

Weight Change in Intensive Insulin Therapy for Type 2 Diabetes Mellitus as a Function of Glycosylated Hemoglobin (A1C) Level Achieved: The Deep South Diabetes Program

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ABSTRACT

Background: The Deep South Diabetes Program (DSDP) conducted a retrospective study to evaluate weight changes associated with intensive basal-bolus insulin therapy. Results of the effectiveness of the treatment algorithm that was used in this study were published in the April 2008 issue of *Insulin*.

Objectives: The current study was designed to further evaluate the results of the DSDP study. The primary objective was to determine the quantitative relationship between weight gain and the patient's final glycosylated hemoglobin (A1C) level achieved. A secondary objective was to gain a qualitative understanding of the treatment parameters underlying the quantitative results.

Methods: Further evaluation of the DSDP treatment algorithm in terms of weight management and A1C levels for achieving normoglycemia or near-normoglycemia was performed retrospectively using data collected in the original DSDP study. This evaluation included all patients who elected intensive basal-bolus insulin therapy and who sustained the treatment for up to 4 years. Glargine was the primary basal insulin, and aspart was the primary bolus insulin. The quantitative relationships among net weight change, net A1C change, and final A1C level achieved were evaluated. A qualitative evaluation of glycemic variability and behavioral variables was made from video recordings of patient visits during the original DSDP study and further observation of study participants after completion of the study.

Results: Quantitative evaluation of change in weight as a function of A1C level achieved at the end of the study showed that for the group of patients who achieved normoglycemia, the mean change in weight was a reduction proportional to the corresponding mean reduction in A1C. For the groups of patients who did not achieve normoglycemia or near-normoglycemia, the mean change in weight was an increase proportional to the corresponding mean reduction in A1C.

Conclusions: When normoglycemia was achieved and sustained using the DSDP's intensive insulin therapy, the weight gain typically seen with conventional insulin therapy did not occur. Weight gain or loss during intensive insulin therapy using the DSDP treatment algorithm was a function of A1C level achieved. (*Insulin*. 2008;3:219–231) © 2008 Excerpta Medica Inc.

Key words: weight management, treatment to normoglycemia, type 2 diabetes, intensive diabetes care, basal-bolus insulin, biomedical engineering.

INTRODUCTION

This paper describes and evaluates further analyses of the results of the Deep South Diabetes Program (DSDP) study¹ that was designed to evaluate weight changes associated with intensive basal-bolus insulin therapy. This retrospective study was conducted at Lifespan Health, a federally qualified health center that serves as a safety net provider for the uninsured, underinsured, and state health programs of Tennessee.

During the original study period, the state health program of Tennessee (Tenn Care) underwent severe retrench-

ment. Many of the patients in the DSDP study either experienced severe rationing of medical care or had no access to medical care other than what was available within the boundaries of the safety net or through charity.²

The first analysis of the DSDP study, published in April 2008,¹ found that weight gain was not a clinical complication of intensive insulin therapy for the treatment of type 2 diabetes mellitus (DM). The treatment approach used in the original DSDP study incorporated a central conclusion from the Diabetes Control and Complications Trial (DCCT)³ that intensive insulin therapy is superior to conventional insulin

therapy. This conclusion from DCCT was adapted to the contemporary practice of intensive insulin therapy in a typical setting in the United States, exploiting the synergistic advantages of aspart and glargine, while dealing with all the constraints and difficulties inherent in practicing intensive diabetes care with disadvantaged patients in the rural safety net.

The DCCT study³ showed that intensive insulin therapy delivered in intensive diabetes care was clearly superior to (ie, 10 times more effective than) conventional insulin therapy. The Epidemiology of Diabetes Interventions and Complications study⁴ established the superiority of early, intensive insulin treatment in type 1 DM.

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Weight Gain as a Common Complication of Insulin Therapy

In the Treating to Target in Type 2 Diabetes (4-T) study,⁵ patients generally gained weight on all regimens, with a greater increase in the prandial group and in the biphasic group than in the basal group.

At the time of publication of the original DSDP study,¹ it was not clear how the DSDP results related to the common finding of weight gain as a clinical complication of insulin therapy. Yki-Järvinen⁶ determined that weight gain was inevitable if insulin therapy was postponed until significant glycosuria occurred, finding that a 1% decrease in glycosylated hemoglobin (A1C) level resulted in a 2-kg increase in body weight specifically. Fritsche and Häring⁷ reported that, in type 2 DM, a positive correlation existed between weight gain and glycemia, with many deleterious effects, including avoidance of insulin therapy by both patients and providers because of fear of weight gain. Westphal and Palumbo⁸ found weight gain to be one reason for deferring insulin therapy.

In contrast, the DSDP study¹ found that patients undergoing intensive insulin therapy for type 2 DM did not gain weight. This retrospective, observational study of 188 patients took place over a period of 4 years (April 2003–March 2007).¹ The patient population consisted of sick, adult patients with significant, often disabling, symptomatic disease. All patients with type 2 DM who elected intensive insulin therapy and who sustained the treatment for up to 4 years were included

The DSDP study found that patients undergoing intensive insulin therapy for type 2 DM did not gain weight.

in the study. Glargine was the primary basal insulin, and aspart was the primary bolus insulin.

The treatment algorithm used in the DSDP study was unique in that it centered around shared medical visits, during which providers and patients worked together to create a culture in which normoglycemia was an expected outcome. This treatment algorithm was described in detail in the original study report.¹

Findings of the Original DSDP Study

Of the 188 patients in the original DSDP study,¹ 20% experienced no net weight change and 47% experienced a net weight change of <7.5 lb. The DSDP study found that, in the setting of a shared medical visit, normoglycemia (A1C <6.0%) could be safely achieved and sustained by adopting intensive diabetes care (instead of conventional care), using basal-bolus insulin titrated quantitatively based on information downloaded from blood glucose meters and from patient logs. The complex daily tasks associated with basal-bolus insulin therapy became automatic to most patients over time. As the daily cost of practicing basal-bolus insulin therapy continued to decrease dramatically, the daily clinical benefits of basal-bolus insulin increased dramatically.

