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

A randomized trial

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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. $0.0 \pm 0.2\%$, $P = 0.05$). 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.

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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

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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.

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

Table 1—*Baseline demographic and clinical data*

	Standard therapy	Combination therapy	*P*
n (female/male)	29 (16/13)	30 (16/14)	—
Age (years)	55 ± 5	52 ± 5	0.07
Duration of diabetes (years)	5 ± 3	4 ± 2	0.24
Diabetes medications (*n*)			
None	3	4	
One	9	10	0.90
Two or more	17	16	
Weight (kg)	112.4 ± 3.9	109.1 ± 3.8	0.55
BMI (kg/m^2)	38.6 ± 0.9	37.8 ± 0.9	0.53
Body fat (kg)	46.6 ± 2.2	45.0 ± 2.1	0.60
Lean body mass (kg)	60.1 ± 2.7	59.7 ± 2.4	0.69
Fasting glucose (mg/dl)	176 ± 8	155 ± 7	0.06
HbA_{1c} (%)	8.2 ± 0.2	8.1 ± 0.2	0.71
Resting pulse (bpm)	78 ± 2	79 ± 2	0.58
Systolic blood pressure (mmHg)	131 ± 3	135 ± 3	0.20
Diastolic blood pressure (mmHg)	75 ± 2	76 ± 2	0.67
Fasting cholesterol (mg/dl)	200 ± 8	204 ± 9	0.73
HDL cholesterol (mg/dl)	39 ± 2	40 ± 2	0.61
LDL cholesterol (mg/dl)*	117 ± 6	124 ± 8	0.45
Fasting triglycerides (mg/dl)†	191 ± 15	220 ± 25	0.33

Data are means ± SEM. *Excludes one subject in the standard therapy group and four subjects in the combination therapy group with fasting triglycerides >400 mg/dl. †Excludes one subject in the standard therapy group with fasting triglycerides >2,000 mg/dl. Conversion factors: glucose mg/dl to mmol/l multiply by 0.0555; cholesterol mg/dl to mmol/l multiply by 0.0259; triglycerides mg/dl to mmol/l multiply by 0.0113.

weight loss between the two groups at the $\alpha = 0.05$ 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

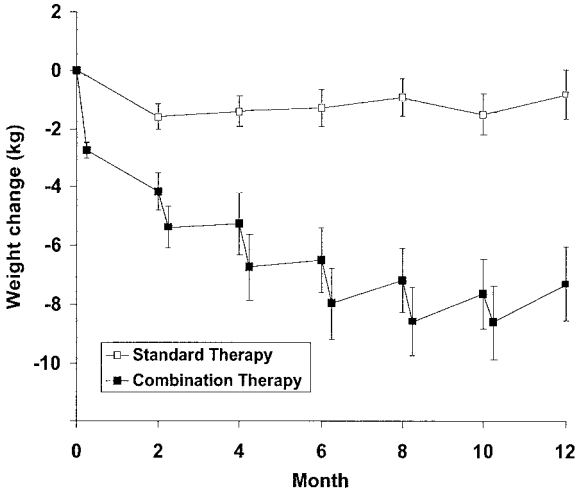

Figure 1—*Mean ± SEM change in weight from baseline in standard therapy and combination therapy groups.*

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

	Standard therapy	Combination therapy	*P*
n (female/male)	27 (14/13)	27 (14/13)	—
Weight loss (kg)	−0.8 ± 0.9	−7.3 ± 1.3	<0.001
BMI (kg/m^2)	−0.3 ± 0.3	−2.6 ± 0.5	<0.001
Body fat (kg)	−0.1 ± 0.7	−4.6 ± 1.0	<0.001
Lean body mass (kg)	−0.8 ± 0.6	−2.8 ± 0.8	0.04
Fasting glucose (mg/dL)	−11 ± 9	−12 ± 9	0.90
HbA_{1c} (%)	0.0 ± 0.2	−0.6 ± 0.3	0.05
Resting pulse (bpm)	0 ± 2	1 ± 2	0.76
Systolic blood pressure (mmHg)	−6 ± 2	−6 ± 3	0.99
Diastolic blood pressure (mmHg)	−6 ± 2	−3 ± 1	0.28
Fasting cholesterol (mg/dl)	−17 ± 9	−16 ± 8	0.90
HDL cholesterol (mg/dl)	1 ± 1	2 ± 1	0.57
LDL cholesterol (mg/dl)*	−13 ± 6	−12 ± 5	0.89
Fasting triglycerides (mg/dl)†	8 ± 18	−46 ± 24	0.07

