Reduction of Glycosylated Hemoglobin and Postprandial Hyperglycemia by Acarbose in Patients With NIDDM

A placebo-controlled dose-comparison study

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OBJECTIVE — To compare the safety and efficacy of three doses of acarbose (100, 200, and 300 mg three times daily) with placebo for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) in patients maintained on dietary therapy alone.

RESEARCH DESIGN AND METHODS — This multicenter double-blind placebo-controlled trial was 22 weeks in duration. The trial consisted of a 2-week screening period, a 4-week placebo run-in period, and a 16-week double-blind treatment period. The primary measure of drug efficacy was the mean change from baseline in HbA_{1c} levels. Additional efficacy variables included the mean change from baseline in fasting and postprandial plasma glucose and serum insulin levels.

RESULTS — After 16 weeks of treatment, acarbose-treated patients had statistically significant reductions in mean HbA_{1c} levels of 0.78, 0.73, and 1.10% (relative to placebo) in the 100-, 200-, and 300-mg t.i.d. groups, respectively. Significant reductions in fasting and postprandial plasma glucose levels, glucose area under the time-concentration curve, and maximum glucose concentration were also observed in acarbose-treated patients. Although there were no statistically significant differences among the 100-, 200-, and 300-mg treatment groups, there was a trend toward a dose-response relationship for most plasma glucose variables that were measured. Gastrointestinal side effects (e.g., abdominal pain, flatulence, and diarrhea) and serum transaminase elevations (e.g., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) were more frequently reported in the acarbose-treated patients than in the placebo-treated control patients. Transaminase elevations occurred only at the 200- and 300-mg dosages and were readily reversible on discontinuation of treatment.

CONCLUSIONS — Acarbose at doses of 100, 200, and 300 mg administered three times daily for 16 weeks significantly reduced HbA_{1c} levels and postprandial hyperglycemia. Treatment with acarbose is a safe and effective adjunct to dietary therapy for the treatment of NIDDM.

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Received for publication 27 September 1994 and accepted in revised form 16 February 1995.

ADA, American Diabetic Association; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; ANOVA, analysis of variance; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; C_{max}, maximum concentration; DCCT, Diabetes Control and Complications Trial; HPLC, high-performance liquid chromatography; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

Initial therapy for non-insulin-dependent diabetes mellitus (NIDDM) typically includes diet and exercise with the goal of maintaining near-normal weight and body fat. As the disease progresses, sulfonylurea drugs are administered. These drugs increase the pancreatic insulin response to blood glucose levels (1,2). Approximately 40% of all patients diagnosed with NIDDM are maintained on sulfonylureas (3). Primary failure, however, occurs in ~15% of sulfonylurea-treated NIDDM patients, with secondary failure reported in 3–5% of treated patients per year (4). When treatment with sulfonylureas fails to achieve adequate glycemic control, insulin therapy, either in combination with sulfonylureas or alone, is initiated. A number of side effects may result from treatment with sulfonylureas and/or insulin including weight gain, hyperinsulinemia, and sustained, possibly fatal, hypoglycemia (5–8).

Acarbose represents a novel therapeutic approach for the management of hyperglycemia in NIDDM patients. This complex oligosaccharide is a potent competitive inhibitor of intestinal brush-border α-glucosidases required for the breakdown of starches, dextrins, maltose, and sucrose to absorbable monosaccharides (9). Studies in animals and humans have shown that orally administered acarbose delays the hydrolysis of ingested complex carbohydrates and disaccharides, resulting in a dose-dependent reduction in postprandial serum insulin and glucose peaks (10–13). Results from clinical trials in patients with insulin-dependent diabetes mellitus (IDDM) and NIDDM have shown that treatment with acarbose results in significant reductions in postprandial hyperglycemia and HbA_{1c} levels (4,11–13). However, to date, there have been no large well-controlled studies conducted in the U.S. that compare the effects of different acarbose dosage regimens on blood glucose and serum insulin responses.

