The Effect of Short Periods of Caloric Restriction on Weight Loss and Glycemic Control in Type 2 Diabetes

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OBJECTIVE — To determine whether an intermittent very-low-calorie diet (VLCD) improves weight loss and glycemic control more than moderate caloric restriction alone.

RESEARCH DESIGN AND METHODS — Individuals with type 2 diabetes (n = 54) who were ≥20% over ideal body weight participated in a 20-week behavioral weight control program. Subjects were randomized to either a standard behavioral therapy (SBT) group or to one of two VLCD groups. SBT subjects received a 1,500–1,800 kcal/day diet throughout. Both VLCD groups followed a VLCD for 5 consecutive days during week 2, followed by either intermittent VLCD therapy for 1 day/week for 15 weeks (1-day) or for 5 consecutive days every 5 weeks (5-day), with a 1,500–1,800 kcal/day diet at other times.

RESULTS — Both VLCD groups lost more weight than the SBT group over the 20 weeks (P = 0.04). Although the groups did not differ in fasting plasma glucose (FPG) changes at 20 weeks, more subjects in the 5-day group attained a normal HbA_{1c} when compared with the SBT group (P = 0.04). This benefit was independent of the effects of weight loss. The best predictor of overall change in FPG and HbA_{1c} was the FPG response during the first 3 weeks of the program.

CONCLUSIONS — Periodic VLCDs improved weight loss in diabetic subjects. A regimen with intermittent 5-day VLCD therapy seemed particularly promising, because more subjects in this group attained a normal HbA_{1c}. Moreover, the glucose response to a 3-week period of diet therapy predicted glycemic response at 20 weeks, and it was a better predictor of the 20-week response than initial or overall weight loss.

Obesity is central in the pathogenesis of type 2 diabetes. Weight loss can improve glycemic control, insulin sensitivity, insulin secretion, and hepatic glucose production (HGP) in these patients (1), but weight loss is difficult to achieve and maintain. Very-low-calorie diet (VLCD) therapy consisting of 400–800 kcal/day used for continuous periods of up to 16 weeks is one approach to promoting weight loss in individuals with type 2 diabetes. Although weight loss occurs rapidly with VLCD therapy, long-term differences in weight loss between VLCDs and lesser degrees of caloric restriction have not been dramatic (2–4).

In an attempt to maximize long-term weight loss, VLCD therapy has been used intermittently for two 12-week periods over the course of 1 year (2,5). Although weight loss with the initial VLCD period was greater than with less severe caloric restriction, reinstitution of the VLCD resulted in a slower rate of weight loss due to reduced adherence to the prescribed therapy (6). Shorter periods (i.e., days rather than weeks) of VLCD therapy may be easier for patients to incorporate into their lifestyle on a long-term basis; however, it is not known whether such brief periods of VLCD therapy can improve weight loss compared with moderate caloric restriction alone.

In type 2 diabetes, VLCD therapy has benefits beyond the effects of weight loss. VLCD therapy resulted in greater improvements in glycemic control, despite similar amounts of weight loss, when compared with lesser degrees of caloric restriction (2,5). The metabolic benefits of VLCD therapy occur relatively quickly. The majority (87%) of the total reduction in fasting plasma glucose (FPG) attained with weight loss is achieved within the first 10 days of VLCD therapy (7). The metabolic changes that account for this decline in FPG parallel those observed with weight loss. Within 7 days of initiation of a VLCD, approximately half of the overall improvement in HGP, peripheral insulin sensitivity, and insulin secretion that is eventually attained with a 13-kg weight loss occurs (8). However, the beneficial effects of caloric restriction on FPG diminish when caloric intake is liberalized, even if weight loss is maintained (7). Reinstitution of VLCD therapy may be necessary to promote sustained improvements in FPG. The optimal time interval for reinstitution of VLCD therapy and the duration of VLCD needed to produce improvements in glycemic control are not known.

To date, there has been no effort to utilize the beneficial effects of short-term intermittent caloric restriction as a clinical approach to the management of type 2 diabetes. The purposes of this study were *1*) to determine whether moderate caloric restriction with intermittent VLCD therapy improves weight loss or glycemic control compared with moderate caloric restriction alone over the course of 20 weeks and 2) to determine an optimal interval for intermittent VLCD therapy (i.e., 1 day/week vs. 5 days every 5 weeks).