Normoglycemia was achieved even by patients who entered the study with relatively high A1C values. The DSDP study found that no net weight gain among the patient population as a whole could be associated with lowering of the A1C level, even when a patient's A1C was lowered from initial values ranging from 10.0% to 13.0% to a final A1C of <6.5% at the end of the study.¹

Furthermore, the DSDP study showed that when normoglycemia was achieved, patients generally maintained their weight. When neither normoglycemia nor near-normoglycemia was achieved, patients generally gained weight. A thorough understanding of the patient's total health picture, supported by video recording of shared medical visits, was essential for extending the power and capacity of intensive insulin therapy in the induction and long-term maintenance of normoglycemia. Careful, thorough information management was critical for providing patients with the clinical benefits of intensive insulin therapy that were proved in the DCCT.¹

The DSDP study showed that when normoglycemia was achieved, patients generally maintained their weight.

Toward the end of the 4-year DSDP study, after using intensive basal-bolus insulin therapy as the primary treatment, clinical acumen suggested that 3 outcome groups emerged from the 188 participants:

- Normal glycemia (A1C <6.0%)
- Near-normal glycemia (A1C ≥6.0% but <7.0%)
- Above-normal glycemia (A1C ≥7.0%)

Objectives of the Current Study

The primary objective of this study was further quantitative analysis of the results of the original DSDP study to better understand the phenomenon of achieving normoglycemia through intensive insulin therapy, particularly the relationship between weight gain and the final A1C level achieved. A secondary objective was to gain a qualitative understanding of the treatment parameters underlying the quantitative results.

PATIENTS AND METHODS

Selection of Patients and Data Collection

In the DSDP at Lifespan Health, all patients were enrolled in observational studies designed to evaluate treatment effectiveness and safety, conducted routinely in cooperation with the US Bureau of Primary Health Care (BPHC) Diabetes Collaborative. Patient Electronic Care System (PECS, 2004) software was used to collect all the information for the study. Information taken from patient medical records was entered into the database daily. Vital statistics from the patients' medical charts such as height, weight, blood pressure, laboratory test results, and physician notes also were entered into the database.

The PECS system was designed for quality management, not research. Error trapping was not built into either the software system or the procedure for data entry of routine clinical data for daily visits. However, all A1C levels were measured at Hardin Medical Center, Savannah, Tennessee, which is accredited by the Joint Commission on the Accreditation of Healthcare Organizations. Both A1C values and body weights were checked for accuracy of data entry.

This analysis was based on data gathered by the DSDP over a period of 4 years. Information on the charts was taken from patient visits beginning April 1, 2003, and ending March 31, 2007. In this observational study, the data accrual period varied, depending on when the patient began intensive basal-bolus insulin therapy (between April 1, 2003, and September 30, 2006). All patients in the study were in treatment at the end of the study (March 31, 2007). The inclusion and exclusion criteria for this analysis were the same as those for the original DSDP study.¹

Treatment Method

Before starting treatment, each patient underwent a physical examination and health status evaluation. Patients were given an option of treatment programs based on the results of the health evaluation. If the patient elected basal-bolus insulin therapy, intensive treatment was initiated according to the algorithm presented in the original DSDP study report.¹ The methods that were used in this study were described in the DSDP treatment algorithm and illustrated in the accompanying detailed flowchart.¹

Medications

Patients in all 3 of the outcome groups that were established during the original study received similar medica-

tions. All of the patients who began insulin therapy were required to stop taking thiazolidinediones and sulfonylureas. It was noted retrospectively that metformin was used more frequently in the outcome groups that failed to achieve normal or near-normal glycemia than in the group that achieved normoglycemia. The standard regimen for type 2 DM was glargine, aspart, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-2 receptor blocker (ARB), a statin, aspirin, and, frequently, either a β -blocker or a thiazide diuretic (Table I).

The medications that were used in this study were a reflection of the choices of medications available to the DSDP patients. During the period of retrenchment in Tenn Care, a total of 5 medications per month were paid for. This included 3 generic and 2 brand drugs. Initially, insulin was included in the total of 5 drugs. Later, insulin was placed on a "protected list" so that patients could receive both glargine and aspart and still receive 3 generic and 2 brand drugs. (During this time, simvastatin was considered a brand drug.)

Treatment choices had to be made for all patients, and all chronic illnesses had to be managed within this regimen. The patient was actively involved in the choice of which drugs would be kept and which would be sacrificed. The absence of antidepressants reflected either an inability to obtain the antidepressant that had previously been effective or simply the patient's choice to forego the antidepressant for a drug that was of greater importance to him or her. In general, patient decision making regarding the available treatments had to be prioritized, based on the number of presenting chronic illnesses (ie, the more chronic illnesses a patient had, the more treatments for other conditions the patient had to forego for diabetes care).

In the latter part of the study, Part D Medicare became available, and drug choices became more generous for some of the DSDP patients. However, the standard treatment for type 2 DM remained the same.

Additional Observations

Qualitative observations of each patient's progress toward normoglycemia were made using a video recording of interviews with the patients. In the DSDP treatment algorithm,¹ nutritional counseling was limited to mastery of carbohydrate counting. Patients were told to eat what they could afford and what they liked. Patients kept a log of insulin and carbohydrate intake. They measured blood glucose levels 6 to 10 times daily. In the video-recorded sessions, patients were observed as they related their daily experience with matching carbohydrate intake to the amount of bolus insulin needed. The patients compared their daily activities to the blood glu-

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Table I. Percentage of patients who used medication in addition to insulin glargine and insulin aspart in the Deep South Diabetes Program study (N = 174).¹

Outcome Group	No. of Patients	ACE Inhibitor/ARB	β -Blocker	Metformin	Statin	Diuretic	Niacin	Antidepressant	Sulfonylurea	Thiazolidinedione	Calcium-Channel Blocker
Normal glycemia (A1C <6.0%)	60	90	23	30	85	31	10	2	0	0	5
Near-normal glycemia (A1C \geq 6.0% but <7.0%)	81	89	17	36	85	23	1	1	0	0	6
Above-normal glycemia (A1C \geq 7.0%)	33	94	21	42	91	33	3	0	0	0	9

ACE = angiotensin-converting enzyme; ARB = angiotensin-2 receptor blocker; A1C = glycosylated hemoglobin.

case levels measured multiple times daily. The patients and the care providers were able to view the blood glucose levels displayed during the video-recorded sessions.

RESULTS

Patient Population

All paper charts for the 188 patients in the original DSDP study¹ were reviewed a second time for this analysis. During the second review, recording errors were discovered, disqualifying 3 patients who were found to have diagnoses of type 1 DM on the paper charts but type 2 DM in the PECS database. Removal of these 3 patients and 11 patients who were not being treated with intensive insulin therapy left a total of 174 patients (96 females, 78 males) who qualified for this analysis. (The 11 patients who were not being treated with intensive insulin therapy were in end-stage type 2 DM and were given basal-bolus insulin for symptomatic relief.)

