The DCCT Research Group

Weight Gain Associated With Intensive Therapy in the Diabetes Control and Complications Trial

Identifiable risks such as increased frequency of hypoglycemia accompany the treatment of insulin-dependent diabetes mellitus (IDDM) with intensive insulin therapy. During yr 1 of the Diabetes Control and Complications Trial (DCCT), weight gain was identified as a sequela of intensive insulin therapy. The DCCT is a multicenter controlled clinical trial designed to determine the long-term effects of two different diabetes treatment regimens on the early vascular and neurologic complications of IDDM. Subjects randomized to the intensive treatment regimen gained significantly more weight (5.1 ± 4.6 kg) than the standard treatment subjects (2.4 ± 3.7 kg, $P < .0001$) during the 1st yr of therapy. Higher baseline HbA_{1c} levels and greater decrements in HbA_{1c} during intensive therapy were both associated with greater weight gain. In addition, intensively treated subjects with one or more severe hypoglycemic episodes gained more weight than the intensively treated subjects with no severe episodes. There was no relationship between reported caloric intake or exercise level and the weight changes. These data suggest that improved utilization of calories through a decrease in glycosuria and perhaps other mechanisms led to the weight gain in the intensively treated subjects. The results from the 1st yr of experience in the DCCT indicate that weight gain accompanies efforts to lower blood glucose levels with intensive insulin therapy. Because of the potential adverse consequences of undesirable weight gain, including diminished long-term compliance with therapy and an adverse effect on blood pressure and lipid status, efforts to prevent undesirable weight gain in the intensively treated group of the DCCT are being pursued. *Diabetes Care* 11:567–73, 1988

Intensive insulin therapy with insulin-delivery devices or multiple daily injections (MDI) is being used increasingly to treat insulin-dependent diabetes mellitus (IDDM). The putative benefit of lowering blood glucose levels with intensive therapy, especially with regard to the development and progression of microvascular complications, is being investigated (1–4). Although the definitive answer to whether such therapy is beneficial must await the completion of long-term controlled clinical trials, the risks of such therapy have begun to be defined. Increased frequency of hypoglycemia has been noted to occur with intensive insulin regimens (4), and diabetic ketoacidosis may be more frequent in insulin-pump–treated patients (5–6). This study from the Diabetes Control and Complications Trial (DCCT) suggests that weight gain may be another consequence of intensive therapy.

The DCCT is a multicenter randomized clinical trial to study the effect of two different diabetes treatment regimens on the development or progression of early vascular complications in people with IDDM. DCCT subjects are randomly assigned either to a standard treatment group or to an experimental treatment group; the goal of the latter is to achieve blood glucose levels as close to the nondiabetic range as possible while minimizing hypoglycemia. Results from the 1st yr of the study reveal that weight gain is associated with experimental therapy. We describe the magnitude of the weight gain and the variables associated with weight gain during intensive insulin therapy.

SUBJECTS AND METHODS

Subjects. DCCT eligibility criteria have been described in detail (7). The eligibility criteria presented here will be limited to those most pertinent to this study. In brief,

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patients between 13 and 39 yr of age with a duration of IDDM of 1–15 yr were recruited. Other eligibility requirements included good general health and, at most, minimal background retinopathy (<P 2 by the Diabetes Retinopathy Study classification; 8). Patients were excluded from entry into the trial if they were >30% above their ideal body weight (IBW) for age and sex as defined by the 1983 Metropolitan Life Insurance norms (9). Patients were excluded if the investigators or subjects felt that they could not adhere satisfactorily to the requirements of either treatment group. Patient performance on a battery of behavioral tasks, administered during eligibility screening, was used to help patients and investigators decide whether the patient could adhere to the study protocol. The behavioral tasks included keeping a 2-wk diary recording daily dietary intake, timing of insulin injections, and results of self-monitoring.

Selected characteristics of the initial cohort of 278 subjects are shown in Table 1 (4). Experimental and standard treatment groups did not differ significantly on any of these baseline characteristics.

Methods. A detailed description of the DCCT treatment protocol is available (7). Only those aspects of the protocol most relevant to this study will be reviewed.

Standard treatment. The standard treatment regimen was designed to approximate conventional treatment of IDDM as carried out by experienced health-care teams. The clinical goals of standard therapy included *1*) absence of symptoms attributable to glycosuria or hyperglycemia, *2*) absence of ketonuria, *3*) maintenance of normal growth and development and IBW, and *4*) freedom from frequent or serious hypoglycemia.

