Two-Year Outcome of a Combination of Weight Loss Therapies for Type 2 Diabetes

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OBJECTIVE — To evaluate the effects over 2 years of a weight loss program combining several weight loss strategies on weight loss and diabetes control in overweight subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 59 overweight or obese individuals with type 2 diabetes were randomly assigned to either a combination therapy weight loss program for 2 years (C therapy) or a standard therapy weight loss program for 1 year followed by a combination therapy weight loss program in the 2nd year (S/C therapy). C therapy combined the use of meal replacement products, repetitive intermittent low-calorie-diet weeks, and pharmacologic therapy with sibutramine. Outcome measures included changes in weight, glycemic control, plasma lipids, blood pressure, and body composition over 2 years.

RESULTS — A total of 48 participants (23 in the C therapy group and 25 in the S/C therapy group) completed 2 years of study. After 2 years, the C therapy group had weight loss of 4.6 ± 1.2 kg ($P < 0.001$) and a decrease in HbA_{1c} of 0.5 ± 0.3% ($P = 0.08$) from baseline. At 2 years, the C therapy group had significant reductions in BMI, fat mass, lean body mass, and systolic blood pressure. The S/C therapy group showed changes in weight and HbA_{1c} in year 2 of the study that were similar to those demonstrated by the C therapy group in year 1.

CONCLUSIONS — This combination weight loss program resulted in significant weight loss and improved diabetes control over a 2-year period in overweight subjects with type 2 diabetes.

Diabetes Care **28:1311–1315, 2005**

Weight loss is an important therapeutic objective for individuals with type 2 diabetes (1). Short-term studies have demonstrated that weight loss in overweight or obese type 2 diabetic subjects is associated with decreased insulin resistance, improved measures of glycemic control, reduced lipemia, and reduced blood pressure (2–4). However, the most recent American Diabetes Association nutrition recommendations concluded that "optimal strategies for preventing and treating obesity long term have yet to be defined" (5).

Long-term options to promote weight loss in people with type 2 diabetes include standard weight-reduction diets and very-low-calorie diets. However, standard weight-reduction diets are usually not effective (5). Very-low-calorie diets produce substantial initial weight loss but do not maintain weight loss long term (6).

Other approaches to weight loss that might be effective in type 2 diabetic subjects include use of meal replacements, repetitive use of low-calorie diets, and weight loss medications. Hensrud (7) reported significant weight loss at 3 months using meal replacements in type 2 diabetic subjects, but weight and measures of glycemic control trended toward baseline values at 1 year. Williams et al. (8) 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 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, but longer-term follow-up was not provided. Sibutramine treatment of type 2 diabetic subjects for 6 months produced weight loss of ~4.5% but had only modest effects on HbA_{1c} in two studies (9,10) and, at a dose of 15 mg daily, produced weight loss of 5.5 kg and a decrement in HbA_{1c} of 0.6% at 1 year in another study (11). Three 1-year trials compared orlistat to placebo in type 2 diabetic subjects (12–14). Weight loss at 1 year ranged from 4 to 6%, and decrements in HbA_{1c} ranged from 0.5 to 0.9%.

With these studies in mind, 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. The 1-year results have previously been reported (15). Herein, we report the 2-year results with primary focus on those subjects who received the combination therapy weight loss program throughout the entire 2 years of study.

RESEARCH DESIGN AND METHODS

— Potential subjects underwent a history and physical examina-

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Received for publication 18 November 2004 and accepted in revised form 21 February 2005.

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

See accompanying editorial, p. 1526.

tion, screening laboratory tests, and an electrocardiogram. Eligibility criteria were age 30–70 years, diagnosis of type 2 diabetes with HbA_{1c} between 7.0 and 10.0%, BMI between 27 and 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 study was approved by the University of Minnesota Institutional Review Board.