RESEARCH DESIGN AND METHODS

Subjects

Subjects with type 2 diabetes between 30 and 70 years of age who were more than

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Abbreviations: ANOVA, analysis of variance; FPG, fasting plasma glucose; HGP, hepatic glucose production; NIH, National Institutes of Health; SBT, standard behavioral therapy; VLCD, very-low-calorie diet.

Table 1—*Study design*

	Week																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
SBT	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1-day	—	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	—	—	—
5-day	—	5	—	—	—	—	5	—	—	—	—	5	—	—	—	—	5	—	—	—

Dashes represent 1,500–1,800 kcal/day. Numbers represent total number of days of VLCD per week.

20% above ideal body weight based on Metropolitan Life Insurance norms (9) and not currently receiving insulin therapy were recruited by newspaper advertisements. Subjects with a history of liver disease, renal disease, or heart disease that would contraindicate the use of a VLCD were excluded. Oral diabetes medications were stopped 2 weeks before participation in the study. Subjects with FPG levels >16.7 mmol/l when medications were discontinued were excluded. All subjects signed a consent form approved by the University of Pittsburgh Biomedical Institutional Review Board.

Design

Eligible subjects were blocked by FPG after 2 weeks off diabetes medication (<7.8, 7.8–11.1, and >11.1 mmol/l) and then randomized, by blocks, to one of three treatment conditions. The three treatment conditions differed primarily in the diets that were prescribed (Table 1). The standard behavioral therapy (SBT) group was prescribed a 1,500–1,800 kcal/day diet throughout the 20 weeks of the treatment program. The remaining groups were also prescribed a 1,500–1,800 kcal/day diet, except for a total of 20 study days during which they consumed a 400–600 kcal/day VLCD. One of these groups (1-day) followed a VLCD for 5 consecutive days during week 2 of the study and then 1 day a week for 15 weeks while the other group (5-day) followed a VLCD for 5 consecutive days during weeks 2, 7, 12, and 17. Thus, totaled over the 20 weeks, the assigned mean caloric intake for the two VLCD groups was identical but 18,000–28,000 kcal lower than the SBT group.

Treatment conditions

Behavioral weight control program. All three groups participated in a 20-week behavioral treatment program. Weekly group meetings were conducted by a multidisciplinary team of therapists (including a behavioral therapist, nutritionist, exercise physiologist, and physician) and included instruction on behavioral modification, exercise, and diet.

Behavior modification strategies were emphasized in the program. Subjects recorded their daily caloric intake and exercise in diaries throughout the program. Stimulus control techniques, including strategies for removing food cues from the environment, slowing the act of eating, and separating eating from other activities, were presented. Techniques for modifying cognitions, for relapse prevention, and for self-reinforcement were taught. Subjects were also instructed to increase their walking and were given weekly exercise goals, starting at 1 mile/week and increasing to 10 miles/week.

Diets. All subjects were given a calorie goal of 1,500–1,800 kcal/day, depending on initial body weight, and were instructed to remain at this calorie goal throughout the program, unless ideal body weight was achieved. Information was presented regarding the differences in caloric content of protein, fat, and carbohydrate, and subjects were encouraged to reduce their total fat intake to 20% of their total daily calories. A registered dietitian reviewed these diaries weekly and provided all subjects with individualized written comments regarding their reported diet and exercise in order to insure compliance with the study protocol.

Subjects in the 1-day and 5-day groups consumed a total of 20 days of a VLCD consisting of 400–600 kcal/day of high-quality protein (lean meat, fish, or fowl) and portion-controlled low-calorie diet entrees. To increase compliance to this diet, all food for the VLCD was provided to the subjects for home use by the General Clinical Research Center during these periods.

Medication. All patients received individual training in the techniques of self-monitoring of blood glucose and were instructed to check their FPG twice weekly and notify the study physician if any of these values were >13.9 mmol/l. If a reading of >13.9 mmol/l was confirmed by our laboratory during week 3 of the study or later, oral diabetes medications were resumed at half of the dose prescribed before the study. Subjects who restarted medications continued in the active treatment portion of the program assigned at randomization.