Subjects in the standard treatment group were routinely seen at 3-mo intervals. Insulin was administered as one or two injections per day and included mixtures of short-acting, intermediate-acting, or long-acting insulin. Self-monitoring was performed with urine or blood glucose testing. Subjects were given individualized meal plans specifying amounts of food and times of food consumption (described in more detail below). There were no specific exercise prescriptions, but exercise was encouraged according to the individual's interest and fitness. Standard group subjects were instructed in the adjustment of insulin and snacks to avoid hypoglycemia associated with exercise.

Experimental treatment. The experimental treatment group shared clinical goals with the standard group and had the additional goal of maintaining blood glucose control as close to normal as possible while minimizing hypoglycemia. Target ranges for glycemic control were as follows: fasting and preprandial blood glucose 70–120 mg/dl, postprandial (90–120 min after meal) blood glucose <180 mg/dl, blood glucose at 0300 >65 mg/dl, and HbA_{1c} within 2SD of the mean for a sample of individuals who do not have IDDM (mean + 2SD = 6.05%). Experimental group subjects could choose either MDI (defined as ≥3 daily injections) or continuous subcutaneous insulin infusion (CSII) with a pump. Experimental treatment was guided by self-monitoring of blood glucose, performed at least four times per day with a sample at 0300 performed once per week. Experimental group subjects were seen frequently during the initiation of experimental treatment and at least monthly thereafter.

The diet for the experimental group subjects followed the same principles as that of standard group subjects. However, greater attention was paid to adjusting diet and insulin, in concert, to achieve the experimental group blood glucose goals. Specific exercise prescriptions were not required, but exercise was encouraged according to interest, as with standard group subjects. Experimental group subjects were instructed on how to adjust insulin and snacks to maintain strict glycemic control during exercise.

Diet. The diet guidelines were designed to promote a health-providing diet for standard and experimental

TABLE 1
Selected baseline characteristics of experimental and standard group patients

	Adolescents		Adults	
	Experimental	Standard	Experimental	Standard
n	45	42	101	90
Percent male	47	41	50	51
Age (yr)	15 ± 1.34*	15 ± 1.3	28 ± 6	28 ± 5.7
Percent ideal body weight†	100 ± 13.4	96 ± 13	106 ± 10	108 ± 9.5
HbA_{1c} (%)	10.14 ± 1.88	9.83 ± 1.81	9.24 ± 1.4	8.98 ± 1.33
Duration of IDDM (mo)	66 ± 40.2	64 ± 38.9	87 ± 50	89 ± 57
Stimulated C-peptide (pmol/ml)	0.08 ± 0.134	0.08 ± 0.13	0.08 ± 0.1	0.08 ± 0.09
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.95 ± 0.34	0.94 ± 0.32	0.62 ± 0.2	0.65 ± 0.19

*Means ± SD.
†Based on the Metropolitan Life Insurance norms (1983) for sex and height.

treatment groups. Individualized diet plans, which specified the amounts of food and identifiable times of consumption, were used. The diet was designed to meet the following goals: *1*) Calories: sufficient calories to achieve and maintain 90–120% of IBW and/or provide for appropriate growth and development; *2*) carbohydrates: 45–55% of total daily calories with no more than 25% of the carbohydrates in the form of simple sugars; *3*) fats: 30% of calories from fat (with 35% as an upper limit), no more than 600 mg/day of cholesterol, and a polyunsaturated-to-saturated ratio of 1; *4*) fiber: encouraged from natural food sources; and *5*) alcohol: in moderation if used. Regularity and consistency of meals and avoidance of simple sugars were stressed. Each center's dietitians used their own preferred teaching methods to implement the diet.

Standard group subjects were seen by the dietitian at randomization and every 6 mo thereafter to reinforce dietary adherence. Experimental group subjects met with the dietitian monthly for the first 6 mo and every 3 mo thereafter. If weight gain (to >120% IBW) or weight loss (to <90% IBW) was observed in subjects of either group, the insulin regimen and the diet were reviewed at the regular office visit and revised as needed.

Measurements. The measurements relevant to this study are described below. They were obtained quarterly on experimental and standard subjects unless otherwise noted.