Demographic Characteristics

The patients in the DSDP study had strong selection biases of poverty, insulin phobia (shared between them and their physicians), and depression. These selection biases appeared to act similarly on all 3 outcome groups. Pertinent patient demographic characteristics, including age, weight, body mass index (BMI), sex, ethnicity, and poverty level, were described in the original DSDP study.¹ Looking back, there were no apparent differences between the 3 outcome groups in terms of baseline demographics.

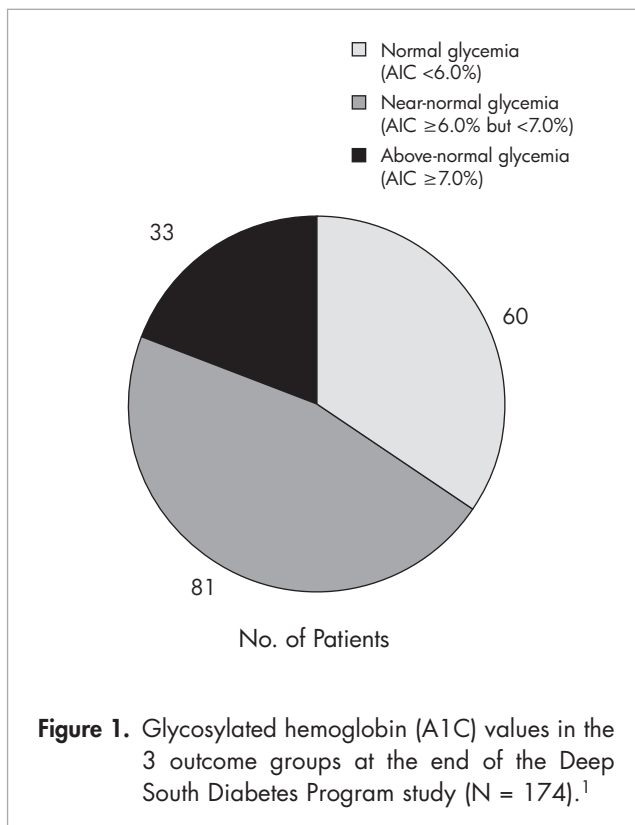
Patient outcomes in the 3 groups established in the original study are shown in **Figure 1**. Patient demographic characteristics for this analysis with respect to the 3 outcome groups are summarized in **Table II**.¹ These 3 outcome groups were used throughout this analysis.

The duration of illness, which was obtained by patient self-report, ranged from 6.4 years to 7.7 years (**Table II**).¹ The duration of illness for all 3 outcome groups appeared to be very short when compared with the patients' disease-related complications.

All 3 outcome groups were similar with regard to duration of illness, BMI, age, smoking preferences, and ethnicity. There were slightly more females than males in all groups, but the predominance of females was greater in the outcome groups that failed to achieve normal or near-normal glycemia. Patients were predominately (98%–100%) white in all 3 outcome groups. The group that achieved normoglycemia contained more patients with disabilities than did the other 2 groups. Overall, at the beginning of the study, the outcome groups could not be predicted by looking at the individual patients.

Chronic Illnesses of the DSDP Patients

The DSDP patients had multiple chronic illnesses at study entry; 97% of the patients had \geq 1 chronic illness in addition to type 2 DM. Most of the DSDP patients lived with some daily combination of discomfort, paresthesias, frank pain, shortness of breath, or absence of psychic pleasure. They were symptomatically ill at the beginning of treatment.



The patients made and sustained their choice of medications based on their perception of which drugs gave them the most immediate symptomatic relief as well as the highest probability of long-term benefit. Intensive insulin therapy would not have been adopted and sustained without its immediate symptomatic relief of pain, fatigue, and anhedonia.

Chronic Illnesses in the Outcome Groups

At baseline, the distribution of chronic illnesses appeared to be similar among the 3 outcome groups (Figure 2). These illnesses are listed as complications of diabetes in Table III, as comorbidities in Table IV, and as other chronic conditions in Table V.¹ The presence of complications at baseline (Table III) appeared to be similar in all 3 outcome groups. Within the limits of the sample size, the comorbidities of diabetes (Table IV) also appeared to be similar among the outcome groups.

Hypertension and hyperlipidemia were included with diabetes as one chronic illness. *Complex hyperlipidemia* was defined as the need for additional drug therapy beyond the standard statin. *Difficult-to-treat hypertension* was defined as hypertension that required more than the standard ACE inhibitor or ARB to reach target levels. *Congestive heart failure* was defined as stage C or D; stage A or B was not counted as a comorbidity.⁹ Again, all outcome groups appeared to be similar at baseline.

Extent of Other Chronic Conditions in Each Outcome Group

Intensive insulin therapy in patients with depression, anxiety, and diabetes is far more complicated than in patients with diabetes alone. This combination was common among patients in the DSDP study (Table V).¹ Depression and anxiety were found in all outcome groups but were particularly common in the groups that achieved normal and near-normal glycemia. The DSDP treatment algorithm appeared to be effective for the patients with depression. Chronic obstructive pulmonary disease (COPD) was common in all 3 outcome groups, and the presence of COPD added significantly to the symptomatic discomfort.

Table II. Patient demographic characteristics in the Deep South Diabetes Program study (N = 174).¹

Outcome Group	No. of Patients	Duration of Illness, Mean (SD), y	Body Mass Index, Mean (SD), kg/m ²	Age, Mean (SD), y	Males, %	Smoking, %	White, %	Disabled, %
Normal glycemia (A1C <6.0%)	60	6.4 (8.1)	34.6 (7.9)	57 (12.5)	44	20	100	41
Near-normal glycemia (A1C ≥6.0% but <7.0%)	81	7.7 (7.8)	33.0 (7.2)	59 (10.0)	52	30	98	17
Above-normal glycemia (A1C ≥7.0%)	33	7.6 (8.7)	35.2 (9.4)	54 (11.9)	27	27	100	12

A1C = glycosylated hemoglobin.