Subjects were evaluated in the University of Minnesota General Clinical Research Center, and 61 eligible subjects were randomly assigned to either a combination therapy weight loss program for 2 years (C therapy) or a standard therapy weight loss program for 1 year followed by the combination therapy weight loss program in the 2nd year (S/C therapy). Randomization was stratified by sex. The S/C therapy group was crossed over to combination therapy after 1 year to promote participant recruitment and retention.

Standard therapy

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- to 1,000-kcal reduction in daily energy intake. Subjects also received an individualized exercise prescription that included, at a minimum, walking for 30 min three times weekly added 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 (16).

Combination therapy

In addition to the standard therapy program described above, the combination therapy weight loss program consisted of the following 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/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 were also seen after each low-calorie-diet week for measurement of weight, pulse, and blood pressure.

After 1 year, the S/C therapy group was crossed over to combination therapy for the 2nd year of the study. The C therapy group continued combination therapy in the 2nd year and thus received 2 continuous years of combination therapy.

At baseline and each follow-up visit, body weight, height, blood pressure, and heart rate were measured. Blood samples for fasting glucose, lipids, and HbA_{1c} were obtained at baseline and 2, 4, 6, 8, 10, 12, 16, 20, and 24 months. Body composition was assessed at baseline and at 2, 6, 12, 16, and 24 months. Diabetes, hypertension, and lipid medications were adjusted, added, or stopped according to a pre-established protocol. All subjects were to attempt to achieve HbA_{1c} values <7% through weight loss. However, 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 two times 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 as previously described (15). LDL cholesterol was calculated unless fasting plasma triglycerides exceeded 400 mg/dl. Body composition was assessed by total-body dual-energy X-ray absorptiometry using a Lunar Prodigy (software version 2.15; General Electric, 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 discontinued study participation before 24 months were excluded from the analysis. Because our main interest was to assess the long-term effects of combination therapy in the C therapy group, the primary outcome was change in weight from baseline to 24 months in the C therapy group. Changes from baseline to 24 months in study parameters were compared within a treatment group by a paired *t* test. A χ^2 test was used to compare categorical data. Relationships between weight loss with C therapy and baseline parameters were examined by least squares linear regression. All data are presented as means ± SE unless otherwise stated. *P* values ≤0.05 were considered significant.

RESULTS — A total of 61 subjects were enrolled and randomly assigned to treatment groups. Two subjects in the S/C therapy group withdrew from the study before their first follow-up visit. Of the remaining 59 subjects, 54 (27 in each group) completed 1 year of the study and 48 (23 in the C therapy group and 25 in the S/C therapy group) completed 2 years of study (77 and 86%, respectively, of the initial study groups). Reasons for early study termination were inability to keep study visits (three subjects), desire to undergo bariatric surgery (one subject), desire to start a commercial weight loss program (two subjects), personal reasons (four subjects), and death as a passenger in a motor vehicle accident (one subject).

Figure 1 shows the weight loss trends for the C therapy and S/C therapy groups. Mean weight loss was greatest at 10 months in the C therapy group. There was then slow regain over the subsequent 14 months. A pattern of weight loss during low-calorie-diet weeks with subsequent