Weight and height measurements were obtained as part of the clinical examination. Percent of IBW was calculated by comparing patients' actual weights to their IBWs based on the 1983 Metropolitan Life Insurance norms (9). Body mass index was calculated by formula (kg/m^2). HbA_{1c} was determined by the Central HbA_{1c} Laboratory as described (10). Investigators were not masked to HbA_{1c} levels in experimental subjects and could use this information to help attain target levels. HbA_{1c} levels of standard subjects were masked, unless the upper action limit (13.11%) was exceeded or the patient became pregnant or began attempting to conceive. Basal and stimulated C-peptide levels were measured by radioimmunoassay by the Central Biochemistry Laboratory with the Novo C-1230 antibody.

Subjects' usual daily intake was assessed by a standardized dietary history at baseline and 1 yr. Dietitians were certified in the coding of data. Dietary data were entered and analyzed by the DCCT Central Nutrition Coding Unit. Level of activity on the job or at school was reported by the subject on a scale of sedentary, moderately active, or strenuously active. Leisure time activity was reported as hours and minutes of light, moderate, hard, or very hard activity during a typical week. Activity was assessed at baseline and 1 yr.

Subjects were instructed to report promptly all adverse events such as hypoglycemia episodes and intercurrent illnesses and were routinely questioned about adverse events at each quarterly visit. Hypoglycemia was defined as an event resulting in seizure, coma, confusion, irrational or uncontrollable behavior, or other symptoms consistent with hypoglycemia (e.g., sweating, palpitations, hunger, or blurred vision) in conjunction with *1*) a laboratory-determined or fingerstick blood glucose <50 mg/dl, *2*) amelioration by treatment that raises blood glucose, or *3*) prodromal symptoms of hypoglycemia (e.g., sweating, palpitations, hunger, or blurred vision) remembered by the subject as occurring shortly before the event. Severe hypoglycemia was defined as hypoglycemia resulting in coma or a seizure or a hypoglycemic episode requiring hospitalization or the administration of glucagon or intravenous glucose. All other hypoglycemic episodes were categorized as mild.

Statistical methods. Data are presented as means ± SD unless otherwise noted. Comparison of the two groups was based on *t* test for continuous variables and a continuity-adjusted χ^2-test for dichotomous variables (10a). Paired *t* tests were used to test for significant change within a group. Analysis of covariance (11) was used to adjust for the effect of several covariates and to test the treatment effect after accounting for possible confounders.

Simple and partial correlation coefficients were calculated to quantify the relationship between selected baseline or treatment characteristics and weight gain within each treatment group. Simple correlations shown in tables are Pearson correlation coefficients for continuous variables and point-biserial correlation for dichot-

TABLE 2
Mean weight at baseline and 1 yr for experimental and standard subjects

	Experimental				Standard				Experimental vs. standard change†
Group	*n*	Baseline	1 yr	Change*	*n*	Baseline	1 yr	Change*	
Female adults	51	61.9	65.8	3.9	43	63.9	65.4	1.5	$P < .002$
Male adults	50	75.4	80.8	5.2	46	75.7	77.5	1.8	$P < .0001$
Female adolescents	24	59.2	65.6	6.4	25	57.1	60.4	3.3	$P < .02$
Male adolescents	21	62.9	69.5	6.6	17	60.8	65.8	5.0	NS
All	146	66.2	71.3	5.1	131	66.4	68.8	2.4	$P < .0001$

Values are mean weights in kg.
*Significant ($P < .005$) by paired two-tailed *t* tests.
†Difference between change in experimental vs. standard group tested for statistical significance by two-tailed *t* test for independent samples.

TABLE 3
Percent of ideal body weight at baseline and 1 yr for experimental and standard subjects

Group	Experimental				Standard				Experimental vs. standard change†
	n	Baseline	1 yr	Change*	*n*	Baseline	1 yr	Change*	
Female adults	51	102.1	108.5	6.4	43	105.5	108.0	2.4	$P < .002$
Male adults	50	105.1	112.5	7.2	46	106.1	108.7	2.5	$P < .0001$
Female adolescents	24	100.3	109.4	9.1	25	96.7	100.2	3.5	$P < .005$
Male adolescents	21	93.7	102.4	8.6	17	90.1	95.6	5.5	NS
All	146	101.6	109.2	7.6	131	100.1	105.1	3.0	$P < .0001$

*Significant ($P < .005$) by paired two-tailed *t* test.
†Difference between changes in experimental vs. standard group tested for statistical significance by two-tailed *t* test for independent samples.

omous variables (12). Partial correlation shown in the same tables are from an analysis of covariance model. All *P* values are for two-tailed tests of significance.