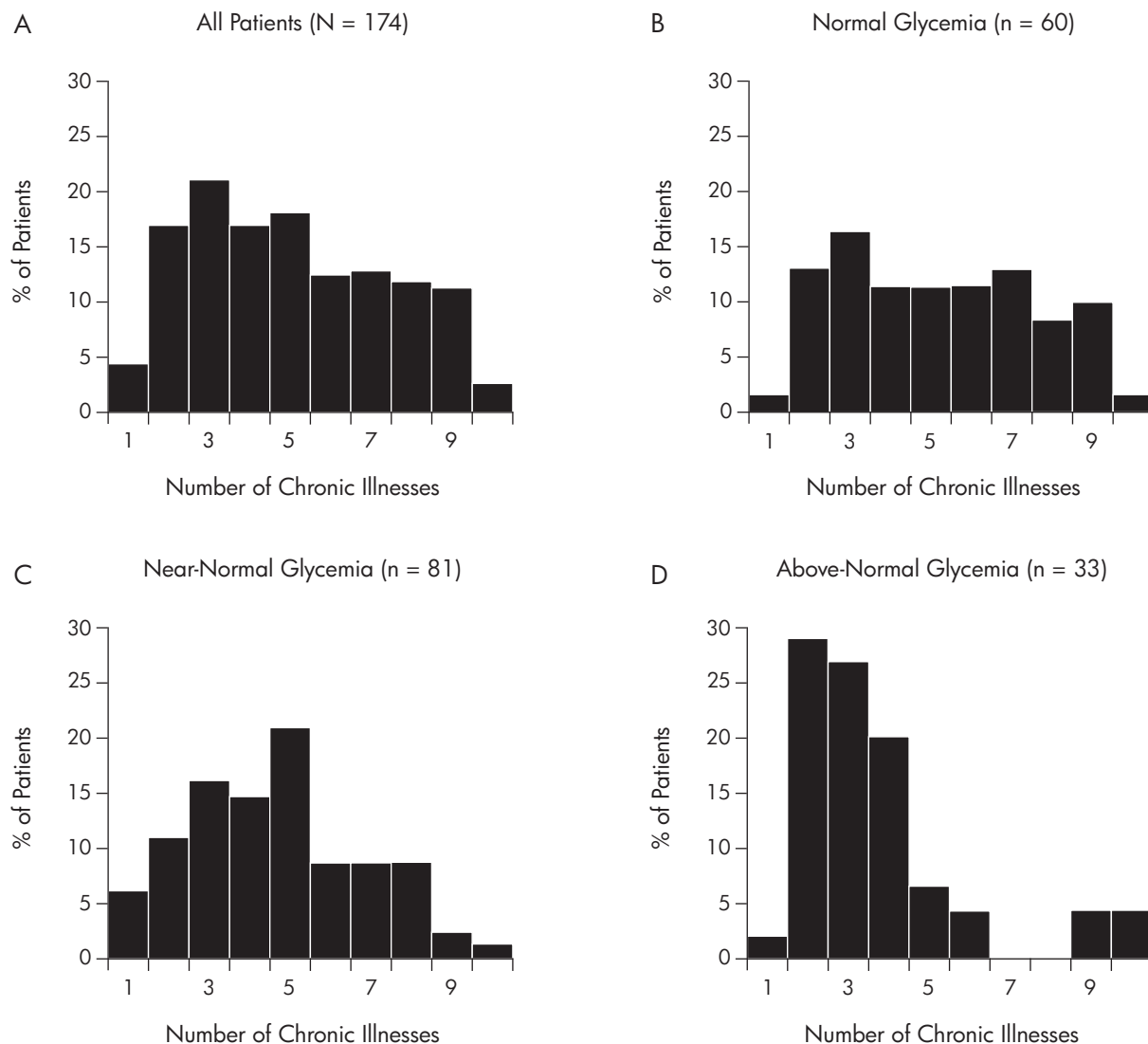


Figure 2. Histograms of chronic illnesses reported for all patients (A) and for patients in each of the 3 outcome groups at the end of the Deep South Diabetes Program study¹: (B) normal glycemia (glycosylated hemoglobin [A1C] <6.0%), (C) near-normal glycemia (A1C ≥6.0% but <7.0%), (D) above-normal glycemia (A1C ≥7.0%).

Deaths in the Study

During the study period, one patient committed suicide; she left a note telling her family that she loved them. A second patient died of pancreatic cancer. One year after conclusion of the study, a patient died of unknown causes. All 3 of these patients were in the group that achieved near-normal glycemia. No other deaths were reported.

Normoglycemia and Weight Gain Associated with Insulin Therapy

Weight change associated with insulin therapy was measured in terms of change in weight per change in A1C level achieved. Four lines representing change in weight as a func-

tion of A1C change are shown in **Figure 3**. Change in weight equals the slope of the line multiplied by the change in A1C level. The slope of these 4 lines changed from -4.4 to 1.18, depending on the outcome group of patients being evaluated. Equations representing the lines are shown on the chart beside each line. In evaluating these lines, it is important to keep in mind the meaning of the slope of the line: a negative slope indicates weight gain with lowering of A1C, whereas a positive slope indicates weight loss with lowering of A1C.

In the DSDP study, the group of patients with the greatest negative slope (-4.4) gained the most weight. Proceeding counterclockwise, as indicated by the arrow in **Figure 3**, the next line had a slope of -1.72, representing the group

Table III. Percentage of patients who had complications of diabetes in the Deep South Diabetes Program study (N = 174).¹

Outcome Group	No. of Patients	Neuropathy	Retinopathy	Microalbuminuria	Nephropathy	Dialysis/Transplant	Coronary Artery Disease	Coronary Angioplasty/CABG	Cerebrovascular Disease	Peripheral Artery Disease	Ulcer	Amputation	Cataract	Gastroparesis
Normal glycemia (A1C <6.0%)	60	56	2	11	13	2	21	5	10	3	5	0	7	2
Near-normal glycemia (A1C ≥6.0% but <7.0%)	81	51	7	19	6	4	28	6	6	5	1	0	2	0
Above-normal glycemia (A1C ≥7.0%)	33	52	9	15	9	0	15	0	3	3	0	0	3	0

CABG = coronary artery bypass graft; A1C = glycosylated hemoglobin.

with the next greatest weight gain. This group of patients had a mean A1C of 7.6% at the end of the study. Again proceeding counterclockwise, the next line had a slope of -0.174; almost no weight change occurred during treatment in this group. These patients had a mean final A1C of 6.4%. Again proceeding counterclockwise, the next line had a positive slope of 1.18, indicating weight loss with treatment. These patients had a mean final A1C of 5.5%. Decreasing the A1C level with treatment increased the slope of the

curve from -4.4 to 1.18, as indicated by the progression of the trend lines.