Dependent measures

Subjects were weighed in street clothes without shoes using a balance-beam scale. Height was measured with a stadiometer. Weekly self-report diaries were used to assess caloric intake throughout the study.

Plasma samples for FPG, insulin, HbA_{1c}, and lipids were drawn on all subjects after a 12-h fast at the following time points: baseline, 10 weeks, and 20 weeks. Insulin and FPG levels were also drawn at 3 weeks in order to assess the short-term effect of the initial VLCD period and to determine whether the initial FPG response could predict overall change in FPG. Blood work in all groups was obtained while subjects were following the 1,500–1,800 kcal/day component of their dietary program. All plasma samples except glucose were frozen at −20°C for subsequent analysis.

FPG was measured by the glucose oxidase method (Yellow Springs Instruments, Yellow Springs, OH). HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad, Hercules, CA). The laboratory normal for HbA_{1c} was 4.3–6.0%. Serum insulin was analyzed by a radioimmunoassay developed by Linco Research (St. Charles, MO). Cholesterol and triglyceride levels were measured on plasma samples taken in eidetic acid tubes. Enzymatic procedures were used to determine total cholesterol (10), triglycerides (11), and HDL cholesterol (12). LDL cholesterol was calculated by the Friedewald equation, omitting subjects with triglycerides >400 mg/dl (13).

Table 2—*Baseline characteristics of subjects in each treatment group*

	SBT	1-day	5-day	*P* value
n	18	18	18	
Women/men	11/7	9/9	11/7	0.74
White/black/Hispanic	16/2/0	15/2/1	12/6/0	0.10
Diet-controlled	6	8	5	0.57
Age (years)	54.1 ± 7.0	51.4 ± 7.9	50.3 ± 8.6	0.34
Weight (kg)	98.9 ± 17.6	103.5 ± 16.8	104.8 ± 13.7	0.52
BMI (kg/m^2)	35.0 ± 5.2	35.4 ± 5.4	37.3 ± 4.8	0.37
FPG (mmol/l)	10.2 ± 3.4	9.8 ± 3.1	10.1 ± 3.2	0.93
HbA_{1c} (%)	8.4 ± 1.9	7.9 ± 1.5	8.0 ± 1.7	0.56
Insulin (pmol/l)	150 ± 60	140 ± 75	120 ± 45	0.38
Total cholesterol (mmol/l)	5.64 ± 1.09	5.58 ± 0.97	5.39 ± 1.02	0.76
Triglycerides (mmol/l)	2.49 ± 1.57	2.35 ± 1.03	2.30 ± 2.7	0.96
HDL cholesterol (mmol/l)	1.20 ± 0.29	1.08 ± 0.21	1.10 ± 0.20	0.26
LDL cholesterol (mmol/l)	3.28 ± 1.23	3.42 ± 0.90	3.39 ± 0.76	0.90

Data are *n* or means ± SD. *P* values represent χ^2 for sex, race, and diet-controlled and one-way ANOVA for remainder of variables. Diet-controlled represents the number of subjects not on diabetes medication before entering the study.

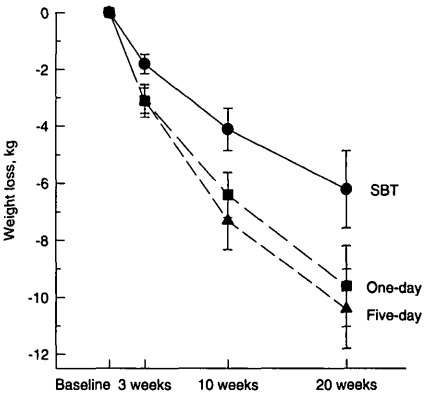

Figure 1—*Weight loss over time by treatment group (mean ± SE). Data shown are for subjects who completed assessments at all four time points (SBT, n = 15; 1-day, n = 16; 5-day, n = 15).*

Statistical analysis

The Statistical Package for the Social Sciences-Personal Computer (SPSS-PC) was used for data analysis. Because insulin and triglyceride levels were not normally distributed, these values were log-transformed before data analysis. One-way analysis of variance (ANOVA) and χ^2 were used to determine whether the treatment groups differed in demographic and metabolic indexes at baseline. One-way ANOVA was also used to compare changes in measured variables at each time point, and post hoc analyses for two-sided *P* values <0.05 were performed using the Newman-Keuls test procedure. The χ^2, with use of Fisher's exact test when appropriate, was used to assess differences in nominal data. Student's *t* test was used when comparing two continuous variables. All available data points were used for comparison to baseline variables. All data are reported as mean ± SD unless otherwise indicated.

