for the comparison among groups).

LIVER-FUNCTION TESTS

Changes in bilirubin, alkaline phosphatase, and alanine aminotransferase levels were similar among the diet groups. Alanine aminotransferase levels were significantly reduced from baseline to 24 months in the Mediterranean-diet and the low-carbohydrate groups (reductions of 3.4±11.0 and 2.6±8.6 units per liter, respectively; $P<0.05$ for the comparison with baseline in both groups).

DISCUSSION

In this 2-year dietary-intervention study, we found that the Mediterranean and low-carbohydrate diets are effective alternatives to the low-fat diet for weight loss and appear to be just as safe as the low-fat diet. In addition to producing weight loss in this moderately obese group of participants, the low-carbohydrate and Mediterranean diets had some beneficial metabolic effects, a result suggesting that these dietary strategies might be considered in clinical practice and that diets might be individualized according to personal preferences and metabolic needs. The similar caloric deficit achieved in all diet groups suggests that a low-carbohydrate, non–restricted-calorie diet may be optimal for those who will not follow a restricted-calorie dietary regimen. The increasing improvement in levels of some biomarkers over time up to the 24-month point, despite the achievement of maximum weight loss by 6 months, suggests that a diet with a healthful composition has benefits beyond weight reduction.

The present study has several limitations. We enrolled few women; however, we observed a significant interaction between the effects of diet group and sex on weight loss (women tended to lose more weight on the Mediterranean diet), and this difference between men and women was also reflected in the changes in leptin levels. This possible sex-specific difference should be explored in further studies. The data from the few participants with diabetes are of interest, but we recognize that measurement of HOMA-IR is not an optimal method to assess insulin resistance among persons with diabetes. We relied on self-reported dietary intake, but we validated the dietary assessment in two different dietary-assessment tools and used electronic questionnaires to minimize the amount of missing data. Finally, one might argue that the unique nature of the workplace in this study, which permitted a closely monitored dietary intervention for a period of 2 years, makes it difficult to generalize the results to other free-living populations. However, we believe that similar strategies to maintain adherence could be applied elsewhere.

The strengths of the study include the one-phase design, in which all participants started simultaneously; the relatively long duration of the study; the large study-group size; and the high rate of adherence. The monthly measurements of weight permitted a better understanding of the weight-loss trajectory than was the case in previous studies.

We observed two phases of weight change: initial weight loss and weight maintenance. The maximum weight reduction was achieved during the first 6 months; this period was followed by the maintenance phase of partial rebound and a plateau. Among all diet groups, weight loss was greater for those who completed the 24-month study than for those who did not. Even moderate weight loss has health benefits, and our findings suggest benefits of behavioral approaches that yield weight losses similar to those obtained with pharmacotherapy.[29]