The present study was designed to

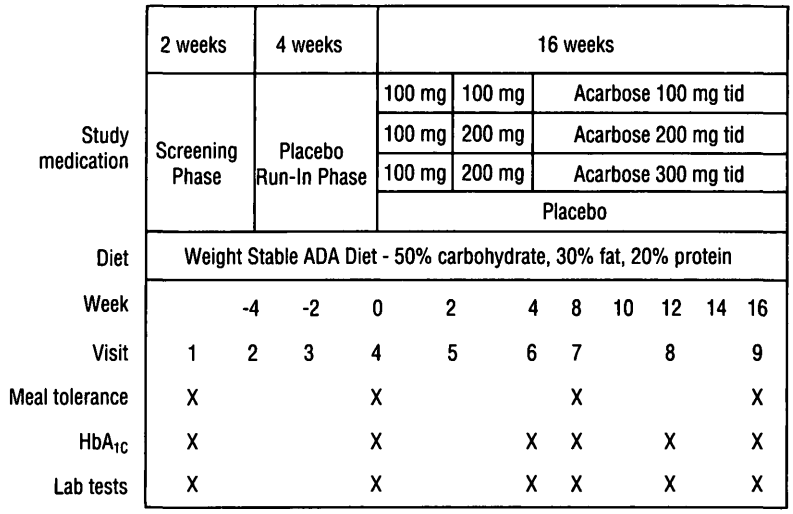

Figure 1—*Study design.*

evaluate the safety and efficacy of three doses of acarbose (100, 200, and 300 mg t.i.d.) in NIDDM patients managed on diet alone. The primary measure of drug efficacy was the change from baseline in HbA_{1c} levels. Secondary measures of efficacy included the change from baseline in fasting and postprandial blood glucose and serum insulin levels. From these results, the effects of acarbose treatment on the risk of long-term microvascular complications have been assessed.

RESEARCH DESIGN AND METHODS

— This study was 22 weeks in duration and consisted of a 2-week screening period, a 4-week single-blind, placebo run-in period, and a 16-week double-blind treatment period (Fig. 1). Men and women over age 30 with NIDDM for at least 3 months were eligible for study enrollment. Patients previously treated with sulfonylureas could be included in the study if these drugs had been discontinued at least 6 weeks before the screening visit and if the patients had achieved stable fasting glucose levels. The population studied was generally healthy apart from having diabetes. Patients were excluded from study participation for any of the following reasons: presence of significant diseases or conditions likely to alter the course of the diabetes or the ability to complete the study; documented gastrointestinal diseases likely to be associated with abnormal gut motility or altered absorption of nutrients; known or suspected lactose intolerance; severe and poorly controlled diabetes (ketonuria, severe hyperglycemia, and/or progressive weight loss suggesting the need for insulin therapy); concomitant therapy with insulin, glucocorticoid, other investigational drugs, or medications that might significantly alter gastrointestinal motility or absorption; elevated creatinine (>2.0 mg/dl), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.8 times the normal, or abnormally low hemoglobin levels (<11.0 g/dl). All patients gave their written informed consent before entering the study.

During the 2-week screening phase, patients had a complete medical history, physical examination, ECG, and specific laboratory tests to determine their eligibility for the study. At the screening visit, each patient was given a standardized meal tolerance test, i.e., a 600-kcal breakfast of 50% carbohydrate (75 g), 30% fat (20 g), and 20% protein (30 g) containing both solid and liquid components. The patients were instructed to ingest the test meal over a period of 20 min. The drug (either active or placebo) was administered with the first bite of the test meal. Blood samples were obtained at 0, 60, 90, and 120 min after the meal to determine plasma glucose and serum insulin levels. A blood sample for determination of HbA_{1c} was also obtained at this visit. Patients were excluded from study entry if HbA_{1c} levels were <6.5% (normal range 4–6%). During the 2-week placebo run-in period, patients were maintained on a diet consisting of at least 50% carbohydrates, recommended by the American Diabetes Association (ADA) at the time the study was conducted (14). At the baseline visit (visit 4), patients were given placebo medication with the meal tolerance test; glucose, insulin, and HbA_{1c} levels were again determined. Patients were then randomly assigned to receive one of three doses of acarbose (100, 200, or 300 mg t.i.d.) or placebo during the subsequent 16-week double-blind treatment period. The dosage was titrated at 2-week intervals beginning with 100 mg t.i.d. and progressing to 300 mg t.i.d., depending on the drug assignment.

The meal tolerance test was repeated at visits 7 and 9, with blood sampled at 0, 60, 90, and 120 min (Fig. 1). Lipoprotein(a) was measured at 7 of the 20 centers on visits 4, 7, and 9. Measurement of HbA_{1c} was repeated on visits 6, 7, 8, and 9.