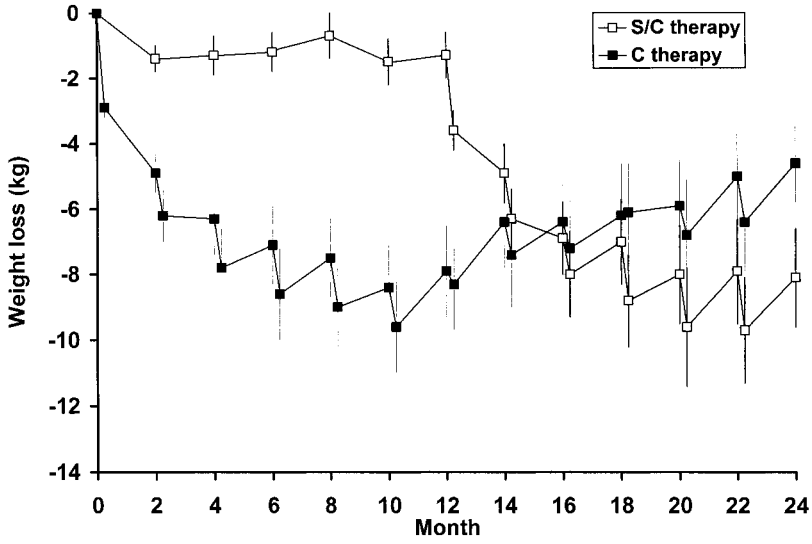

Figure 1—*Mean (±SE) change in weight from baseline in the S/C therapy and C therapy groups.*

weight regain in the period between low-calorie-diet weeks was observed throughout the study. At the end of 2 years, weight loss in the C therapy group was 4.6 ± 1.2 kg ($P = 0.001$).

As previously reported, the S/C therapy group lost little weight during year 1 of standard therapy (15). After starting combination therapy at the beginning of year 2, this group demonstrated a pattern of weight loss similar to that observed during year 1 in the C therapy group. Weight loss in the S/C therapy group at 2 years was 8.1 ± 1.6 kg ($P < 0.001$).

Figure 2 shows HbA_{1c} values for the two groups during the study. Baseline HbA_{1c} was 8.1 ± 0.2% for both groups. HbA_{1c} at 2 years decreased 0.5 ± 0.3% in the C therapy group ($P = 0.08$). HbA_{1c} at 2 years decreased 0.3 ± 0.2% in the S/C therapy group ($P = 0.18$).

The focus of our study was the long-term effects of the combination weight loss program, and Table 1 compares baseline and 24-month metabolic, cardiovascular, and lipid parameters for the C therapy group. Most parameters showed improvement at 2 years compared with baseline, but only the changes in weight, BMI, fat mass, lean body mass, and systolic blood pressure were significant. Changes in HbA_{1c} and diastolic blood pressure were on the threshold of significance. At the end of 2 years, diabetes medications in the C therapy group were unchanged from baseline in six subjects, increased from baseline in eight subjects, and decreased from baseline in nine subjects. Thus, 65% of subjects in the C therapy group were on the same or a reduced dose of diabetes medications after 2 years.

Seventy-seven percent of subjects initially assigned to combination therapy completed the entire 2 years of study. Compliance with the intermittent low-calorie-diet weeks was generally good, as evidenced by the repetitive demonstration of weight loss during these weeks. During the 2nd year of the study, there was less weight loss during low-calorie-diet weeks and more weight gain during intervening weeks. This led to a gradual increase in weight during the 2nd year of study. Over the course of 2 years, subjects in the C therapy group lost a total of 14.3 kg during low-calorie-diet weeks and regained a total of 9.7 kg between low-calorie-diet weeks.

We examined the relationship between weight loss with C therapy and various factors that might predict response to the weight loss intervention. Independent variables analyzed were age, sex, duration of diabetes and baseline weight, HbA_{1c}, waist circumference, and percent body fat. Weight loss (percent of initial weight) was the dependent variable. Women had significantly greater weight loss than men after 12 months of C therapy (8.6 ± 1.5 vs. 4.7 ± 0.9%, $P = 0.03$). Percent body fat at baseline was also significantly correlated with weight loss ($r = 0.49$, $P = 0.02$). Women had significantly greater percent body fat than men, so sex and body fat are not independent of each other. None of the other variables tested was a significant predictor of weight loss during C therapy.

