Weight Loss, Glycemic Control, and Cardiovascular Disease Risk Factors in Response to Differential Diet Composition in a Weight Loss Program in Type 2 Diabetes: A Randomized Controlled Trial

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OBJECTIVE

To test whether a weight loss program promotes greater weight loss, glycemic control, and improved cardiovascular disease risk factors compared with control conditions and whether there is a differential response to higher versus lower carbohydrate intake.

RESEARCH DESIGN AND METHODS

This randomized controlled trial at two university medical centers enrolled 227 overweight or obese adults with type 2 diabetes and assigned them to parallel in-person diet and exercise counseling, with prepackaged foods in a planned menu during the initial phase, or to usual care (UC; two weight loss counseling sessions and monthly contacts).

RESULTS

Relative weight loss was 7.4% (95% CI 5.7–9.2%), 9.0% (7.1–10.9%), and 2.5% (1.3–3.8%) for the lower fat, lower carbohydrate, and UC groups ($P < 0.001$ intervention effect). Glycemic control markers and triglyceride levels were lower in the intervention groups compared with UC group at 1 year (fasting glucose 141 [95% CI 133–149] vs. 159 [144–174] mg/dL, $P = 0.023$; hemoglobin A_{1c} 6.9% [6.6–7.1%] vs. 7.5% [7.1–7.9%] or 52 [49–54] vs. 58 [54–63] mmol/mol, $P = 0.001$; triglycerides 148 [134–163] vs. 204 [173–234] mg/dL, $P < 0.001$). The lower versus higher carbohydrate groups maintained lower hemoglobin A_{1c} (6.6% [95% CI 6.3–6.8%] vs. 7.2% [6.8–7.5%] or 49 [45–51] vs. 55 [51–58] mmol/mol) at 1 year ($P = 0.008$).

CONCLUSIONS

The weight loss program resulted in greater weight loss and improved glycemic control in type 2 diabetes.

More than two-thirds of adults in the U.S. (69.2%) are overweight or obese (1). Of the many health conditions that are associated with obesity, type 2 diabetes is among the most prevalent (2). Achieving and maintaining a healthy body weight is a primary strategy for the management of type 2 diabetes (3). Participation in a

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face-to-face tailored lifestyle intervention that involves diet modification, increased physical activity, and behavior therapy, such as that of the Action for Health in Diabetes (Look AHEAD) trial intervention, can result in a degree of weight loss for overweight patients with diabetes that improves glycemic control and cardiovascular disease risk factors (4,5). However, most overweight or obese individuals with type 2 diabetes do not receive this degree of support for changes in diet and physical activity to promote weight loss in their clinical care partly due to constraints of time and training for most health-care providers and clinicians (6,7).

The intervention in the present study was a commercial weight loss program that includes one-to-one behavioral counseling, a low-energy-density diet, prepackaged foods, and increased physical activity. In a randomized clinical trial, the program was shown to effectively promote weight loss in generally healthy adults compared with a usual care (UC) control condition, resulting in an average 1-year weight loss of ~10% and an average 2-year weight loss of ~7% (8). The effectiveness of this multifaceted intervention has not been previously examined in a randomized trial targeting individuals with type 2 diabetes who have high rates of cardiovascular disease morbidity and mortality as well as a high risk for secondary and tertiary medical complications if glycemic control is not achieved and maintained.

Although a deficit in total energy intake relative to expenditure is the most critical dietary factor that determines weight loss, increasing evidence suggests that macronutrient composition of the diet may also influence weight loss and metabolic response (9). In a few previous studies, effects on atherogenic dyslipidemia and glycemic control have been observed to be more favorable with a lower versus higher carbohydrate diet, after adjusting for weight loss, in individuals with insulin resistance or type 2 diabetes (10–12).

The first aim of the present study was to test in a randomized controlled trial whether participation in this structured weight loss program promotes greater 1-year weight loss and maintenance in overweight or obese adults with type 2 diabetes compared with UC conditions. A secondary aim was to describe the effect of participating in the program (vs. UC) on markers of glycemic control (fasting glucose, hemoglobin A_{1c} [HbA_{1c}]), cardiovascular disease risk factors (triglyceride, HDL cholesterol, C-reactive protein [CRP] levels), cardiopulmonary fitness, quality of life, and plasma carotenoids (a biomarker of vegetable and fruit intake). An exploratory aim was to examine whether there is a differential response to dietary macronutrient composition (higher vs. lower carbohydrate) in weight change and markers of glycemic control and cardiovascular disease risk.