A plot of the slope of each of these trend lines is presented in **Figure 4** as a function of the mean A1C achieved by each treatment group. As the A1C achieved with treatment decreased, the slope of the weight loss curve increased (ie, the better the final A1C, the better the weight management). The area to the left of zero on the horizontal axis represents a region of weight gain with treatment. The crossover point between

Table IV. Percentage of patients who had comorbidities of diabetes in the Deep South Diabetes Program study (N = 174).¹

Outcome Group	No. of Patients	Complex Lipids	Obese, BMI ≥30 kg/m ²	Obese, BMI ≥40 kg/m ²	Difficult-to-Treat Hypertension	Congestive Heart Failure
Normal glycemia (A1C <6.0%)	60	11	75	26	8	16
Near-normal glycemia (A1C ≥6.0% but <7.0%)	81	7	64	19	5	9
Above-normal glycemia (A1C ≥7.0%)	33	3	64	27	6	21

BMI = body mass index; A1C = glycosylated hemoglobin.

Table V. Percentage of patients who had other chronic conditions in the Deep South Diabetes Program study (N = 174)1: Chronic obstructive pulmonary disease (COPD) and psychiatric illnesses.

Outcome Group	No. of Patients	Asthma/COPD	Depression	Anxiety	Other Axis 1
Normal glycemia (A1C <6.0%)	60	18	43	21	2
Near-normal glycemia (A1C ≥6.0% but <7.0%)	81	9	43	10	0
Above-normal glycemia (A1C ≥7.0%)	33	12	27	9	0

A1C = glycosylated hemoglobin.

weight gain and weight loss occurs at an A1C of 6.3%. The R² value of 0.9982 for the trend line is based on mean values of patients grouped according to breaks following guidelines for normal, near-normal, and above-normal A1C values in the 3 outcome groups. The R² value is based on the mean of each of the treatment groups and must be interpreted in this light. Error bars represent standard error of the mean of A1C levels to the 95% confidence level. Clearly, the slope of the curve is

negative, but the intercept of 6.3% could vary anywhere from 6.0% to 6.8% within the 99% confidence level. The intercept represents the transition between weight loss and weight gain as a function of A1C achieved.

Qualitative Observation of Behavioral Changes

In acquiring the capacity to self-manage their glucose, patients learned how to match carbohydrates to bolus insu-

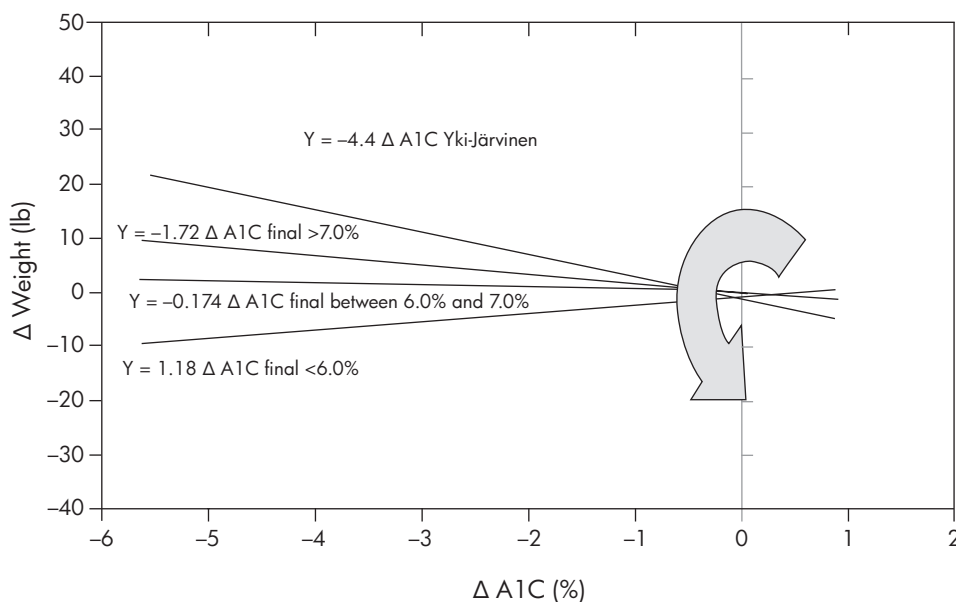


Figure 3. Change in weight (Δ weight) with respect to change in glycosylated hemoglobin (Δ A1C) for groups of patients achieving an A1C as represented by the following trend lines: Results of the study done by Yki-Järvinen,⁶ and results of the Deep South Diabetes Program study,¹ where patients in the above-normal glycemia, near-normal glycemia, and normal glycemia outcome groups achieved mean A1C values of 7.6%, 6.4%, and 5.5%, respectively, at the end of the study.

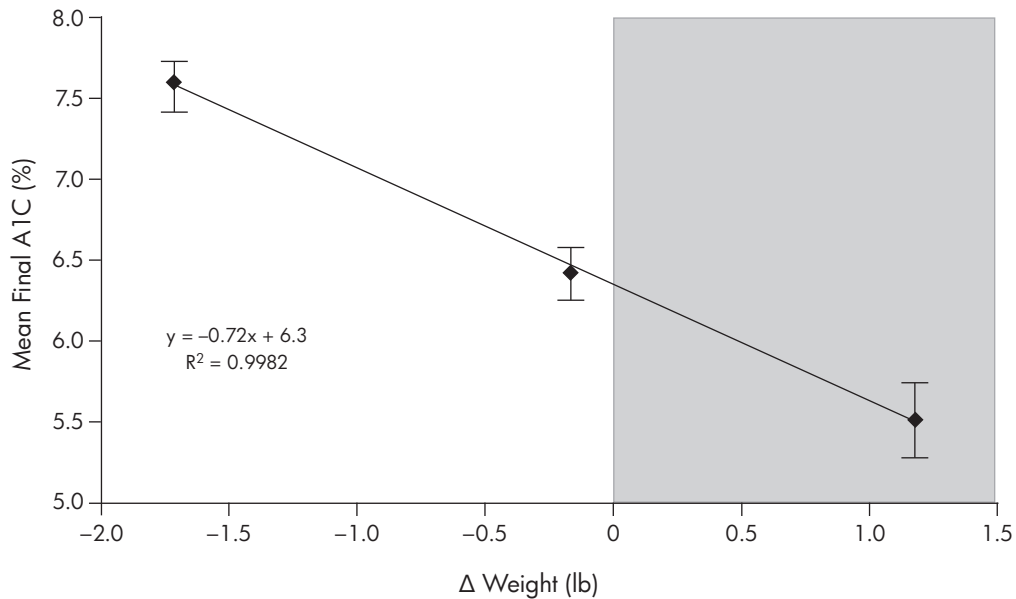


Figure 4. Change in weight (Δ weight) with respect to change in glycosylated hemoglobin (A1C) as a function of A1C achieved at the end of the Deep South Diabetes Program study.¹ Data points represent the groups that achieved normal glycemia, near-normal glycemia, and above-normal glycemia, containing 60, 81, and 33 patients, respectively.