Laboratory evaluations of complete blood count, chemistry profile, urinalysis, and a serum pregnancy test for all women younger than age 55 were obtained on visits 1, 4, 7, 8, and 9. The glucose, insulin, chemistry profile, complete blood count, urinalysis, and pregnancy tests were performed at Nichols Laboratory. HbA_{1c} and lipoprotein(a) assays were performed at the University of Missouri and the Medlantic Research Institute, respectively.

The primary efficacy variable was the mean change in HbA_{1c} levels from baseline to visit 9 after 16 weeks of study drug treatment. HbA_{1c} levels were as-

Table 1—*Baseline demographic and disease characteristics*

Variable	Patients valid for efficacy				Patients valid for safety			
		Acarbose				Acarbose		
	Placebo	100 mg	200 mg	300 mg	Placebo	100 mg	200 mg	300 mg
n	64	58	54	53	73	73	72	72
Mean age (years)	54	55	56	54	55	54	57	56
Mean weight (kg)	93	86	89	85	91	87	90	85
Mean height (cm)	171	168	170	169	170	169	171	169
Men (%)	58	52	59	58	56	55	58	60
Caucasian (%)	81	74	74	75	78	74	76	76
Black (%)	5	14	9	8	7	14	10	6
Hispanic (%)	9	10	15	9	10	10	11	11
Oriental (%)	0	0	2	4	1	0	1	4
Other (%)	5	2	0	4	4	3	1	3
Mean body mass index (kg/m^2)	32	31	31	30	31	30	31	30
Mean duration of NIDDM (years)	5	6	5	5	5	6	5	6
Discontinued sulfonylurea to enter study (%)	30	31	46	49	32	30	43	49

sayed using the Diamat high-performance liquid chromatography (HPLC) method. The primary comparison was between the 100-mg t.i.d. group and the placebo group. Comparisons between the other acarbose dose regimens were also made. Statistical comparisons of continuous variables were made using an analysis of variance (ANOVA) model controlling for center, treatment, and center-by-treatment effects. If there was no significant interaction effect, it was dropped from the model. From these models, the least-square means were calculated for each treatment group. Baseline values and sulfonylurea discontinuation status were explored as covariates when appropriate. Changes from baseline (visit 4) in fasting plasma glucose, fasting serum insulin, postprandial plasma glucose and serum insulin levels at the 60-, 90-, and 120-min time points, plasma glucose and serum insulin maximum concentration (C_{max}), and the area under the plasma glucose and serum insulin time-concentration curves were evaluated using similar ANOVA models. The study was designed to provide a power of 0.90 to detect a difference of 0.70% in HbA_{1c} levels using a two-tailed test at $P = 0.05$ for the primary efficacy comparison. A priori calculations for the sample size also allowed for 70–80% power to detect a difference of 0.40% in HbA_{1c} levels between the acarbose dose groups at $P = 0.05$ using a one-tailed test of equivalence. Categorical demographic and responder data were analyzed using the Mantel-Haenszel method.

Safety was assessed by comparing incidence rates of adverse events and abnormal laboratory values. Two-level categorical data were analyzed with either Fisher's exact test or the chi-squared test, depending on cell sizes. Time-to-event curves of adverse events were analyzed using Wilcoxon's test.

All 290 patients who were randomized to receive the study drug were included in the safety analysis. Of these, 229 were valid for the efficacy analysis: 64 in the placebo group, 58 in the 100-mg group, 54 in the 200-mg group, and 53 in the 300-mg group. The primary reasons for patient data exclusion from the efficacy analyses were either failure to meet the required 28 days of therapy after visit 6 (8 in the placebo group, 14 in the 100-mg group, 13 in the 200-mg group, and 17 in the 300-mg group) or inadequate washout from the patients' previous antidiabetic medication (4 in the 200-mg group and 1 in each of the other acarbose groups and in the placebo group).

RESULTS— The four treatment groups were comparable with respect to all demographic and disease characteristics analyzed with the exception of the percentage of patients who discontinued sulfonylurea therapy to participate in the study (Table 1). The baseline efficacy variables for the treatment groups are outlined in Table 2. Although the groups differed in a number of baseline characteristics, adjustment for these differences (including sulfonylurea discontinuation status) did not alter the efficacy results (see below).