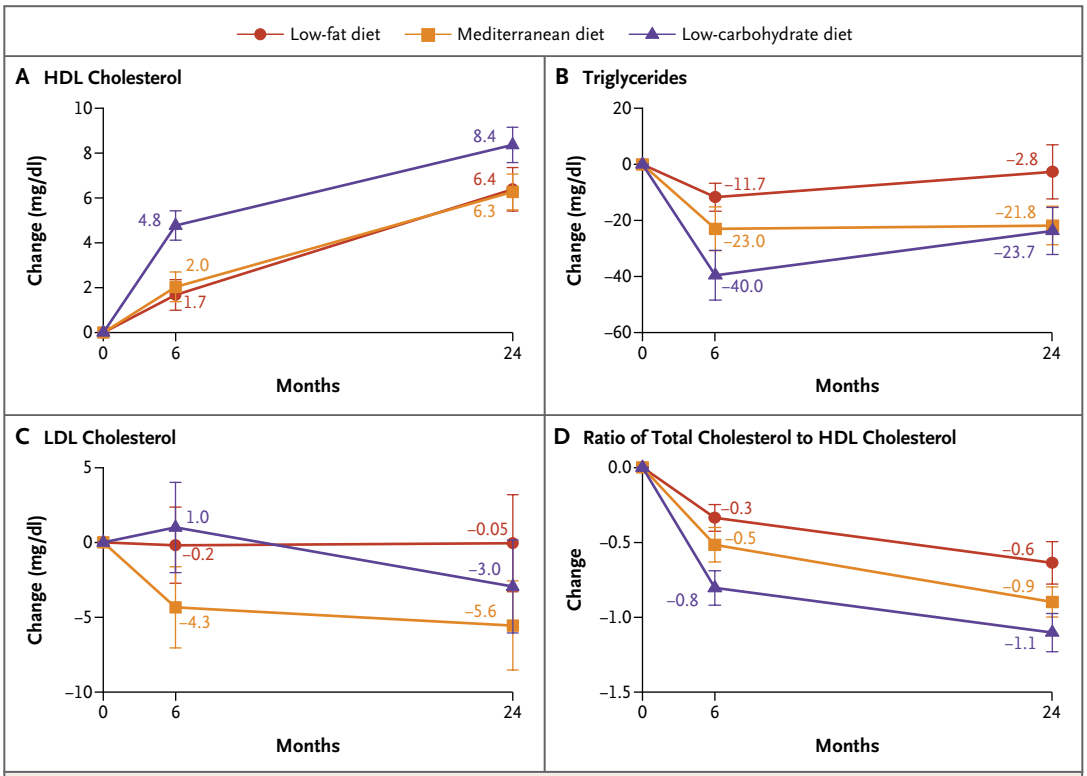

Figure 3. Changes in Cholesterol and Triglyceride Biomarkers According to Diet Group during the Maximum Weight-Loss Phase (1 to 6 Months) and the Weight-Loss Maintenance Phase (7 to 24 Months) of the 2-Year Intervention.

Panel A shows the results for serum high-density lipoprotein (HDL) cholesterol, Panel B for serum triglycerides, Panel C for serum low-density lipoprotein (LDL) cholesterol, and Panel D for the ratio of total cholesterol to HDL cholesterol. Vertical bars indicate standard deviations. To statistically evaluate the changes in weight measurements over time, generalized estimating equations were used, with the low-fat group as the reference group. The explanatory variables were age, sex, time point, and diet group. Results are presented for the 82% of the study population (263 participants) with blood-sample data at all time points (90 in the low-fat group, 92 in the Mediterranean-diet group, and 81 in the low-carbohydrate group). The P values for the comparison between the low-fat group and the Mediterranean-diet group are 0.94 for HDL cholesterol, 0.21 for triglycerides, 0.41 for LDL cholesterol, and 0.23 for the ratio of total cholesterol to HDL cholesterol. The P values for the comparison between the low-fat group and the low-carbohydrate group are 0.01 for HDL cholesterol, 0.03 for triglycerides, 0.94 for LDL cholesterol, and 0.01 for the ratio of total cholesterol to HDL cholesterol. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

We distinguished between changes in levels of biomarkers (leptin, adiponectin, and high-sensitivity C-reactive protein) that are apparently related to loss of adipose tissue and changes in biomarkers (triglycerides, HDL cholesterol, glucose, and insulin) that apparently reflect, in part, the effects of specific diet composition. The changes we observed in levels of adiponectin and leptin,[30] which were consistent in all groups, reflect loss of weight. Consumption of monounsaturated fats is thought to improve insulin sensitivity,[14,31,32] an effect that may explain the favorable effect of the Mediterranean diet on glucose and insulin levels. The results imply that dietary composition modifies metabolic biomarkers in addition to leading to weight loss. Our results suggest that health care professionals might consider more than one dietary approach, according to individual preferences and metabolic needs, as long as the effort is sustained.

This trial also suggests a model that might be applied more broadly in the workplace. As Okie recently suggested,[33] using the employer as a health coach could be a cost-effective way to improve health. The model of intervention with the use of dietary group sessions, spousal sup-