RESEARCH DESIGN AND METHODS

Study Participants

Men and women were recruited and enrolled at two study sites (University of California, San Diego [UCSD]; University of Minnesota, Minneapolis). Participants were recruited through word of mouth, direct marketing letters mailed to large cohorts, radio advertisements, local e-mail subscription services, ClinicalTrials.gov, social media, and flyers. Eligibility criteria were a history of type 2 diabetes confirmed by a physician; aged ≥18 years; BMI 25–45 kg/m^2; not pregnant or breastfeeding or planning to become pregnant in the next year; willing to participate in any of the study diet arms over a 1-year period; no eating disorders, food allergies, or food intolerances; no history of bariatric surgery; and willing and able to perform a step test for assessing cardiopulmonary fitness. Current active involvement in another diet intervention study or organized weight loss program; weight loss >10 lb in the past 3 months; or having a history or presence of a significant psychiatric disorder or any other condition that, in the investigator's judgment, would interfere with participation in the trial disqualified participants. Other exclusion criteria were HbA_{1c} >11% (97 mmol/mol), fasting triglyceride level >600 mg/dL, and serum creatinine level ≥1.4 mg/dL (women) or 1.5 mg/dL (men).

Participants were randomly assigned to a weight loss program with a higher carbohydrate, lower fat (LF) diet plan; a weight loss program with a lower carbohydrate, higher fat (LC) diet plan; or a UC program (Supplementary Fig. 1). Randomization was stratified by study site and BMI using a web-based application with a sequence generated by the study statistician. Participants were reimbursed $25 for each data collection clinic visit, with incremental increases over the course of the study to compensate for rising fuel costs, but no compensation was provided for participation in the intervention or counseling sessions. Institutional review boards at both universities approved the study protocol, and all participants provided written informed consent.

Intervention

Participants in the two commercial weight loss program arms of the study received weight loss counseling and all program materials free of charge, including prepackaged foods. Three entrees and one to two snacks were provided for 7 days/week during the initial weight loss phase (months 1–6) and for 5 days/week during a transition phase (months 7–9), and one entree and one snack daily was provided, as desired, during the maintenance phase (months 10–12). Participants were encouraged, especially during the initial period, to follow the menu plan with prepackaged foods (41–76% of energy). The prepackaged foods provided more than one-half to two-thirds of energy intake for most participants and somewhat less for those at higher levels of dietary energy prescription during the initial period. Grocery foods, such as vegetables, fruit, cereal/grain products, dairy products, lean meat, and unsaturated fat sources, were recommended to achieve the total prescribed energy and macronutrient intake. Participants also were provided guidance for how to choose grocery and restaurant foods that would meet the meal plan to accommodate special occasions and other needs.

One-to-one counseling sessions with trained program staff were offered for the 1-year period, with follow-up telephone and website/message board availability. Weekly counseling visits were recommended during the first 9 months after which participants had the option to move from weekly to biweekly or monthly consultations. Program materials encouraged basic diabetes self-management strategies, such as monitoring of blood glucose and symptoms of hypoglycemia and hyperglycemia, as well as tracking of

food intake and physical activity. Counselors were not blinded to the identity of study participants. Prepared foods, program materials, products, and counselors were provided by Jenny Craig, Inc. (Carlsbad, CA).

Both commercial weight loss program diet meal plans were reduced in energy relative to expenditure (typically 1,200–2,000 kcal/day). The LF diet plan provided 60% energy from carbohydrates, 20% from fat, and 20% from protein. The LC diet plan provided 45% energy from carbohydrates, 30% from fat, and 25% from protein. Nutrient content of the two diet meal plans was otherwise similar. In both diet meal plans, strategies to reduce energy density of the diet, such as incorporating vegetables and water-rich foods in meals and snacks, were encouraged.

Increased physical activity was encouraged, with the goal of 30 min of physical activity on ≥5 days/week. Program materials and counseling addressed attitudes about weight, food, and physical activity, and materials included recipes, guidance for eating in restaurants, digital videos and exercise equipment to increase physical activity, and online education and support.

After randomization and at 6 months, participants assigned to UC received a 1-h individual weight loss counseling session with a dietitian. In the first session, participants were advised to consume a deficit of 500–1,000 kcal/day to achieve a weight loss of 10% of initial weight. Participants were encouraged to use web-based tracking programs that guide toward the macronutrient distribution recommended in the Dietary Guidelines for Americans (20–35% [average 30%] of energy from fat, 45–65% [average 55%] from carbohydrates, and 10–35% [average 15%] from protein) (13). Counseling and print materials encouraged strategies and skills for weight loss and maintenance (e.g., estimating portion sizes, self-monitoring). This session was followed by monthly check-in through e-mail or telephone calls, and progress was discussed in the follow-up counseling session. Participants in UC also received a standardized checklist of recommendations for general diabetes care, including regular glucose monitoring, awareness of symptoms of hypoglycemia and hyperglycemia, and the importance of adherence to prescribed medications and good hygiene practices.