RESULTS — Fifty-four subjects (31 women; 23 men) entered the treatment study. The three treatment groups did not differ in baseline characteristics (Table 2). Forty-seven (87%) of the 54 subjects completed week 20 assessments. Dropout rate was similar across treatment conditions. Reported reasons for dropping out included illness in the family, a change in work schedule, or a move to another region of the country that precluded attendance at the weekly treatment meetings. Baseline characteristics of dropouts were not different from subjects who completed the study. Attendance rates at weekly treatment meetings did not differ between groups (*P* = 0.62).

Weight loss

Weight loss for subjects who completed all four assessments is shown in Fig. 1. The intermittent VLCD therapy groups lost nearly twice as much weight over the course of 20 weeks as the SBT group.

Analyses done on all subjects available at a given time point confirmed the pattern seen in Fig. 1. Over the full 20-week program, the 5-day group lost 10.4 ± 5.4 kg (*n* = 15) and the 1-day group lost 9.6 ± 5.7 kg (*n* = 16) compared with a weight loss of only 5.4 ± 5.9 kg (*n* = 16) in the SBT group (*P* = 0.04). Although the mean weight losses in the two VLCD groups did not differ, 93% of the subjects in the 5-day group lost >5 kg over the course of 20 weeks compared with only 50% of the subjects in the SBT group (*P* = 0.02). In the 1-day group, 69% of the subjects lost >5 kg over the course of 20 weeks, which was not significantly different from either the 5-day (*P* = 0.17) or the SBT (*P* = 0.28) groups.

The majority of the difference in weight loss between the SBT and VLCD groups occurred during the first 10 weeks of the study. The mean weight losses were 7.4 ± 3.9 kg (*n* = 16) in the 5-day group, 6.2 ± 3.2 kg (*n* = 17) in the 1-day group, and 4.0 ± 2.8 kg (*n* = 16) in the SBT group (*P* = 0.02). The three groups did not differ in weight loss between weeks 10 and 20 (*P* = 0.46), with the 5-day group losing 3.1 ± 2.4 kg (*n* = 15), the 1-day group losing 3.2 ± 3.1 kg (*n* = 16), and the SBT group losing 2.0 ± 2.8 kg (*n* = 15).

Sex differences in weight loss were determined by ANOVA, controlling for baseline weight. Men and women did not differ in overall weight loss across treatment groups (*P* = 0.66), but a treatment by sex interaction was found (*P* < 0.01). Men in both the 5-day (*n* = 5) and 1-day (*n* = 9) groups lost more weight (14.7 ± 5.5 and 11.6 ± 5.0 kg, respectively) than men in the SBT group (1.5 ± 6.9 kg, *n* = 5, *P* < 0.05). In contrast, women achieved similar weight loss with SBT (7.8 ± 3.7 kg, *n* = 10), 5-day (8.2 ± 4.1 kg, *n* = 10), and 1-day (7.0 ± 5.7 kg, *n* = 7) therapies.

Glycemic control

The three groups did not differ in number of subjects who met the safety criterion for restarting oral diabetes medications based on FPG values >13.9 mmol/l (*P* = 0.60 for differences between groups). Three subjects in the SBT group, one subject in the 1-day group, and three subjects in the 5-day group met this criterion. Compared with the remainder of the study subjects, the seven who restarted medications had higher baseline FPG values (15.1 ± 1.2 vs. 9.3 ± 2.7 mmol/l, respectively, *P* < 0.01) and lower baseline insulin levels (100 ± 30 vs. 140 ± 60 pmol/l, *P* = 0.07). Subjects who restarted medications had similar improvements in FPG from baseline to 3 weeks compared with subjects who did not restart medications (*P* = 0.91); however, despite these improvements, their FPG exceeded 13.9 mmol/l at 3 weeks (*n* = 2) or 10 weeks (*n* = 5). They also had similar weight