The mean changes from baseline in the major efficacy variables after 16 weeks of treatment are summarized in Table 3. HbA_{1c} levels at the end of the treatment were significantly reduced in all acarbose treatment groups relative to baseline. These reductions ranged from 0.40% in the 200-mg group to 0.77% in the 300-mg group. In the placebo group, the HbA_{1c} levels increased by 0.33% during the treatment period. The net effect of

Table 2—*Baseline efficacy variables*

Variable	Placebo	Acarbose		
		100 mg	200 mg	300 mg
HbA_{1c} (%)	8.67‡	8.69‡	8.96	9.54
Weight (kg)	91.3	85.9	87.9	84.5
Fasting plasma glucose (mg/dl)	202.5†‡	202.3†	238.0	227.8
Postprandial plasma glucose (mg/dl)				
60 min	297.1	299.1	328.9	324.2
90 min	299.2	297.6	330.0	330.2
120 min	287.0	287.6	317.7	316.2
Plasma glucose AUC ($mg \cdot min^{-1} \cdot dl^{-1}$)	36,343	35,564	40,735	38,599
Plasma glucose C_{max} (mg/dl)	308.5	311.6	341.1	339.9
Fasting serum insulin (μU/ml)	19.0	17.4	16.5	18.2
Postprandial serum insulin (μU/ml)				
60 min	53.4†‡	45.2	41.0	39.3
90 min	61.8‡	53.8	48.4	42.8
120 min	62.4	52.2	47.1	44.1
Serum insulin AUC ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	6,295†‡	5,263	4,827	4,666
Serum insulin C_{max} (μU/ml)	70.5‡	58.1	55.7	49.0
Lipoprotein(a) (mg/dl)	25.6	19.9	11.8	36.4
Total cholesterol (mg/dl)	207.6	216.3	210.0	210.3
Total triglycerides (mg/dl)	201.5	204.8	189.0	230.3
Uric acid (mg/dl)	5.1	4.9	4.5	4.8

† Significantly different from 200-mg group. ‡ Significantly different from 300-mg group.

acarbose treatment (placebo-subtracted) was a mean reduction in HbA_{1c} levels of between 0.73 and 1.10%. Adjustments to the mean changes in HbA_{1c} levels, taking into account differences between treatment groups in baseline HbA_{1c} levels and in sulfonylurea discontinuation status, are presented in Table 4. Although the inclusion of these covariates in the model slightly reduced the difference between treatment means, the conclusions remain unchanged.

The mean changes from baseline in HbA_{1c} levels after 4, 8, 12, and 16 weeks of treatment are displayed in Fig. 2. HbA_{1c} levels tended to increase over time in the placebo-treated patients. In contrast, in acarbose-treated patients, HbA_{1c} levels steadily decreased during treatment. The magnitude of these decreases (relative to placebo) was statistically significant at weeks 8, 12, and 16 for all acarbose treatment groups.

There were significant reductions in all plasma glucose variables that were measured (i.e., fasting and postprandial glucose, glucose AUC, and glucose C_{max}) in the acarbose-treated patients compared with the placebo-treated control patients. At the end of the treatment period (week 16), fasting plasma glucose levels were reduced by 7 mg/dl to 19 mg/dl in the acarbose-treated patients (relative to baseline), compared with a 20 mg/dl increase in placebo-treated patients. Postprandial glucose levels (at the end of treatment) were also significantly different among treatment groups (Table 3). At 60 min after administration of a test meal, glucose levels were reduced by 43, 53, and 98 mg/dl in the 100-, 200-, and 300-mg dose groups, respectively, relative to baseline. In comparison, in the placebo group, the plasma glucose concentrations increased by 32 mg/dl. At 90 and 120 min after administration of the test meal, the acarbose-treated patients still retained significant reductions in plasma glucose levels (relative to placebo). A time course depicting plasma glucose concentration after the test meal challenge suggests that acarbose has a dose-related effect on postprandial glucose concentration (Fig. 3).

Analyses of fasting and postprandial serum insulin levels indicate no statistically significant differences between treatment groups. For all insulin variables that were measured (e.g., fasting and postprandial levels, insulin AUC, and insulin C_{max}), however, there were reductions in the 200- and 300-mg treatment arms compared with placebo, with the magnitude of these reductions related to the dose of acarbose.