Outcomes and Follow-up

At data collection clinic visits, weight, waist circumference, height (baseline only), and blood pressure were measured, and questionnaires [the Beck Depression Inventory (14), 36-item short-form health survey quality-of-life questionnaire (15), and Godin Leisure-Time Exercise Questionnaire (16)] were collected by institution research staff who usually were unblinded. The 3-min step test was used to assess aerobic fitness. This test measures heart rate during the first 30 s of recovery from stepping, and although less accurate than measuring VO_{2max}, the test has high reliability and is sensitive to change (17).

Fasting (≥6 h) blood samples were collected at each clinic visit. Glucose, cholesterol, triglyceride, HDL cholesterol, and creatinine (at baseline screening visit only) levels were measured with the Kodak Ektachem Analyzer system (Johnson & Johnson Clinical Diagnostics, Rochester, NY). LDL cholesterol values were calculated by the Friedewald equation (18). The ADVIA Centaur assay, a double-antibody immunoassay with chemiluminescent detection, was used for insulin quantification. HbA_{1c} was measured in washed erythrocytes with ion exchange high-performance liquid chromatography (D10 System, Bio-Rad Laboratories, Hercules, CA). High-sensitivity CRP was assayed using a polystyrene-enhanced turbidimetric in vitro immunoassay (19,20). Plasma carotenoid concentrations, an indicator of fruit and vegetable consumption, were measured by high-performance liquid chromatography (21).

Statistical Analysis

Weight change, the primary study outcome, was analyzed as intention to treat, with baseline substitution for missing data. This approach assumes that participants who did not complete clinic visits or dropped out returned to their baseline weight and is recommended based on usual recidivism after weight loss (22). Change over time (weight, laboratory values, blood pressure, and psychosocial variables) was examined in longitudinal mixed models, based on an interaction between study group and time, and controlled for sex. We also examined weight data for completers, recognizing a likely bias because dropouts may be less adherent and may exhibit weight rebound. To improve normality of distributions, log transformation was applied to laboratory values in analysis, but untransformed means are presented in text and tables for ease of interpretation. Models for glucose, HbA_{1c}, and insulin were controlled for use of insulin and other diabetes medications. A subject-specific intercept, representing baseline levels of each modeled outcome, was included as a random effect in each model. Proportions of participants who stopped or decreased medications were compared with Fisher exact test. Statistical significance was two-sided without adjustment for multiple comparisons. All analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC) statistical software.

Power calculations were based on data from a previous clinical trial of the weight loss program (8) and biochemical laboratory data in individuals with diabetes (4). Using mean (SD) effect sizes of 6.8 (8.8) in the intervention groups and 2.0 (7.2) in the control group, there was 90% power for the primary aim with 75 participants per arm and a dropout rate of up to 20%. There was also 90% power to discern between-group HbA_{1c} differences of 0.5% (6 mmol/mol).

RESULTS

The study sample comprised 227 men and women aged 24–75 years (mean 56 years) (Table 1) who were recruited between March and August 2012. During the study period, two participants (one LF and one LC) died, one of cardiovascular disease before the 6-month visit and the other of cancer before the 12-month visit. Primary outcome data were obtained at study end from 90% of the participants who were randomized. Attrition did not differ by study group (Supplementary Fig. 1). Over the year of active involvement, counseling visits in the weight loss program intervention groups ranged from 1 to 69, with a median of 41 visits.

At baseline, mean (SD) weight was 105.5 (17.6) kg. At 6 months, those in the LF group had reduced initial weight by 8.6% (95% CI 7.2–10.0%), those in the LC group by 10.4% (8.9–12.0%), and those in UC group by 2.3% (1.3–3.2%) (Table 2). Participants in the intervention arms lost