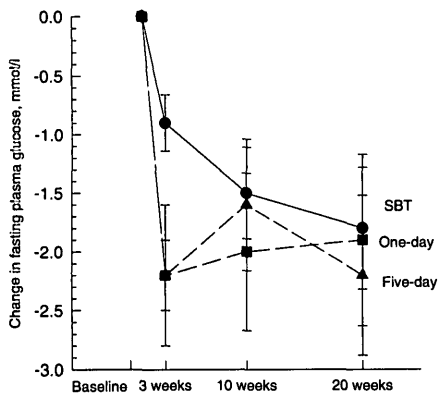

Figure 2—*Change in FPG over time by treatment group (mean ± SE). Data shown are for subjects who completed assessments at all four time points (SBT [●], n = 15; 1-day [■], n = 16; 5-day [▲], n = 15). At week 10, two subjects in the SBT group had restarted oral diabetes medications. At week 20, three subjects in the SBT group, one subject in the 1-day group, and three subjects in the 5-day group had restarted oral diabetes medications. The last FPG value obtained before restarting oral diabetes medications was used at these time points.*

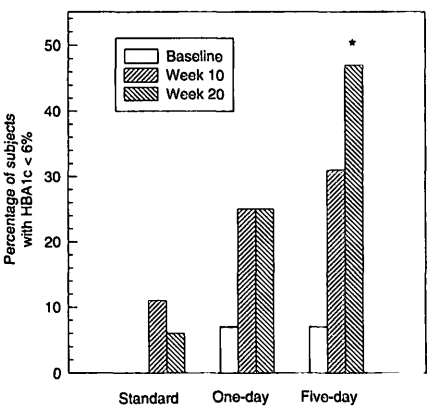

Figure 3—*Percentage of subjects with HbA_{1c} values in the normal range in each treatment group at baseline, week 10, and week 20. *P < 0.05 compared with standard treatment group, χ^2.*

loss at 20 weeks compared with subjects who did not restart medications ($P = 0.64$). Because oral diabetes medications can affect glucose, HbA_{1c}, insulin, and lipid levels, the last values obtained for these dependent variables before reinitiating medication were used in analyses of all subsequent time points. This method assumes that these variables would have neither worsened nor improved with continued diet and weight-loss therapy. Excluding these subjects from the data analysis completely did not influence the statistical interpretation of the differences between the three groups.

Both VLCD groups had greater improvements in FPG than the SBT group at 3 weeks (Fig. 2). FPG levels at 3 weeks decreased by 2.2 ± 2.3 mmol/l ($n = 17$) in the 1-day group and by 2.3 ± 1.5 mmol/l ($n = 18$) in the 5-day group compared with a decrease of only 0.8 ± 0.9 mmol/l ($n = 17$) in the SBT group ($P = 0.02$). The three groups did not differ in FPG at the end of the 20-week study ($P = 0.85$), but 74% ($n = 23$) of patients in the VLCD groups ended the study with an FPG ≤7.8 mmol/l compared with only 47% ($n = 7$) of the patients in the SBT group ($P = 0.07$). After controlling for differences in weight loss between groups, logistic regression showed no effect of treatment group on attainment of an FPG ≤7.8 mmol/l at 20 weeks.

Overall changes in HbA_{1c} also did not differ significantly between conditions over 0–10 weeks (SBT: −0.03 ± 1.03%, $n = 14$; 1-day: −0.65 ± 1.35%, $n = 16$; 5-day: −0.40 ± 1.14%, $n = 16$; $P = 0.30$) or over 0–20 weeks (SBT: −0.23 ± 1.04%, $n = 15$; 1-day: −0.71 ± 1.59%, $n = 16$; 5-day: −0.97 ± 1.70%, $n = 15$; $P = 0.38$). However, the groups differed in the percentage of patients who attained a normal HbA_{1c} at 20 weeks (Fig. 3). Seven subjects (47%) in the 5-day group achieved a normal HbA_{1c} at 20 weeks compared with only 1 (8%) subject in the SBT group ($P = 0.04$). Five subjects (31%) in the 1-day group achieved a normal HbA_{1c} level at 20 weeks, which did not differ significantly from the SBT group ($P = 0.17$) or the 5-day group ($P = 0.38$). Logistic regression, using attainment of a normal HbA_{1c} (<6%) at week 20 as the dependent variable and weight loss and treatment group (with two dummy variables) as the independent variables, showed no significant effect of weight loss on whether a normal HbA_{1c} was achieved. However, there was an effect of treatment condition, with subjects in the 5-day group more likely to attain a normal HbA_{1c} value compared with subjects in the SBT group ($P = 0.05$).