lin requirements, producing a change in their blood chemistry. Data downloaded from blood glucose meters revealed that patients who excelled in this procedure were able to maintain tight glycemic control, thereby greatly reducing the need for carbohydrate intake to correct for low blood glucose levels. Patients began mastering the matching of carbohydrate intake to bolus insulin requirements by nearly eliminating blood glucose levels >200 mg/dL. Next, they began to increase the percentage of the multiple daily measurements of blood glucose that fell in the range of 70 to 120 mg/dL. No diets were prescribed. However, in the shared medical visits, we maintained throughout treatment a relentless, sustained focus on mastering carbohydrate counting for successful estimation of bolus insulin requirements.

As patients progressed in self-awareness and self-mastery, those who achieved and sustained normoglycemia learned that they could not eat what they had eaten previously. Success in achieving and maintaining normoglycemia almost uniformly was associated with a significant change in eating habits.

DISCUSSION

To enhance our understanding of the relationship between insulin therapy and weight management, we compared and contrasted the results of the present study with those of previous studies on weight gain associated with insulin treatment—the DCCT,³ the United Kingdom Prospective Diabetes Study (UKPDS),¹⁰ and the 4-T study.⁵

Comparison of Selection Criteria from DCCT, UKPDS, 4-T, and DSDP

The DCCT³ and the UKPDS¹⁰ were randomized controlled trials; the 4-T study⁵ was an open-label, controlled, multicenter trial. The DCCT³ was sponsored by the National Institutes of Health, whereas both the UKPDS¹⁰ and the 4-T study⁵ were sponsored by the Oxford Diabetes, Endocrinology, and Metabolism Centre of the University of Oxford, Oxford, United Kingdom. In contrast, the DSDP study was an observational trial that grew out of the diabetes collaborative of the BPHC.¹¹ The mission of the BPHC is to ensure that underserved and vulnerable people obtain primary health care.¹²

The selection criteria for the DCCT were strict.¹³ “Patients who were assessed as too unstable or unmotivated on the rigorous tasks of intensive insulin therapy were not permitted in the study. Each DCCT participant had to complete a series of demanding behavioral tasks during the run-in before randomization. Thus, the DCCT study population was a young, generally healthy, highly motivated sample that was steadily employed and lived in a stable home environment.” If the DSDP study had employed the same eligibility criteria as the DCCT, few, if any, patients would have received treatment.

Between 1977 and 1991, general practitioners in the United Kingdom referred patients 25 to 65 years of age with newly diagnosed diabetes to a UKPDS clinic.¹⁰ The criterion for referral was a fasting plasma glucose level >6 mmol/L

(108 mg/dL) on 2 mornings. The exclusion criteria included a serum creatinine level $>175 \mu\text{mol/L}$ (1.12 mg/dL), myocardial infarction during the past year, current angina or heart failure, >1 major vascular event, retinopathy requiring laser treatment, malignant hypertension, an uncorrected endocrine disorder, an occupation that precluded use of insulin, severe concurrent illness that would limit life or require extensive systemic treatment, or inadequate understanding of the language or study requirements. The socioeconomic factors defining the patient cohort in the UKPDS were not stated by the authors.¹⁰ Likewise, the extent of psychiatric illness in that patient cohort was not stated.¹⁰

In comparing the selection criteria of the UKPDS¹⁰ and the DSDP study,¹ the intent of the UKPDS was to include patients with very early-stage disease who did not exhibit certain comorbidities or other chronic illnesses. In contrast, the DSDP study accepted any patient who wished to begin intensive insulin therapy.

From November 1, 2004, to July 31, 2006, the 4-T Study Group⁵ recruited patients in 58 clinical centers in Ireland and the United Kingdom. All of their patients had suboptimal glycemic control (A1C, 7.0%–10.0%) and had been receiving maximally tolerated doses of metformin and sulfonylureas for ≥ 4 months. The patients' BMI had to be $\leq 40 \text{ kg/m}^2$. Exclusion criteria included a history of thiazolidinedione therapy or triple antidiabetic treatment within the previous 6 months, sight-threatening retinopathy, a plasma creatinine level $\geq 1.47 \text{ mg/dL}$, hepatic disease, uncontrolled hypertension, hypoglycemic unawareness or recurrent major hypoglycemia, or cardiac disease (history of unstable angina or myocardial infarction during the previous 6 months or New York Heart Association class 3 or 4 congestive heart failure).⁵ The socioeconomic factors defining the patient cohort in the 4-T study and the extent of psychiatric illness were not reported.

In comparing the patients enrolled in the 4-T study with those who elected intensive insulin treatment in the DSDP study, similarities were noted between the 2 cohorts in terms of age and race. However, in the DSDP study, there were no exclusion criteria for weight, A1C level, severity of illness, or presence of comorbidities. Many of the patients in the DSDP study had A1C values $>10.0\%$, BMI $>40 \text{ kg/m}^2$, depression, and other chronic illnesses.

Also in contrast, the DSDP study accepted any patient who elected intensive insulin therapy. In the DSDP practice setting, the following forces shaped which patients chose to see us:

- Poverty
- Insulin phobia
- Self-selection of patients with comorbid depression

The first selection bias in the DSDP study was poverty. The impact of poverty and social effect as selection criteria in medical care in the United States are well understood. As early as 1968, Duff and Hollingshead¹⁴ studied the powerful impact of social class on medical care at Eastern University. The Institute of Medicine¹⁵ stated that a consistent body of research showed the existence of health care disparity and

unequal care. Glasgow et al¹⁶ showed that factors related to lower quality of life in patients with diabetes included less education, lower income, older age, being uninsured or a recipient of Medicare/Medicaid, the number of diabetes complications, and the number of comorbid illnesses. DSDP patients had all of the above.