Table 1—Characteristics of participants at study entry

	LF (*n* = 74)	LC (*n* = 77)	UC (*n* = 76)
Age (year)	55.5 (9.2)	57.3 (8.6)	56.8 (9.3)
Sex			
Male	39 (52.7)	40 (52.0)	32 (42.1)
Female	35 (47.3)	37 (48.1)	44 (57.9)
Race/ethnicity			
Non-Hispanic white	59 (79.7)	63 (81.8)	59 (77.6)
Hispanic	4 (5.4)	6 (7.8)	7 (9.2)
African American	7 (9.5)	2 (2.6)	4 (5.3)
Asian	4 (5.4)	4 (5.1)	2 (2.6)
Multiple and other*	0	2 (2.6)	4 (5.3)
Clinical site			
UCSD	36 (48.7)	37 (48.1)	37 (48.7)
University of Minnesota	38 (51.4)	40 (52.0)	39 (51.3)
BMI			
Overweight (25–29.99 kg/m^2)	4 (5.4)	6 (7.8)	6 (7.9)
Obese I (30–34.99 kg/m^2)	28 (37.8)	27 (35.1)	26 (34.2)
Obese II (35–39.99 kg/m^2)	24 (32.4)	26 (33.8)	26 (34.2)
Obese III (40–45 kg/m^2)	18 (24.3)	18 (23.4)	18 (23.7)
Comorbidities			
Current smoking	5 (6.8)	1 (1.3)	2 (2.7)
History of invasive cancer	5 (6.8)	3 (3.9)	3 (4.0)
Bone or joint problems	14 (18.9)	16 (20.8)	10 (13.2)
Hypertension	46 (62.2)	60 (77.9)	57 (75.0)
High cholesterol	46 (62.2)	54 (70.1)	56 (73.7)
Coronary artery disease (angina, MI)	5 (6.8)	4 (5.2)	1 (1.3)
Asthma	9 (12.2)	8 (10.4)	2 (2.6)
Diabetes medication use (year)	6 (6)	5 (5)	5 (5)

Data are mean (SD) or *n* (%). MI, myocardial infarction. *Includes those who reported being part Native American, part Asian, part Hispanic, or fully Pacific Islander/Native Hawaiian.

more weight than those in the UC arm (10.3 [95% CI 9.2–11.5] vs. 2.8 [1.6–4.1] kg, $P < 0.001$). At study end, maintained weight loss was greater in the intervention arms (8.2% of initial weight) than in the UC arm (2.5% of initial weight, $P < 0.001$). The LF and LC groups did not differ in weight loss at 12 months in the intention-to-treat analysis, although among the completers, LC lost more weight than LF (10.2 vs. 7.9%, $P = 0.035$). A majority (86 of 149) of participants in the weight loss program maintained at least a 5% loss of initial body weight at study end compared with less than one-quarter (18 of 76) of UC participants ($P < 0.001$). At study end, a ≥10% weight reduction was achieved by 38% of the weight loss program participants (57 of 149) and 9% of the UC participants (7 of 76, $P < 0.001$). At 6 months, diastolic blood pressure was lower in the weight loss program participants (77 [95% CI 75–79] mmHg) than in the UC participants (82 [78–85] mmHg, $P = 0.006$).

At 6 months, participants in both weight loss program groups but not in the UC group reported increased moderate/vigorous physical activity of ~1.5 h more than their baseline levels or than UC ($P < 0.001$ for each) (Table 2). Participants in all three groups had lower recovery heart rates after the step test at 6 months than they had at baseline ($P < 0.001$). Weight loss program participants also had lower depression scores than UC participants (5 [95% CI 4–6] vs. 7 [5–9], $P = 0.009$) and better physical quality-of-life scores (80 [77–83] vs. 72 [67–78], $P = 0.005$) at 6 months (Table 2).

None of the laboratory measures differed among the three groups at study entry. However, glycemic control markers (glucose, HbA_{1c}, and insulin) and triglyceride levels were lower in both LF and LC than in UC at 6 months (glucose 132 [95% CI 126–138] vs. 148 [137–160] mg/dL, $P = 0.006$; HbA_{1c} 6.4% [6.3–6.6%] vs. 7.2% [6.8–7.6%] [or 46 (45–49) vs. 55 (51–60) mmol/mol], $P < 0.001$; insulin 21 [18–24] vs. 29 [21–37] μIU/mL, $P = 0.006$; triglycerides 143 [130–157] vs. 181 [160–203] mg/dL, $P < 0.001$), and these differences were sustained at 12 months (glucose 141 [133–149] vs. 159 [144–174] mg/dL, $P = 0.023$; HbA_{1c} 6.9% [6.6–7.1%] vs. 7.5% [7.1–7.9%] or 52 [49–54] vs. 58 [54–63] mmol/mol, $P = 0.001$; insulin 21 [18–25] vs. 25 [20–30] μIU/mL, $P = 0.016$; triglycerides 148 [134–163] vs. 204 [173–234] mg/dL, $P < 0.001$) (Table 3). Participants in the LC diet group had lower mean glucose concentration ($P = 0.037$) and HbA_{1c} ($P = 0.024$) than those in the LF diet group at 6 months, and the HbA_{1c} difference between LC and LF was sustained at 12 months ($P = 0.021$) (Table 3). At study end, 62% of weight loss program participants (83 of 133) and 45% of the UC participants (30 of 66) met the recommended HbA_{1c} general goal of <7% (53 mmol/mol) for diabetes care (71% [47 of 66] and 54% [36 of 67] of LC and LF participants, respectively; $P = 0.037$) (23). Total and LDL cholesterol levels did not differ between the groups at either follow-up time point. Compared with the UC group, the weight loss program groups had higher HDL cholesterol and total carotenoid levels and lower CRP levels at study end (Table 3).