Men and women did not differ in baseline FPG or HbA_{1c}, and no sex, treatment, or sex by treatment effects were found for changes in either FPG or HbA_{1c}.

Predictors of glycemic response

Subsequent analyses were done to determine whether it was possible to predict overall improvement in FPG or HbA_{1c} (0–20 weeks) using either baseline data or initial changes (0–3 weeks) observed. Data from the three treatment groups were combined for these analyses (Table 3). There was a highly significant correlation between initial changes in FPG (0–3 weeks) and overall changes in FPG (0–20 weeks). This association, which had an r of 0.73 ($P < 0.01$) is shown in Fig. 4. Initial changes in FPG also predicted overall changes in HbA_{1c} ($r = 0.45$, Table 3). Although initial changes in weight (0–3 weeks) and overall changes in weight (0–20 weeks) were also significantly associated with improvements in FPG and HbA_{1c} (Table 3), these effects were not independent of the effects of initial changes in FPG.

Insulin and lipids

The groups did not differ in changes in

Table 3—*Univariate predictors of overall changes in glycemic control*

	Week 20 − baseline			
	Change in FPG		Change in HbA_{1c}	
	r	P	r	P
Baseline				
FPG	−0.24	0.12	0.13	0.39
HbA_{1c}	−0.07	0.63	−0.08	0.61
Weight	−0.21	0.17	−0.24	0.10
Insulin	−0.17	0.26	−0.26	0.08
Change, week 3 − baseline				
FPG	0.73	<0.01	0.45	<0.01
Weight	0.39	<0.01*	0.31	0.04*
Insulin	0.11	0.48	0.04	0.81
Change, week 20 − baseline				
Weight	0.57	<0.01*	0.33	0.03*
Insulin	0.14	0.37	0.08	0.62

*After adjusting for changes in FPG (0–3 weeks), these associations became nonsignificant.

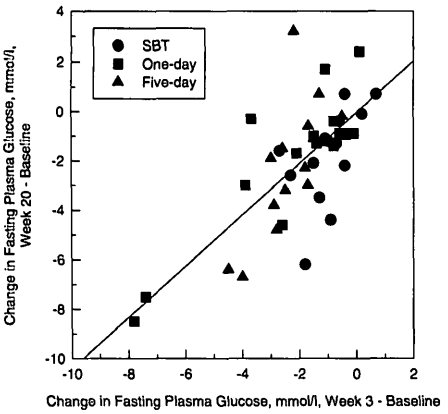

Figure 4—*Regression plot of change in FPG between week 3 and baseline against change in FPG between week 20 and baseline by treatment group (r = 0.73, P < 0.01).*

insulin or lipids at any time point. All groups had lower insulin, total cholesterol, and triglyceride levels but no difference in LDL and HDL cholesterol at 20 weeks compared with baseline (Table 4).

Table 4—*Mean fasting insulin and lipid values at each time point by treatment group*