The second selection bias that occurred in the DSDP study involved patients with insulin phobia. The cultural bias against insulin in the United States is well recognized. Both physicians and nurses in the United States believe that insulin therapy should be delayed until absolutely necessary.¹⁷ DSDP patients shared in this cultural belief; they held the common American perceptions that insulin is ineffective and that they were to blame for having to use insulin.¹⁷ DSDP patients believed that insulin therapy was punishment for their lack of personal success.¹⁸ Because of this underlying selection bias, the tendency was for DSDP patients to have advanced disease after years of failure on oral antihyperglycemia regimens.

The third selection bias in the DSDP study was depression. Black et al¹⁹ stated that the coexistence of depression and diabetes had a synergistic effect, predicting higher incidences of death, complications, and disabilities. Depression has been shown to be closely associated with hyperglycemia.²⁰ Lustman et al²¹ showed that cognitive behavioral therapy for depression in type 2 DM was an effective nonpharmacologic treatment for major depression. Jacobson and Weinger²² stated that depressed patients typically had negative distortions about their ability to achieve goals and carry out tasks of daily living. In the DSDP study,¹ shared medical visits, with behaviorally anchored treatment methods designed to help patients overcome negative thinking about insulin, appeared to attract patients with both diabetes and depression.

Comparison of Insulin Therapy Outcomes in the 4-T and DSDP Studies

The 4-T study⁵ and the DSDP study¹ had very different patient selection criteria. To compare the 2 sets of criteria, a subset of 94 patients from the DSDP study was formed from the group of patients who entered the study with A1C values of 7.0% to 10.0%. The outcomes for this subset of patients are shown in **Figure 5**.

The graph in **Figure 6** includes only this subset of 94 DSDP patients whose baseline A1C was identical to the admission criterion of the 4-T study, permitting a direct comparison of outcomes between patients with the same baseline range of A1C values. This graph shows the outcomes associated with 4 different insulin titration delivery systems. Of particular interest is the comparison of the patients in the prandial arm of the 4-T study and the patients who received intensive insulin therapy in the DSDP study. Aspart was used in the prandial arm of the 4-T study and was the principal bolus insulin used in the DSDP study. The duration of experience reported with aspart in the 4-T study was 1 year, whereas the duration of experience with aspart in the DSDP study was up to 4 years.

In the 4-T study, aspart alone lowered A1C values to the same extent as biphasic aspart, with no significant differ-

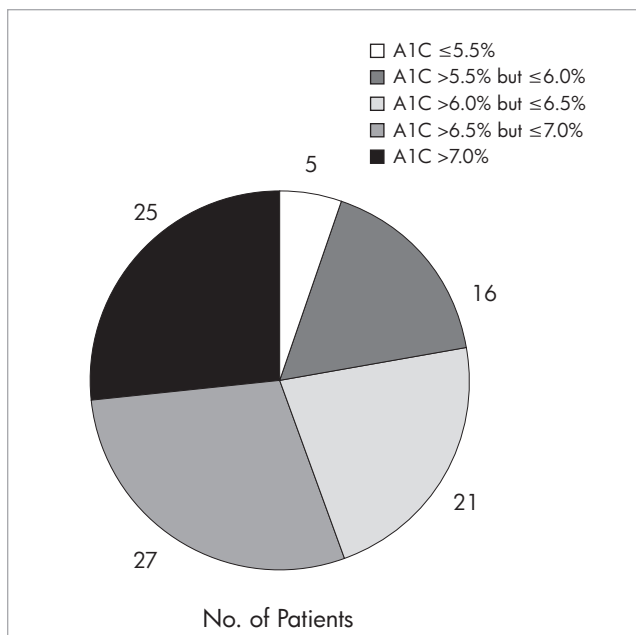


Figure 5. Outcomes for the subset of patients in the Deep South Diabetes Program study¹ who entered treatment with glycosylated hemoglobin (A1C) values from 7.0% to 10.0% (n = 94).

ences seen between aspart alone and biphasic aspart for patients with a baseline A1C value of ≤8.5%. Furthermore, with aspart alone, there was no improvement in performance over biphasic aspart with an associated weight gain of 21%.⁵ In the DSDP study,¹ aspart was found to be an effective insulin, which, in conjunction with glargine, could be depended on to produce and sustain normoglycemia.

Normoglycemia and Weight Gain Associated with Insulin Therapy

We hypothesize that outcomes that are commonly ascribed to an individual insulin are, in fact, a property of the insulin delivery system. Furthermore, the insulin delivery system has 4 critical components:

- The insulin(s) chosen
- The method of titration
- The organizational delivery system in which the titration occurs
- The choice of clinical target used to define treatment success or failure

The results of the study of normoglycemia and weight gain associated with insulin therapy tie together what, at first glance, seems to be an anomaly. The weight change outcome of insulin therapy depends on the final A1C achieved as a result of treatment. Both weight loss and weight gain are associated with insulin therapy (Figure 4).