Self-reported medication use changed during the course of the study (Table 4). Eighteen percent of the participants (*n* = 41) used insulin at study entry, with a mean duration of 4 years. Of these participants, 72% (21 of 29) in the weight loss program groups decreased or discontinued insulin use by study end compared with 8% (1 of 12) in the UC group. Similarly, oral hypoglycemic, cholesterol-lowering, and blood pressure medication use was reduced or discontinued more often among the weight loss program participants than among the UC participants ($P = 0.007$, 0.024, and 0.032, respectively). Only 4% of study participants reported any use of glucon-like peptide agonists during the trial, among whom three subjects stopped and two started these medications.

CONCLUSIONS

A commercially available structured weight loss program involving diet modification, increased physical activity, and behavioral counseling produced weight loss and improved glycemic control in type 2 diabetes comparable with that achieved in a well-funded clinical trial (4). At 1 year, participants in the weight loss program intervention lost 8.2% of initial weight compared with a 2.5% weight loss in the control group. Several cardiovascular disease risk factors also

Table 2—Body measurements* and blood pressure, behavioral, and psychosocial measures†

	LF			LC			UC		
	Baseline	6 months	12 months	Baseline	6 months	12 months	Baseline	6 months	12 months
Weight change (%)		−8.6 (5.9)	−7.4 (7.6)		−10.4 (6.9)	−9.0 (8.4)		−2.3 (4.2)	−2.5 (5.5)
P value‡								<0.001	<0.001
Weight (kg)	105.4 (17.8)	96.5 (17.5)	97.7 (18.0)	106.4 (18.3)	95.0 (17.9)	96.7 (19.7)	104.6 (16.9)	102.2 (17.3)	101.9 (17.4)
P value‡							0.87	<0.001	0.005
BMI (kg/m^2)	36.2 (4.3)	33.2 (4.4)	33.5 (4.7)	36.2 (4.7)	32.4 (4.8)	33.0 (5.5)	36.3 (4.4)	35.5 (4.7)	35.4 (4.6)
P value‡							0.86	<0.001	0.001
Waist (cm)	119.9 (11.5)	112.7 (11.8)	113.2 (13.3)	121.3 (12.3)	111.8 (13.3)	112.3 (14.6)	119.9 (11.9)	117.7 (13.1)	117.1 (13.0)
P value‡							0.93	<0.001	0.007
Systolic blood pressure (mmHg)	133 (15)	125 (14)	127 (16)	131 (19)	125 (77)	127 (15)	133 (15)	129 (16)	126 (14)
P value‡							0.66	0.024	0.72
Diastolic blood pressure (mmHg)	84 (11)	77 (9)	77 (10)	82 (12)	76 (11)	78 (11)	83 (11)	82 (12)	78 (12)
P value‡							0.97	0.006	0.99
Moderate/vigorous activity (h/week)	1.8 (2.4)	3.4 (3.6)	3.1 (3.6)	2.2 (2.5)	3.6 (3.2)	3.8 (3.9)	1.8 (2.6)	1.8 (2.1)	2.0 (1.9)
P value‡							0.75	<0.001	0.003
BDI	7 (6)	5 (5)	4 (4)	6 (5)	5 (7)	5 (7)	7 (6)	7 (8)	6 (7)
P value‡							0.95	0.009	0.28
SF-36									
Physical	78 (15)	80 (17)	82 (15)	80 (15)	80 (19)	80 (21)	80 (15)	72 (22)	80 (16)
P value‡							0.70	0.005	0.52
Mental	80 (16)	82 (14)	82 (14)	79 (17)	79 (18)	74 (20)	82 (16)	80 (17)	80 (18)
P value‡							0.44	0.049	0.72