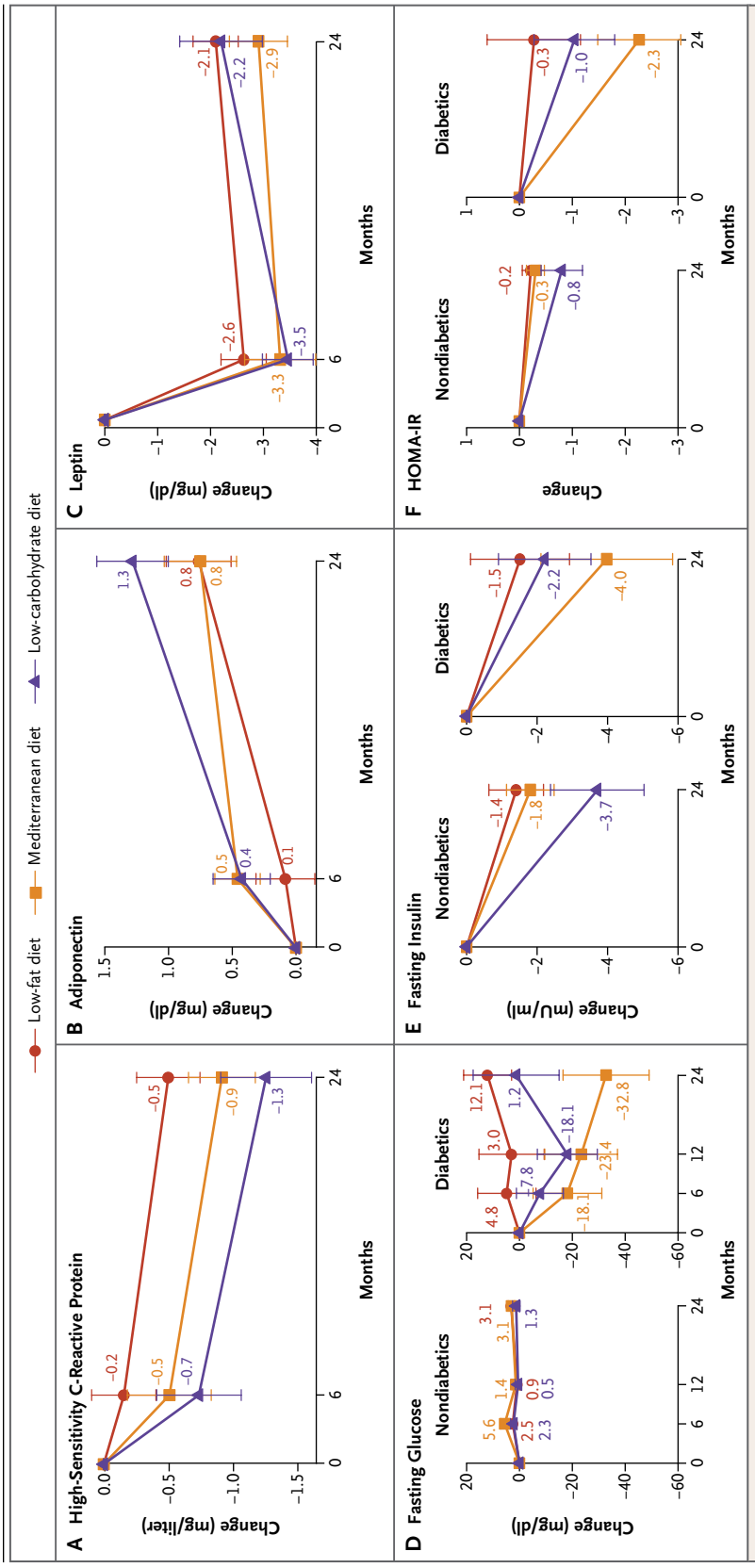

Figure 4. Changes in Biomarkers According to Diet Group and Presence or Absence of Type 2 Diabetes.

Panel A shows the results for plasma high-sensitivity C-reactive protein, Panel B for plasma adiponectin, Panel C for plasma leptin, Panel D for fasting plasma glucose, Panel E for fasting plasma insulin, and Panel F for the homeostasis model assessment of insulin resistance (HOMA-IR). Vertical bars indicate standard deviations. To statistically evaluate the response of weight measurements over time, generalized estimating equations were used, with the low-fat group as the reference group. The explanatory variables were age, sex, time point, and diet group. Data were available for 36 participants with type 2 diabetes: 11 in the low-fat group, 13 in the Mediterranean-diet group, and 12 in the low-carbohydrate group. The P values for the comparison between the low-fat group and the Mediterranean-diet group are 0.49 for high-sensitivity C-reactive protein, 0.50 for adiponectin, 0.54 for leptin, <0.001 for fasting glucose, 0.78 for fasting insulin, and 0.04 for HOMA-IR. The P values for the comparison between the low-fat group and the low-carbohydrate group are 0.12 for high-sensitivity C-reactive protein, 0.32 for adiponectin, 0.47 for leptin, 0.12 for fasting glucose, 0.20 for fasting insulin, and 0.27 for HOMA-IR. The P values for the interaction among diabetes and Mediterranean diet and time are <0.001 for fasting glucose and 0.04 for HOMA-IR. To convert values for glucose to millimoles per liter, multiply by 0.05551.

port, food labels, and monthly weighing in the workplace within the framework of a health promotion campaign might yield weight reduction and long-term health benefits.