	Standard	1-day	5-day	*P* value
n	14	16	15	
Fasting insulin (pmol/l)				
Baseline	139 ± 59	142 ± 77	115 ± 41	0.43
3 weeks*	116 ± 41	109 ± 47	120 ± 43	0.69
10 weeks*	119 ± 58	106 ± 55	118 ± 55	0.69
20 weeks*	106 ± 40	103 ± 52	104 ± 34	0.88
Total cholesterol (mmol/l)				
Baseline	5.46 ± 1.17	5.60 ± 1.01	5.26 ± 0.91	0.66
3 weeks*	5.02 ± 0.62	4.91 ± 0.84	4.80 ± 0.73	0.72
10 weeks*	5.03 ± 0.95	5.10 ± 1.39	5.01 ± 0.85	0.98
20 weeks*	5.21 ± 1.06	5.29 ± 1.33	4.96 ± 0.76	0.69
LDL cholesterol (mmol/l)				
Baseline	3.31 ± 1.01	3.48 ± 0.87	3.36 ± 0.69	0.87
3 weeks*	3.08 ± 0.64	3.23 ± 0.77	3.09 ± 0.66	0.80
10 weeks*	3.08 ± 0.66	3.15 ± 1.08	3.21 ± 0.63	0.92
20 weeks	3.12 ± 0.71	3.33 ± 1.08	3.17 ± 0.56	0.77
HDL cholesterol (mmol/l)				
Baseline	1.20 ± 0.30	1.10 ± 0.20	1.09 ± 0.17	0.40
3 weeks*	1.10 ± 0.30	1.03 ± 0.17	1.00 ± 0.15	0.49
10 weeks*	1.07 ± 0.24	1.03 ± 0.19	1.06 ± 0.21	0.91
20 weeks	1.05 ± 0.30	1.13 ± 0.23	1.08 ± 0.22	0.76
Triglycerides (mmol/l)				
Baseline	2.55 ± 1.78	2.23 ± 0.94	1.76 ± 0.84	0.21
3 weeks*	1.84 ± 0.56	1.40 ± 0.47	1.55 ± 0.78	0.10
10 weeks*	2.37 ± 2.07	1.98 ± 0.82	1.61 ± 0.63	0.51
20 weeks*	1.89 ± 1.01	1.08 ± 0.96	1.54 ± 0.79	0.46

Data are means ± SD. *P* values represent between-group comparisons by one-way ANOVA. *$P < 0.05$ compared with baseline for all three groups combined by paired-samples Student's *t* test.

CONCLUSIONS — This is the first study to examine, as a clinical strategy, the effects of brief (1- to 5-day) periods of VLCD therapy on weight loss and glycemic control in subjects with type 2 diabetes. The principal finding is that periodic VLCD produced nearly twice as much weight loss as SBT alone. In addition, an initial period of 5 days of VLCD therapy resulted in more rapid improvements in FPG than did SBT. Although overall improvements in FPG and HbA_{1c} did not differ between groups, more subjects in both VLCD groups achieved FPG values ≤7.8 mmol/l at the end of the study, and more subjects in the 5-day group attained a normal HbA_{1c} value at the end of 20 weeks when compared with those receiving SBT. Attainment of a normal HbA_{1c} value was independent of the effects of weight loss in the 5-day group. In all groups combined, initial change in FPG after 3 weeks of caloric restriction was predictive of overall change in FPG regardless of overall weight loss achieved.

The differences in weight loss between the VLCD groups and the SBT group were greater than anticipated by the differences in prescribed caloric restriction. The overall prescribed caloric intake was only 10% lower in the VLCD groups, yet these groups lost nearly twice as much weight as the SBT group. Although the groups did not differ in attendance rates at weekly behavioral therapy meetings, the greater weight loss in the VLCD groups suggests these subjects were more compliant with the assigned therapy than those in the SBT group. Provision of the food for the 20 days of the VLCD may have helped increase compliance, but provision of food for this brief period over the course of the 140 days of the study would not be expected to have such a large effect on weight. All groups received identical exercise prescriptions, had their food and exercise diaries reviewed weekly by a dietitian, and received individualized written comments to ensure compliance with the study protocol. Thus, it is unlikely that differences in exercise between groups contributed significantly to the observed differences in weight loss.

Although intermittent 1- to 5-day VLCD therapy appeared to be particularly useful for men in this study, opposite sex-specific findings were found in a prior study (5). When VLCD therapy used at 3-month intervals was compared with continuous intake of 1,000 kcal/day, women attained the greatest weight-loss advantage from the VLCD, while men achieved equal weight loss regardless of therapy (5). Conclusions regarding sex-specific responses to therapy in this study are limited by the small sample size in sex by treatment comparisons.