RESULTS

Weight change in experimental and standard group subjects. On average, experimental group subjects gained 5.1 ± 4.6 kg (mean ± SD) from baseline to 1 yr, compared to 2.4 ± 3.7 kg for standard group subjects ($P < .0001$). Table 2 shows that weight gains of experimental subjects were significantly greater than those of standard group subjects for female adults ($P < .002$), male adults ($P < .0001$), and female adolescents ($P < .02$). Analyses of the individual clinics showed that weight gain between baseline and 1 yr was significant ($P < .05$) for experimental subjects in 17 of 21 clinics. After adjusting for baseline HbA_{1c}, weight, insulin dose (U/kg), and stimulated C-peptide, weight gain of experimental subjects still remained significantly greater than that of standard subjects ($P < .0001$). Weight gain was greater among males than females ($P < .02$) and among adolescents than adults ($P < .003$).

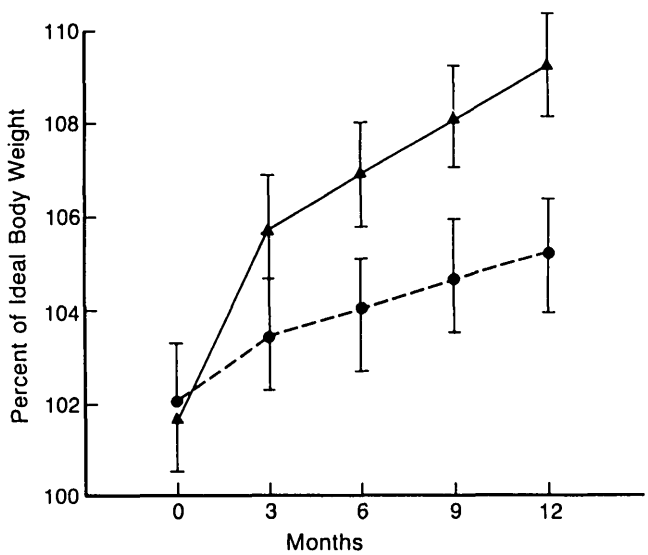

FIG. 1. Percent of ideal body weight for standard (●) and experimental (▲) group subjects at baseline and quarterly visits through 1 yr.

Change in percent overweight. Experimental and standard group subjects were also compared for changes in percent of IBW and body mass index because these measures correct for changes in height. Results from the two measures were comparable. Consequently, we have presented only the percent of IBW. Changes in percent of IBW were significantly greater for experimental subjects than for standard subjects for all age-sex groupings (Table 3). Analysis of covariance, adjusting for baseline weight, insulin dose, and stimulated C-peptide showed that the only variables that were significantly related to change in percent IBW were treatment group ($P < .0001$) and baseline HbA_{1c} ($P < .0001$). Neither sex nor age group was significantly related to changes in percent IBW.

Figure 1 shows the percent IBW of experimental and standard subjects at baseline and each quarterly visit. No differences between treatment groups were observed at baseline but experimental subjects had significant increases in percent IBW between each quarterly visit ($P < .001$), whereas standard subjects had significant increases in percent IBW only during the first quarter of the study. Note that despite this weight change, experimental subjects were still only 9% above IBW at 1 yr of follow-up. Moreover, the number of subjects who were >120% IBW did not differ significantly between the experimental and standard group at baseline or 1 yr. At baseline, 4.4% of experimental and 4.7% of standard subjects were >120% IBW. At 1 yr of follow-up, 11% of experimental and 7.7% of standard subjects were >120% IBW (*P* NS).