After 2 years, 14 subjects (61%) in the C therapy group were taking sibutramine (15 mg daily in 13 subjects and 10 mg daily in one subject). Sibutramine was discontinued by nine subjects for a variety of reasons, which included starting antidepressant therapy (one subject), possible side effects (constipation, dry mouth, and difficulty with urination, one subject each), concern over possible blood pres-

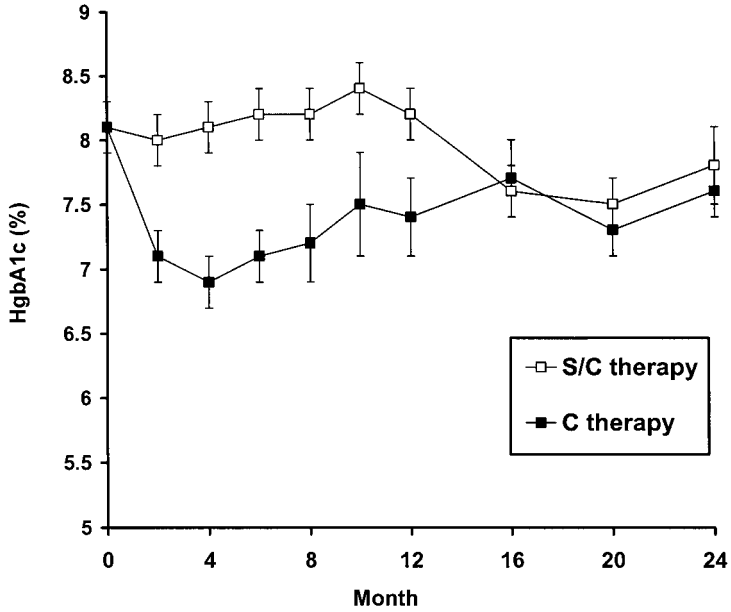

Figure 2—*Mean (±SE) HbA_{1c} values in the S/C therapy and C therapy groups.*

Table 1—*Comparison of baseline and 2-year data for subjects on C therapy*

	Baseline	2-year	Change	*P*
n (women/men)	23 (11/12)	23 (11/12)		
Age (years)	51 ± 2			
Duration of diabetes (years)	4 ± 1			
Diabetes medications				
None	2	1		
One	7	5		0.62
Two or more	14	17		
Weight (kg)	113.2 ± 4.4	108.6 ± 4.2	−4.6 ± 1.2	0.001
BMI (kg/m^2)	38.5 ± 1.1	36.9 ± 1.0	−1.6 ± 0.4	0.001
Body fat (kg)	46.8 ± 2.5	44.8 ± 2.2	−2.0 ± 0.8	0.03
Lean body mass (kg)	62.6 ± 3.0	60.0 ± 2.9	−2.6 ± 0.8	0.002
Fasting glucose (mg/dl)	158 ± 9	148 ± 12	−9 ± 15	0.56
HbA_{1c} (%)	8.1 ± 0.2	7.6 ± 0.2	−0.5 ± 0.3	0.08
Resting pulse (bpm)	80 ± 2	79 ± 2	−1 ± 2	0.55
Systolic blood pressure (mmHg)	139 ± 2	132 ± 2	−7 ± 3	0.03
Diastolic blood pressure (mmHg)	77 ± 2	73 ± 2	−4 ± 2	0.06
Fasting cholesterol (mg/dl)	197 ± 10	185 ± 9	−12 ± 11	0.29
HDL cholesterol (mg/dl)	40 ± 2	38 ± 2	−1 ± 1	0.37
LDL cholesterol (mg/dl)*	115 ± 8	102 ± 6	−13 ± 9	0.14
Fasting triglycerides (mg/dl)	233 ± 32	225 ± 43	−8 ± 42	0.85

Data are means ± SE. *Excludes four subjects with fasting triglycerides >400 mg/dl at baseline. 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.

sure effects (three subjects), and personal reasons (two subjects).

There were no serious adverse events related to the study protocol. Some subjects experienced mild hypoglycemia during low-calorie-diet weeks and required temporary reductions in diabetes medications. There were no episodes of serious hypoglycemia. No subject dropped out of the study because of adverse effects caused by the combination therapy intervention. Sibutramine was discontinued as a precaution in one subject in the S/C therapy group after an episode of transient atrial fibrillation and in another subject in the S/C therapy group after a possible seizure.