Supported by the Nuclear Research Center Negev (NRCN), the Dr. Robert C. and Veronica Atkins Research Foundation, and the S. Daniel Abraham International Center for Health and Nutrition, Ben-Gurion University, Israel.

No potential conflict of interest relevant to this article was reported.

We thank the 322 participants in the Dietary Intervention Randomized Controlled Trial (DIRECT) for their consistent cooperation, as well as the consultants and health care providers (Yitzhak Gurevitz, Hassia Krakauer, Meir Yoseffi, Meyer Aviv, Ilanit Asulin, Zvi Zur, Sapir Medikar, Haim Strasler, Avraham Shlonsky, Dr. Abby Bloch, and Dr. Ayala Canfi), the workplace cafeteria managers (Naftali Tal, Yitzchak Chen, Yair Tubul, and the Norcate Company), the adviser researchers (Drs. Ofra Paz-Tal, Assaf Rudich, Amir Tirosh, Ilana Harman-Bohem, and Ronit Andvelt), and the members of the DIRECT steering committee (Prof. Shimon Weitzman, Prof. Uri Goldbourt, and Prof. Eran Leitersdorf) for their invaluable contributions.

REFERENCES

1. Obesity: preventing and managing the global epidemic: report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1-253.

2. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA 1994;272:205-11.

3. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898-918.

4. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 2007;297:969-77. [Erratum, JAMA 2007;298:178.]

5. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003;88:1617-23.

6. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082-90.

7. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778-85.

8. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004;140:769-77.

9. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293:43-53.

10. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:285-93. [Erratum, Arch Intern Med 2006;166:932.]

11. Covas MI, Nyyssönen K, Poulsen HE, et al. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. Ann Intern Med 2006;145:333-41.

12. Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean diet: a systematic review. Nutr Rev 2006;64:Suppl 1:S27-S47.

13. McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. Int J Obes Relat Metab Disord 2001;25:1503-11.

14. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440-6.

15. Malik VS, Hu FB. Popular weight-loss diets: from evidence to practice. Nat Clin Pract Cardiovasc Med 2007;4:34-41.

16. Dansinger ML, Tatsioni A, Wong JB, Chung M, Balk EM. Meta-analysis: the effect of dietary counseling for weight loss. Ann Intern Med 2007;147:41-50.

17. Thomas H. Obesity prevention programs for children and youth: why are their results so modest? Health Educ Res 2006;21:783-95.

18. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.

19. Mayer-Davis EJ, Sparks KC, Hirst K, et al. Dietary intake in the Diabetes Prevention Program cohort: baseline and 1-year post randomization. Ann Epidemiol 2004;14:763-72.

20. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000;102:2284-99.

21. Willett WC, Skerrett PJ. Eat, drink, and be healthy: The Harvard Medical School guide to healthy eating. New York: Simon & Schuster, 2001.

22. Atkins RC. Dr. Atkins' new diet revolution. New York: Avon, 2002.

23. Shai I, Vardi H, Shahar DR, Azrad BA, Fraser D. Adaptation of international nutrition databases and data-entry system tools to a specific population. Public Health Nutr 2003;6:401-6.

24. Shai I, Rosner BA, Shahar DR, et al. Dietary evaluation and attenuation of relative risk: multiple comparisons between blood and urinary biomarkers, food frequency, and 24-hour recall questionnaires: the DEARR study. J Nutr 2005;135:573-9.

25. Shai I, Shahar DR, Vardi H, Fraser D. Selection of food items for inclusion in a newly developed food-frequency questionnaire. Public Health Nutr 2004;7:745-9.

26. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81-6.

27. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:9 Suppl:S498-S504.

28. Haffner SM, Miettinen H, Stem MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1997;20:1087-92.

29. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007;335:1194-9.

30. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006;17:4-12.

31. Schwenke DC. Insulin resistance, low-fat diets, and low-carbohydrate diets: time to test new menus. Curr Opin Lipidol 2005;16:55-60.

32. Lara-Castro C, Garvey WT. Diet, insulin resistance, and obesity: zoning in on data for Atkins dieters living in South Beach. J Clin Endocrinol Metab 2004;89:4197-205.

33. Okie S. The employer as health coach. N Engl J Med 2007;357:1465-9.