Baseline correlates of weight gain in experimental subjects. Multiple regression analyses were done to determine which baseline characteristics were related to weight gain or changes in percent IBW among experimental subjects. The baseline characteristics used were weight, sex, age (≤18 yr vs. >18 yr), insulin dose, and HbA_{1c} and stimulated C-peptide levels. Table 4 presents

TABLE 4
Simple and partial correlations with weight change

		Experimental (n = 145)		Standard (n = 132)	
	Correlation*	Weight	Percent overweight	Weight	Percent overweight
Baseline characteristics					
Age at entry	S	−.20	−.15	−.34†	−.21
	P	.13	.09	.23‡	.13§
Baseline weight	S	−.02	−.05	−.14	−.09
	P	−.04	−.05	−.05	−.05
Sex	S	−.10	−.03	−.11	−.10
	P	−.12	−.06	−.16	−.13
HbA_{1c} at baseline	S	.47†	.44†	.10	−.07
	P	.41†	.39†	.01	.01
Total insulin (U/kg at baseline)	S	−.05	−.07	.18§	.12
	P	−.13	−.13	.02	.03
Stimulated C-peptide	S	−.00	−.00	.01	.01
	P	−.05	−.05	.00	.00
Treatment and 1-yr characteristics					
Change in HbA_{1c}	S	−.35†	−.31‡	−.13	−.16
	P	−.42†	−.38†	−.10	−.02
Total insulin (U/kg annually)	S	.18§	.15	.23§	.18§
	P	.11	.07	.22§	.18§
Severe hypoglycemia (yes, no)	S	.18§	.17§	−.08	−.09
	P	.15§	.14	−.09	−.11
Mild hypoglycemia (yes, no)	S	.21§	.18§	−.04	−.04
	P	.08	.05	−.01	−.01
HbA_{1c} at 1 yr	S	.20§	.21§	−.01	−.07
	P	.28§	.29‡	.00	−.05

*S, simple; P, partial.
†$P < .0001$.
‡$P < .001$.
§$P < .05$.

the simple and partial correlations between these baseline variables and weight gain. Baseline HbA_{1c} was positively related to changes in weight ($P < .0001$) and percent IBW ($P < .0001$), and remained significant after controlling for the other baseline variables. Baseline weight, insulin dose, stimulated C-peptide, age, and sex were not significantly related to weight gain or change in percent IBW.

Relationship between glucose control and weight gain in experimental subjects during yr 1. At baseline, mean HbA_{1c} levels for the experimental group adults and adolescents were 9.24 ± 1.4 and 10.14 ± 1.88%, respectively. There was a significant decrease in experimental adults to 6.70 ± 0.8% and experimental adolescents to 7.73 ± 1.34% at 1 yr.

Changes in HbA_{1c} were significantly related to changes in weight (Table 4): those subjects who had the greatest decreases in HbA_{1c} during experimental treatment had the largest weight gains ($P < .0001$) and greatest increases in IBW ($P < .0001$). Weight change and change in percent IBW were also related to the absolute level of HbA_{1c} at 1 yr ($P < .05$); patients who gained the most weight had the highest HbA_{1c} levels at 1 yr. During the 1st yr of the study, 29 subjects in the experimental group experienced one or more episodes of severe hypoglycemia. These subjects gained 6.8 ± 4.8 kg compared to 4.7 ± 6.3 kg for subjects with no severe hypoglycemic episodes ($P < .05$). The presence of severe hypoglycemia was related to weight gain in experimental subjects even after controlling for HbA_{1c} at 1 yr and change in HbA_{1c}. The occurrence of mild hypoglycemia was not related to weight change after controlling for other variables. The partial correlation between insulin dose at 1 yr and weight change, controlling for HbA_{1c} at 1 yr, change in HbA_{1c}, and severe hypoglycemia, was not significant. There were also no differences in weight gain for experimental subjects who selected MDI (n = 89) and those who selected CSII (n = 54; weight gains of 5.6 and 4.3 kg, respectively).

Caloric intake and activity. The diet history data were used to determine whether changes in caloric intake were related to the difference in weight gain for experimental and standard subjects. Caloric intake decreased significantly from baseline to 1 yr in both experimental (2592 cal at baseline vs. 2050 cal at 1 yr, $P < .0001$) and standard group subjects (2432 cal at baseline vs. 2187 cal at 1 yr, $P < .0002$). The decrease in reported caloric intake was greater in experimental group than in

standard group subjects ($P < .003$). The correlation between change in reported caloric intake and change in weight in experimental subjects was not significant ($r = -.03$, NS). Experimental and standard group subjects did not differ significantly in level of self-reported activity on the job (or at school) or in leisure-time activity.