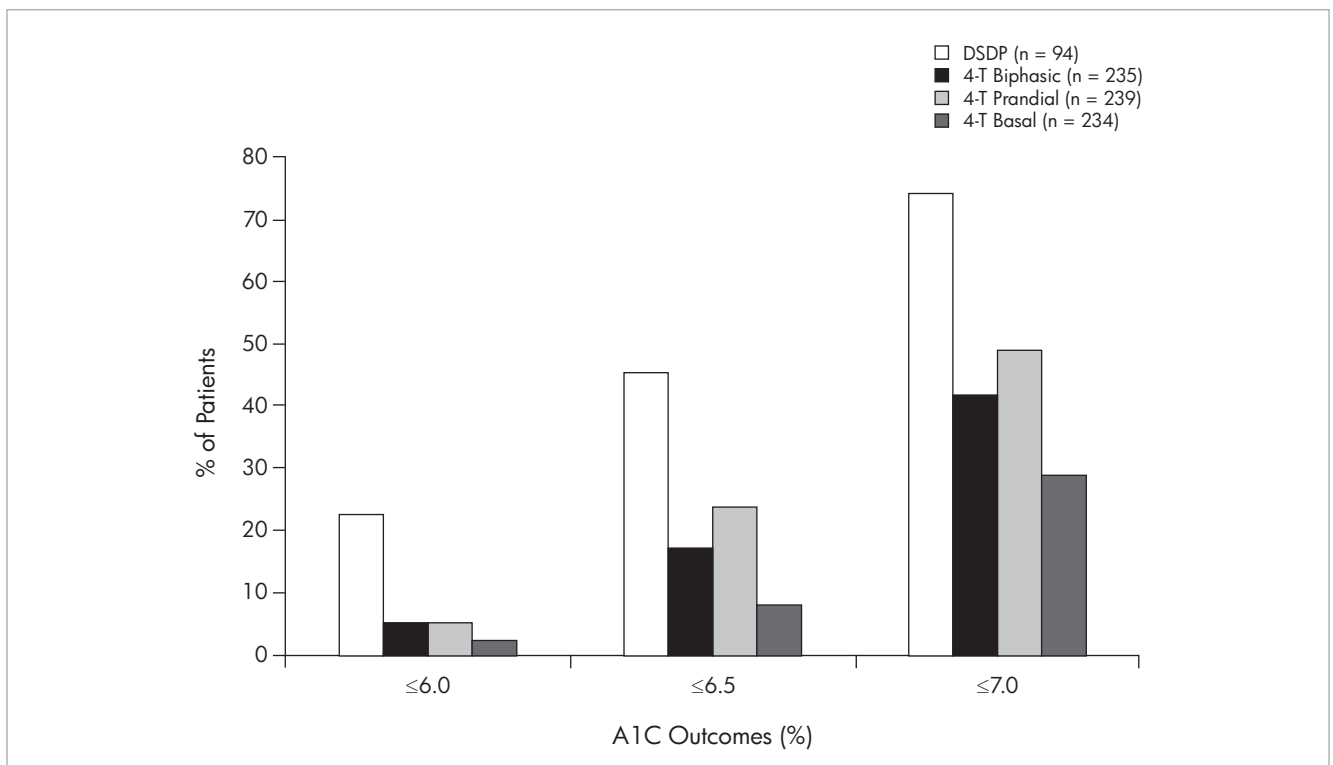


Figure 6. Comparison of insulin therapy outcomes for the subset of patients who entered the Deep South Diabetes Program (DSDP) study¹ with glycosylated hemoglobin (A1C) values from 7.0% to 10.0%, and for patients in the 3 treatment arms of the Treating to Target in Type 2 Diabetes (4-T) study.⁵

Insulin therapy that does not achieve normal or near-normal glycemia falls into the weight gain region of **Figure 4**; achievement of normal glycemia falls into the weight loss region. This is consistent with the outcomes of the 4-T study, in which normoglycemia was achieved for, at best, 5% of the patient population, and all treatment methods produced weight gain.

DSDP Study Limitations

The DSDP study was limited inherently by its retrospective, observational nature. In particular, a comprehensive review of the treatment parameters that drive weight management outcomes was beyond the scope of the study. In addition, this study makes no claim that the clinical acumen used to guide treatment decisions has been validated elsewhere.

Clinical Implications of the DSDP Observational Study

In the DSDP study,¹ diabetes was the primary disease treated; other chronic illnesses were considered secondary. Intensive insulin therapy was the core competency. Care given to patients with diabetes in the DSDP study was organized to deliver intensive insulin therapy as the primary, central treatment. The DSDP staff worked together as a team for the purpose of titrating insulin. This 4-year observational study showed the effectiveness of making intensive insulin therapy the central treatment in a setting where treatment of diabetes was the focus of the practice.

The rural safety net produced a strong selection bias that funneled patients to DSDP. Patients were poor, depressed, and chronically ill. They had been exposed to the deleterious effects of hyperglycemia from failure of oral regimens for many years. In other words, these patients were like many of the patients seen in ordinary clinical practice throughout the United States.

With regard to duration of illness, Harris et al²³ stated that the onset of noninsulin-dependent (type 2) DM occurs at least 4 to 7 years before clinical diagnosis. Thus, it is likely that most of the patients in the DSDP study had undiagnosed DM for years. It is also likely that the DSDP patients had been on prior regimens that did not focus on achieving normoglycemia or near-normoglycemia as an objective, resulting in a long period of treatment failure.

The historic circumstances of health care retrenchment that surrounded the DSDP observational study made insulin the central treatment available to our patients. The multitude of therapeutic choices used commonly for the treatment of hyperglycemia was not available to our patients. The clinical outcomes of the DSDP study were long term, and they were not confounded by other treatments for hyperglycemia.

The DSDP study showed the effectiveness of intensive insulin therapy in sick patients in an ordinary practice setting. It demonstrated that achieving and sustaining therapeutic normoglycemia was feasible and sustainable in ordinary practice settings in the United States with eco-

nomically impoverished, depressed, and chronically ill patients.

From the results of the qualitative study, we hypothesize that the weight neutrality or loss seen with normoglycemia is a function of the long-term adaptation of the patients to near-physiological insulin replacement. This adaptation is behavioral, biochemical, and physiological. The biochemical adaptation occurs from the lowering of blood glucose to normal or near-normal levels as a result of intensive insulin therapy delivered in accordance with the DSDP treatment algorithm for intensive insulin therapy. The behavioral adaptation occurs as an indirect result of treatment as patients redefine their dietary habits in accordance with the requirements of intensive insulin therapy. These requirements include multiple daily measurements of blood glucose levels and the matching of carbohydrate intake to bolus insulin requirements.

Intensive insulin therapy worked in the DSDP study as the central treatment for diabetes. Use of the DSDP treatment algorithm,¹ with compulsive attention to all of the components of the insulin delivery system, could make therapeutic normoglycemia the expected clinical outcome, not the exception.

CONCLUSIONS

The apparent anomaly in the relationship between insulin and the weight gain or weight loss associated with insulin therapy has been elucidated. Quantitative analysis showed that intensive insulin therapy using insulin glargine and insulin aspart together can produce either weight gain or weight loss, depending on the A1C level achieved.

The DCCT study clearly showed that intensive insulin therapy and conventional insulin therapy achieved radically different results. Intensive insulin therapy in the DCCT study produced much more effective clinical outcomes than did conventional insulin therapy. It is not surprising that in our setting, with the use of glargine and aspart, different clinical outcomes were obtained, depending on the A1C level achieved. It appears that the closer the patient gets to achieving and sustaining normoglycemia, the better insulin treatment is tolerated with regard to weight gain. In our setting, intensive insulin therapy in which patients achieved normoglycemia (A1C <6.0%) was better tolerated than insulin therapy in which patients achieved above-normal glycemia (A1C ≥7.0%).

When normoglycemia was achieved and sustained using the DSDP's treatment algorithm for intensive insulin therapy, the weight gain typically seen with conventional insulin therapy did not occur. Weight gain or loss in intensive insulin therapy using the DSDP treatment method was a function of the A1C achieved.

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