CONCLUSIONS — The purpose of our study was to combine several weight loss treatments in an effort to produce and maintain substantial weight loss over an extended period in subjects with type 2 diabetes. We have previously reported that this combination program for weight loss produced significantly more weight loss and improved diabetes control compared with a standard weight loss program at 1 year (15). We now report that subjects who followed the combination therapy program for 2 years maintained significant weight loss of 4.6 kg and had a decrement in HbA_{1c} of 0.5%. This occurred in the setting of constant or reduced doses of diabetes medications in two-thirds of the subjects. Lipid and cardiovascular parameters tended to be lower at 2 years in these subjects, although the changes were small and only the change in systolic blood pressure reached statistical significance. Because 61% of subjects in the C therapy group were still taking sibutramine at the end of the study, it appeared that weight loss was able to mitigate any blood pressure–raising effect of sibutramine.

Because we have previously reported the effects of the combination therapy program in the initial year after implementation (15), we have not focused in this report on the effects of combination therapy in the S/C therapy group. It is apparent from Figs. 1 and 2 that the S/C therapy group experienced similar changes in weight and glycemic control when combination therapy was initiated.

The long-term treatment effect of combination therapy would have been better assessed if we had an appropriate control group throughout the entire study. Although the S/C therapy group provided an appropriate control for the initial study year, this group was allowed to crossover to combination therapy for the 2nd year. This was done for retention purposes because we felt it unlikely that subjects would remain active participants in standard therapy for 2 years. Data from the U.K. Prospective Diabetes Study and the Diabetes Prevention Program suggest that the natural history of glycemic control in obese individuals with type 2 diabetes or glucose intolerance is one of gradually increasing HbA_{1c} (17,18). In these studies, mean HbA_{1c} levels increased by 0.05–0.15% annually. Therefore, our observed decrement in HbA_{1c} of 0.5% at 2 years compared with the baseline value may underestimate the clinical benefit of weight loss on long-term diabetes control.

Because of our study design, 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. The relative contributions of the three components probably varied among subjects. It is noteworthy that the gradual weight regain over the latter portion of our study was accompanied by decreased weight loss during low-calorie-diet weeks, increased weight regain between low-calorie-diet weeks, and decreased use of sibutramine by subjects. This suggests that the weight regain observed was due to decreased adherence to the combination therapy program, perhaps because the novelty of the program decreased over time.

Few controlled prospective studies have examined strategies for or effects of long-term weight loss in people with type 2 diabetes (19). We are not aware of any prospective study that has reported 2-year outcomes of weight loss in subjects with type 2 diabetes. Results of the Diabetes Prevention Program showed that over an average follow-up period of 2.8 years, modest amounts of weight loss (similar to that observed in our study) and increased physical activity reduced the risk of developing type 2 diabetes. The ongoing Action for Health in Diabetes (Look AHEAD) study is an 11-year prospective controlled multi-center clinical trial sponsored by the National Institutes of Health that will specifically examine the question of whether long-term weight loss is achievable and beneficial in overweight individuals with type 2 diabetes

(www.niddk.nih.gov/patient/SHOW/lookahead.htm).

In summary, overweight or obese people with type 2 diabetes receiving a weight loss intervention that combined intermittent low-calorie diets, daily meal replacements, and the medication sibutramine achieved and maintained significant weight loss over a 2-year period. This was accompanied by improvement in diabetes control. The intervention used was simple and easy for subjects to understand and implement. The cost of the program was about $6 per day, from which the cost of usual meals and snacks that were omitted (two to six per day) should be subtracted. Our data suggest that weight loss at 2 years of 4–5 kg (~4% of initial body weight) for people with type 2 diabetes can produce improvements in diabetes control that are likely to be clinically significant.

Acknowledgments— This study was supported by grant M01RR00400 from the Division of Research Resources, National Institutes of Health, and grants from Abbott Laboratories and Slim Fast Nutrition Institute.

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

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