Data are mean (SD). BDI, Beck Depression Inventory; SF-36, 36-item short form health survey quality-of-life questionnaire. *Weight, BMI, and waist data are analyzed as intention to treat with baseline substitution. †Blood pressure, behavioral, and psychosocial data were analyzed for those with measured data (missing data at 6 months: n = 2 LF, n = 2 LC, n = 12 UC; missing data at 12 months: n = 7 LF, n = 9 LC, n = 8 UC). ‡P values for differences between UC and aggregated weight loss program participants, as specified in the primary specific aim, came from longitudinal mixed models controlled for sex.

were favorably improved at 1 year in the weight loss intervention participants compared with control participants. Data were available from 90% of participants at study end, so little ambiguity exists in drawing conclusions from this study, which is not typical for weight loss trials. Structured, intensive weight loss and diet interventions are recognized as useful and recommended for managing type 2 diabetes, but the challenge of delivering this type of intervention in clinical practice is a recognized problem in diabetes management (3). Findings from the current study suggest that clinicians can refer patients to and use a commercial weight loss program that is evidence based to optimize weight loss and diabetes care.

Optimal macronutrient distribution of weight loss diets has not been established. The Institute of Medicine (24), American Diabetes Association (3), and American Heart Association (AHA) (25) recommend the following spectrum of dietary composition for the general adult population: 20–35% of energy (AHA 25–35%) from fat; 45–65% of energy (AHA 50–60%) from carbohydrates; and 10–35% of energy (at least 0.8 g/kg) from protein. Dietary carbohydrate intake is the primary determinant of blood glucose values, and evidence suggests that the quantity, and perhaps quality, of carbohydrate sources can influence metabolic response to a weight loss diet in diabetes management (26,27). The lower and higher carbohydrate diets studied in this trial are both within the range of recommended intake. The moderately reduced level of carbohydrate intake examined as an exploratory aim in this study is likely to be sustainable, which is a concern with low-carbohydrate diets in both the general population (28,29) and patients with type 2 diabetes (11).

In the Look AHEAD study (N = 5,145), a weight loss and physical activity intervention that included liquid meal replacements and the option of weight loss medications, an average weight loss of 8.6% of initial weight at 1 year was achieved (4). In Look AHEAD, the mean HbA_{1c} at 1 year was reduced from 7.3 to 6.6% (56–49 mmol/mol) in the intervention group compared with 7.2% (55 mmol/mol) in the diabetes education control group. A few previous studies compared the effect of a

Table 3—Laboratory measurements

	LF			LC			UC		
	Baseline	6 months	12 months	Baseline	6 months	12 months	Baseline	6 months	12 months
n	77	71	67	74	73	66	76	60	65
Glucose (mg/dL)	145 (44)	139 (40)	149 (59)	146 (52)	125 (32)*	133 (34)	145 (45)	148 (46)‡	159 (60)†
HbA_{1c} (%)	7.5 (1.2)	6.7 (1.0)	7.2 (1.5)	7.3 (1.4)	6.2 (0.8)*	6.6 (1.0)*	7.4 (1.1)	7.2 (1.5)‡	7.5 (1.5)‡
HbA_{1c} (mmol/mol)	58 (13)	50 (11)	55 (16)	56 (15)	44 (9)*	49 (11)*	57 (12)	55 (16)‡	58 (16))‡
Insulin (μIU/mL)	29 (33)	22 (18)	25 (25)	27 (19)	19 (15)	18 (14)	33 (42)	29 (32)‡	25 (19)†
Triglycerides (mg/dL)	172 (96)	150 (87)	156 (96)	177 (99)	137 (78)	140 (73)	181 (93)	181 (83)‡	204 (123)‡
Total cholesterol (mg/dL)	155 (34)	158 (41)	168 (38)	153 (36)	157 (39)	164 (36)	161 (40)	168 (39)	170 (38)
HDL cholesterol (mg/dL)	37 (8)	46 (10)	51 (12)	39 (10)	48 (11)	54 (11)	39 (11)	46 (14)	49 (14)‡
LDL cholesterol (mg/dL)	80 (34)	82 (35)	86 (30)	79 (36)	81 (33)	83 (32)	83 (39)	86 (34)	81 (37)
CRP (mg/L)	4.2 (4.3)	3.6 (4.4)	2.3 (2.4)	3.5 (3.5)	2.7 (3.5)	2.0 (2.4)	4.2 (3.9)	3.6 (3.9)†	5.1 (9.1)‡
Total carotenoids (μmol/L)	1.3 (0.5)	—	1.9 (1.1)	1.4 (0.6)	—	2.0 (1.0)	1.4 (1.1)	—	1.6 (1.4)‡

Data are mean (SD). All models were controlled for sex. SI (International System of Units) conversion factors: To convert carotenoids to mg/dL, divide by 0.01863; CRP to nmol/L, multiply by 9.524; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. *$P < 0.05$ compared with LF plan. †$P < 0.05$ compared with aggregated weight loss program intervention. ‡$P < 0.01$ compared with aggregated weight loss program intervention.

very-low-carbohydrate diet (20–24% of energy) to the more conventional low-fat diet in individuals with type 2 diabetes. Similar weight loss but more favorable effects on lipids and glycemic control (although often transient) were observed, but declining adherence over even 1 year of study involvement and a higher attrition rate constrain interpretation of the results (10,11,30).