Weight change in standard group subjects. The variables associated with weight gain in standard group subjects differed from those observed in the experimental group (Table 4). After adjusting for baseline HbA_{1c}, weight, and insulin dose, the only baseline variable significantly related to weight gain among standard subjects was age at entry ($r = -.21$, $P < .001$). Weight gain was not significantly related to change in HbA_{1c} or to HbA_{1c} at 1 yr, but was related to insulin dose at 1 yr ($r = .22$, $P < .05$). Change in caloric intake was also associated with weight gain ($r = -.18$, $P < .04$). The direction of this association suggested that decreased intake was associated with greater weight gain, perhaps reflecting changes in dietary prescription in response to weight gain.

DISCUSSION

These results from the 1st yr of experience in the DCCT suggest that efforts to normalize blood glucose are associated with weight gain in IDDM diabetic patients. The strongest predictors of weight gain were higher baseline HbA_{1c} concentration and larger decrements in HbA_{1c} over the year.

These findings confirm and extend the results of previous uncontrolled studies with smaller sample sizes that have suggested that weight gain occurs frequently with intensive insulin regimens (13–15). Capper et al. (13), reporting on 15 patients (age 24–44 yr) who were treated with CSII, found an average weight gain of 3.3 kg at 16 mo. Eleven of 15 patients gained weight. Percent IBW increased from 101.5 to 107%, results quite similar to those in our study. Hamet et al. (14) found an average weight gain of 2 kg after 52 wk of CSII with 7 of 8 patients experiencing a weight gain. Home and associates (15) also found a weight gain with CSII therapy that was significantly greater than with a thrice-daily insulin-injection regimen.

Our study is the first to examine the variables associated with weight gain. The finding that baseline HbA_{1c} and changes in HbA_{1c} were the best predictors suggests that patients who were initially in poor control and losing calories in the form of glycosuria were the ones most likely to gain weight when glycemic control improved. An alternative hypothesis is that experimental subjects were eating more in order to treat or prevent hypoglycemia. We have reported previously that experimental treatment is associated with a two- to threefold increase in both severe and mild hypoglycemic episodes compared with standard therapy (4). A similarly increased risk for hypoglycemia with experimental treatment has been reported in other studies (1,2). The greater weight gain in the subjects with severe hypoglycemia tends to support the hypothesis that subjects treated with intensive therapy may overeat to treat or prevent severe hypoglycemia. Finally, intensively treated subjects may recognize and take advantage of their ability to eat larger meals more frequently and give themselves extra insulin to cover the meals.

It should be noted, however, that weight gain in experimental subjects was not associated with self-reported changes in caloric intake or activity. In fact, whereas the experimental group subjects had greater weight gain than the standard group, they reported significantly greater decreases in caloric intake. However, caloric intake was assessed only at baseline and the annual visit. It is possible that experimental subjects initially increased their intake, but as weight gain became apparent, the dietitians may have decreased the prescribed caloric intake in these subjects. A study by Leslie et al. (16) demonstrated that basal metabolic rate decreases in intensively treated IDDM subjects. This observation may help to explain weight gain in experimental group subjects despite the reported decrease in caloric intake.

The clinical significance of the weight gain remains unclear. At the start of the study, many subjects were below IBW, and despite the weight gain, patients still averaged only 9% above IBW. Furthermore, only 10% of experimental subjects were ≥120% IBW at 1 yr follow-up. Data were not collected on body fat and thus it is impossible to determine the percent of the gain that was lean body mass versus fat.

Weight gain could have two negative implications for long-term treatment with intensive regimens. First, undesirable weight gain could diminish long-term compliance to intensive therapy. Given the preoccupation with thinness in our society, subjects who gain weight on intensive therapy may choose to discontinue this form of treatment. Second, if weight gain continued, it could be associated with increases in blood pressure and serum lipid levels, and might have an adverse effect on the risk for cardiovascular disease.

Because of these potential adverse consequences of weight gain, efforts to prevent undesirable weight gain in the experimental group of the DCCT are being pursued. Subjects who are randomly assigned to experimental therapy are advised of the possibility of weight gain, and calorie intake is reduced to a level appropriate to prevent such an occurrence. Further study is needed to determine whether improved glycemic control can be achieved in IDDM subjects on intensive insulin therapy without undesirable weight gain.

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