Data are means ± SEM. *Excludes three subjects in the standard therapy group and four subjects in the combination therapy group with fasting triglycerides >400 mg/dl at baseline or 1 year. †Excludes one subject in the standard therapy group with fast triglycerides >2,000 mg/dl at baseline. For conversion factors, see footnote to Table 1.

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

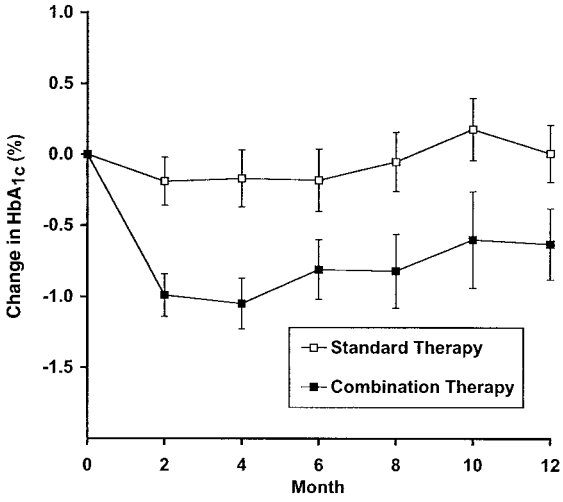

Figure 2—*Mean ± SEM change in HbA_{1c} from baseline in standard therapy and combination therapy groups.*

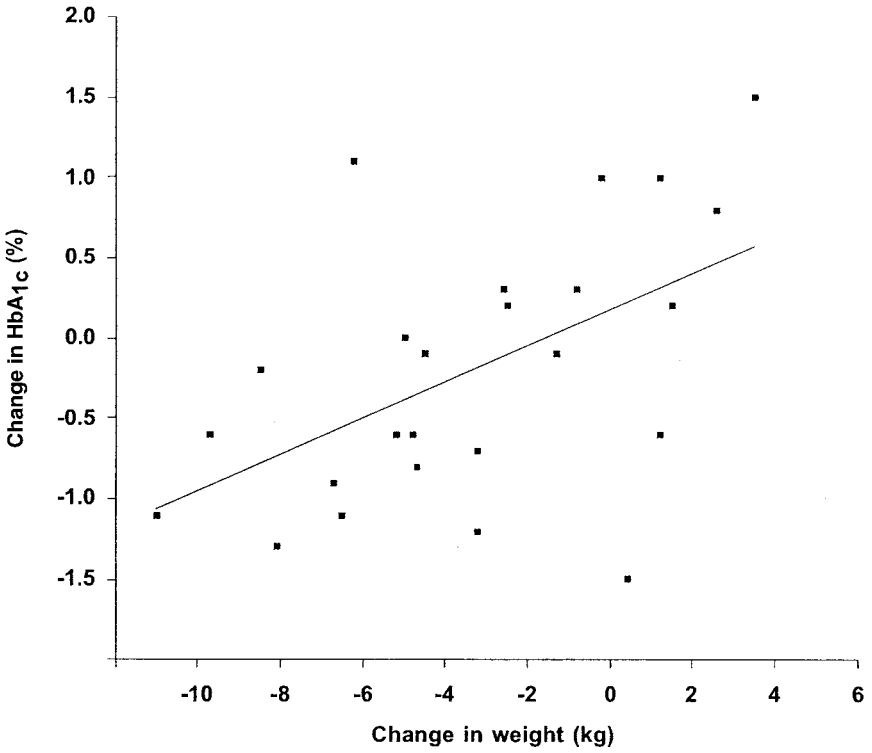

Figure 3—*Plot of change in weight versus change in HbA_{1c} at 1 year for 25 subjects (10 subjects in the standard therapy group and 15 subjects in the combination therapy group) whose diabetes medications did not change from baseline. The fitted regression equation was (HbA_{1c} change) = 0.11(weight 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%.*

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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