The response to another commercially available weight loss program that includes prepackaged foods was examined in 100 obese patients with type 2 diabetes in a 6-month study (31). Participants assigned to the weight loss program lost 7.8% of initial weight compared with 2.1% in a control group provided general diabetes management education, and HbA_{1c} declined from 7.6 to 6.9% (60–52 mmol/mol) vs. 7.9–7.5% (63–58 mmol/mol) in the control group. A role for meal replacement products, which are composite food products (beverages, snack bars, or ready-to-mix powders) has been proposed for promoting weight loss in diabetes management (32). In contrast with prepackaged portion-controlled regular food, those products contain essential nutrients but generally lack bioactive food components and do not illustrate how to make good choices in response to food exposures in grocery stores and restaurants. Additionally, behavioral counseling, education, frequent contact, support, and increased physical activity, elements incorporated in the program examined in the current study, are determinants of successful long-term weight management (33,34) and are recommended to promote long-term weight management and glycemic control in diabetes care (3). Although greater weight loss in response to a lower versus higher carbohydrate diet has been observed in insulin resistant, nondiabetic individuals in a few previous studies (35,36), intention-to-treat analysis did not reveal differential weight loss in response to the two levels of carbohydrate intake examined in the current study. Previous studies comparing a very-low-carbohydrate diet with a low-fat diet in patients with type 2 diabetes also did not report differential effects on weight loss over 1–2 years (10,11,30). In those studies, the very-low-carbohydrate diet resulted in more favorable effects on cardiovascular disease risk factors (e.g., HDL cholesterol and triglyceride levels), as observed in the current study. A favorable effect on the level of CRP, an inflammatory marker, also was observed in response to participation in the weight loss program in the current study.

Table 4—Medication use and change in medication use during the study

Medication type	LF	LC	UC	*P* value*
Diabetes (insulin)				<0.001
Baseline	19	10	12	
Stopped/decreased	12	9	1	
Started/increased	2	0	3	
Diabetes (oral hypoglycemic)				0.007
Baseline	62	69	62	
Stopped/decreased	24	22	10	
Started/increased	6	6	8	
Cholesterol				0.024
Baseline	49	52	57	
Stopped/decreased	10	11	4	
Started/increased	4	3	4	
Hypertension				0.032
Baseline	52	65	60	
Stopped/decreased	13	18	7	
Started/increased	3	1	6	

Data are counts. The counts shown are the number of participants reporting medications in each category at baseline and the number who at study end had changed dosage of one or more medications in the category relative to baseline use. Those who substituted one medication for another in the same category were not counted. *UC vs. weight loss program intervention.

This study as some limitations. An important limitation is the lack of information about adherence to the prescribed diets. The target was a free-living population, so variability in adherence is likely. Self-reported dietary data have well-recognized limitations in accuracy, which are characterized as substantial underreporting and misreporting among overweight and obese individuals. An implication of this limitation is that it is not known whether the more-favorable response in those assigned to a lower-carbohydrate diet may be due to better adherence or even greater weight loss, as was observed among participants for whom data were available at all time points. The intervention and prepackaged foods were provided without cost to the participants, as was also the case in Look AHEAD and other weight loss and diet intervention studies (4,31), which may affect generalizability. Compared with the cost of a comprehensive weight loss program, the medical costs of type 2 diabetes that is not optimally managed are considerable. A larger proportion of participants in the weight loss program (vs. the control condition) in the current study was able to reduce or discontinue diabetes, hypertension, and lipid-lowering medications and, thus, medical costs. Although aimed toward prevention, the Diabetes Prevention Program demonstrated that an intensive lifestyle intervention is cost-effective because of the high cost of medical care associated with diabetes (37). Another limitation is that the weight loss program counselors were unblinded, although they were instructed to provide the program and services as delivered to paying customers.

In summary, the structured weight loss program resulted in greater weight loss and improved glycemic control in overweight or obese individuals with type 2 diabetes compared with a UC control group receiving less intensive counseling.