Previous studies have also shown greater weight loss with VLCD therapy over the course of 6 months compared with more moderate caloric restriction (2–5). The majority of these studies have used VLCD therapy for 3-month periods. In this study, the equivalent of 1 day of VLCD therapy per week resulted in greater weight loss than SBT alone regardless of whether subjects followed the VLCD for 1 day/week or for 5 days every 5 weeks. The advantage of intermittent 1- to 5-day periods of VLCD therapy is that this therapy may be continued indefinitely while offering the patient some degree of flexibility in choosing the days to follow the VLCD. However, because previous studies have not shown substantial differences in weight loss at 1 year in subjects who received 3-month periods of VLCD therapy compared with subjects who received less severe degrees of caloric

restriction, long-term studies are needed to determine the ability of intermittent VLCD to promote sustained differences in weight loss beyond a 20-week period.

No adverse effects of the intermittent VLCD therapy were observed in this study or studies with 8- to 12-week VLCDs (2–5). Future studies that use intermittent VLCD therapy for longer periods could add measures of psychological and physiological stress. This would be particularly interesting because prior studies have shown that subjects find it most difficult to comply with the first few days of VLCD therapy (14), suggesting that compliance with intermittent VLCD therapy may be more difficult than continuous VLCD therapy.

In addition to the differences in weight loss, the VLCD groups showed greater initial improvements in FPG than did the SBT group. This finding is consistent with previous reports of marked improvement in FPG before substantial weight loss is achieved with the initiation of continuous 400–800 kcal/day diets (7,8). The metabolic changes responsible for the early decline in FPG in response to the VLCD include early improvement in HGP, peripheral insulin sensitivity, and insulin secretion (7,8). Subjects in the VLCD groups had greater FPG changes at 3 weeks, but the groups did not differ in FPG changes at the end of 20 weeks. This pattern of change in FPG suggests that while all groups may have attained similar improvements in metabolic parameters, the improvements occurred earlier in the VLCD groups. Although the groups did not differ in overall change in FPG, more patients in the VLCD groups attained an FPG <7.8 mmol/l at 20 weeks. Final FPG values were obtained while all subjects followed a 1,500–1,800 kcal/day diet for at least 3 weeks in order to assess the sustained benefit of the VLCD intervention. Because FPG levels progressively decline for up to 10 days of VLCD therapy and begin to rise when VLCD therapy is discontinued, even if weight is not regained (7), changes in HbA_{1c} may better reflect the dynamic changes in FPG that occurred during the study. The groups did not differ in overall change in HbA_{1c}; however, more patients in the 5-day group attained a normal HbA_{1c} at the end of the study when compared with the SBT group. Subjects in the 5-day group achieved normal HbA_{1c} values independent of the effects of overall weight loss, suggesting that this form of VLCD therapy may inherently benefit glycemic control.

All patients did not achieve similar benefits in glycemic control from the treatment programs. Because the primary goal of dietary therapy in type 2 diabetes is to improve glycemic control, identification of factors early in the course of behavioral therapy that will predict the ultimate improvement in glycemic control can help identify patients who are candidates for continued intensive dietary intervention or initiation of diabetes medications. Subjects with higher baseline FPG levels (15,16), higher baseline fasting insulin levels, a greater insulin response to an oral glucose tolerance test (17), and lower FPG levels after a 2- to 5-kg weight loss (18) have been shown to have greater improvements in glucose levels in response to dietary therapy. For individual subjects in this study, the initial decline in FPG at 3 weeks predicted the overall glycemic response achieved at 20 weeks, independent of baseline insulin levels, initial weight loss, or final weight loss. The extent of improvement in FPG early in the course of dietary therapy may reflect the extent to which HGP, insulin sensitivity, and insulin secretion can be improved in a given patient with continued caloric restriction and eventual weight loss (7,8). Thus, a short trial period of dietary therapy may help clinicians identify those patients in whom continued diet therapy may be most effective. Whether the glycemic response to a 3-week, or shorter, trial of dietary therapy can predict the glycemic response over a longer period of time requires further study.

In summary, intermittent VLCD therapy combined with moderate caloric restriction resulted in more rapid improvements in glycemic control and greater weight loss than moderate caloric restriction alone. Although the VLCD groups did not differ from the SBT group in overall changes in FPG or HbA_{1c} at 20 weeks, subjects receiving intermittent 5-day VLCD were more likely to normalize their HbA_{1c} values at 20 weeks, independent of weight loss. Long-term studies are needed to determine whether continued intermittent VLCD therapy produces either greater long-term weight loss or better glycemic control than SBT alone.

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