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References

1. Ogden C, Carroll M, Kit B, Flegal K. Prevalence of obesity in the United States, 2009–2010 [article online]. Available from http://www.cdc.gov/nchs/data/databriefs/db82.pdf. Accessed 5 March 2014
2. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States [article online]. Available from http://www.cdc.gov/diabetes/pubs/factsheet11.htm. Accessed 5 March 2014
3. Bantle JP, Wylie-Rosett J, Albright AL, et al.; American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008;31(Suppl. 1): S61–S78
4. Pi-Sunyer X, Blackburn G, Brancati FL, et al.; Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007;30:1374–1383
5. Wing RR; Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010; 170:1566–1575
6. Alexander SC, Ostbye T, Pollak KI, Gradison M, Bastian LA, Brouwer RJ. Physicians' beliefs about discussing obesity: results from focus groups. Am J Health Promot 2007;21:498–500
7. Ruelaz AR, Diefenbach P, Simon B, Lanto A, Arterburn D, Shekelle PG. Perceived barriers to weight management in primary care—perspectives of patients and providers. J Gen Intern Med 2007;22:518–522
8. Rock CL, Flatt SW, Sherwood NE, Karanja N, Pakiz B, Thomson CA. Effect of a free prepared meal and incentivized weight loss program on weight loss and weight loss maintenance in obese and overweight women: a randomized controlled trial. JAMA 2010;304:1803–1810
9. Abete I, Astrup A, Martínez JA, Thorsdottir I, Zulet MA. Obesity and the metabolic syndrome: role of different dietary macronutrient distribution patterns and specific nutritional components on weight loss and maintenance. Nutr Rev 2010;68:214–231
10. 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;140:778–785
11. Guldbrand H, Dizdar B, Bunjaku B, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia 2012;55:2118–2127
12. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–2081
13. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans*. 7th ed. Washington, DC, U.S. Government Printing Office, 2010
14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
15. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992;305:160–164
16. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 1985;10:141–146
17. McArdle W, Katch F, Katch V. *Exercise Physiology: Energy, Nutrition, and Human Performance*. 6th ed. Baltimore, MD, Lippincott Williams & Wilkins, 2006
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502
19. Roberts WL, Moulton L, Law TC, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. Clin Chem 2001;47:418–425
20. Mills PJ, Natarajan L, von Känel R, Ancoli-Israel S, Dimsdale JE. Diurnal variability of C-reactive protein in obstructive sleep apnea. Sleep Breath 2009;13:415–420
21. Gamboa-Pinto AJ, Rock CL, Ferruzzi MG, Schowinsky AB, Schwartz SJ. Cervical tissue and plasma concentrations of alpha-carotene and beta-carotene in women are correlated. J Nutr 1998;128:1933–1936
22. Ware JH. Interpreting incomplete data in studies of diet and weight loss. N Engl J Med 2003;348:2136–2137

23. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl. 1):S11–S63
24. Food and Nutrition Board, Institute of Medicine of the National Academies. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC, National Academies Press, 2005
25. Lichtenstein AH, Appel LJ, Brands M, et al.; American Heart Association Nutrition Committee. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82–96
26. Rivellese AA, Giacco R, Costabile G. Dietary carbohydrates for diabetics. Curr Atheroscler Rep 2012;14:563–569
27. Acheson KJ. Carbohydrate for weight and metabolic control: where do we stand? Nutrition 2010;26:141–145
28. 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
29. Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med 2010;153:147–157
30. Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care 2009;32:1147–1152
31. Foster GD, Wadden TA, Lagrotte CA, et al. A randomized comparison of a commercially available portion-controlled weight-loss intervention with a diabetes self-management education program. Nutr Diabetes 2013;3:e63
32. Hamdy O, Zwiefelhofer D. Weight management using a meal replacement strategy in type 2 diabetes. Curr Diab Rep 2010;10:159–164
33. Jeffery RW, Drewnowski A, Epstein LH, et al. Long-term maintenance of weight loss: current status. Health Psychol 2000;19(Suppl.):5–16
34. Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. Obes Res 2004;12(Suppl.):151S–162S
35. Pittas AG, Das SK, Hajduk CL, et al. A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion but not in overweight adults with low insulin secretion in the CALERIE Trial. Diabetes Care 2005;28:2939–2941
36. Cornier MA, Donahoo WT, Pereira R, et al. Insulin sensitivity determines the effectiveness of dietary macronutrient composition on weight loss in obese women. Obes Res 2005;13:703–709
37. Herman WH, Edelstein SL, Ratner RE, et al.; Diabetes Prevention Program Research Group. Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care 2013;19:194–202