A number of different variables (e.g., age, sex, race, body mass index, duration of diabetes, baseline HbA_{1c}, baseline fasting plasma glucose level, changes from baseline to week 16 in fasting plasma glucose level, and sulfonylurea discontinuation status) were examined for their relationship to the mean change from baseline in HbA_{1c} levels (data not shown). Most of these variables had no significant effect on HbA_{1c} levels. However, patients who discontinued sulfonylurea treatment to enter the study showed

Table 3—*Changes from baseline in major efficacy parameters after 16 weeks of treatment*

Variable	Placebo	Acarbose 100 mg	Acarbose 200 mg	Acarbose 300 mg
HbA_{1c} (%)	0.33*†‡	−0.45	−0.40	−0.77
Weight (kg)	−0.37	−0.19	−0.80	−0.45
Fasting plasma glucose (mg/dl)	19.80*†‡	−7.33	−19.11	−16.79
Postprandial plasma glucose (mg/dl)				
60 min	31.83*†‡	−42.55‡	−52.61‡	−97.61
90 min	24.49*†‡	−45.08	−56.67	−67.19
120 min	29.71*†‡	−38.12	−57.03	−60.26
Plasma glucose AUC ($mg \cdot min^{-1} \cdot dl^{-1}$)	3,482.6*†‡	−3,151.9‡	−5,523.8	−6,560.7
Plasma glucose C_{max} (mg/dl)	25.52*†‡	−42.03	−58.80	−64.38
Fasting serum insulin (μU/ml)	1.16	1.74	0.45	−1.76
Postprandial serum insulin (μU/ml)				
60 min	3.12	0.21	−0.13	−4.51
90 min	4.03	−0.52	−1.21	−1.77
120 min	1.01	3.06	0.03	−4.80
Serum insulin AUC ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	417.70	341.99	−8.98	−429.80
Serum insulin C_{max} (μU/ml)	1.05	2.91	−1.53	−4.20
Lipoprotein(a) (mg/dl)	−2.17	−3.15	−0.66	−1.28
Total cholesterol (mg/dl)	−2.08	3.26	0.27	−1.07
Total triglycerides (mg/dl)	26.46	9.09	−8.37	12.18
Uric acid (mg/dl)	0.04	−0.01	−0.01	0.07

* Significantly different from 100-mg group. † Significantly different from 200-mg group. ‡ Significantly different from 300-mg group.

greater reductions in mean HbA_{1c} levels than did patients who had not been taking sulfonylureas before entering the study. In addition, patients who had lower baseline HbA_{1c} levels (≤7.7%) had smaller reductions at the end of treatment in their HbA_{1c} levels than did patients whose baseline levels were higher. A similar trend was observed for patients with lower fasting plasma glucose (≤177 mg/dl). However, when these variables were entered into the ANOVA model as covariates, the overall results were not affected, and they were not therefore included as covariates in the final model.

Analysis of the percentage of patients exhibiting a positive response to acarbose (any patient with a baseline HbA_{1c} ≤7% and a change from baseline of at least 0.5% at the end of the study or any patient with a reduction of at least 1% from baseline HbA_{1c}, irrespective of the baseline HbA_{1c}) indicated that there were significantly more responders in the acarbose treatment groups (33, 26, and 40% in the 100-, 200-, and 300-mg groups, respectively) than in the placebo group (11%). There were no significant differences in the other efficacy variables that were measured [i.e., weight gain, lipoprotein(a), total cholesterol, total triglycerides, or uric acid].

The incidence of adverse events (including intercurrent illnesses) was higher in the three acarbose treatment groups than in the placebo group (96, 96, and 97% vs. 81% in the 100-, 200-, and 300-mg groups vs. placebo). The majority of adverse events were gastrointestinal (Table 5). There were significantly more reports of flatulence and diarrhea in the acarbose-treated patients than in the placebo-treated control patients. Abdominal pain also occurred with greater frequency in the acarbose treatment groups (18, 15,

Table 4—*Adjusted mean HbA_{1c} values from ANOVA and ANCOVA*

Treatment	ANOVA (%)	ANCOVA with covariate: Baseline HbA_{1c} covariate (%)	ANCOVA with covariate: Baseline sulfonylurea covariate (%)
Placebo	0.33*†‡	0.31*†‡	0.30*†‡
Acarbose			
100 mg	−0.45	−0.48	−0.48
200 mg	−0.40	−0.40	−0.39
300 mg	−0.77	−0.72	−0.75

* Significantly different from 100-mg group. † Significantly different from 200-mg group. ‡ Significantly different from 300-mg group.

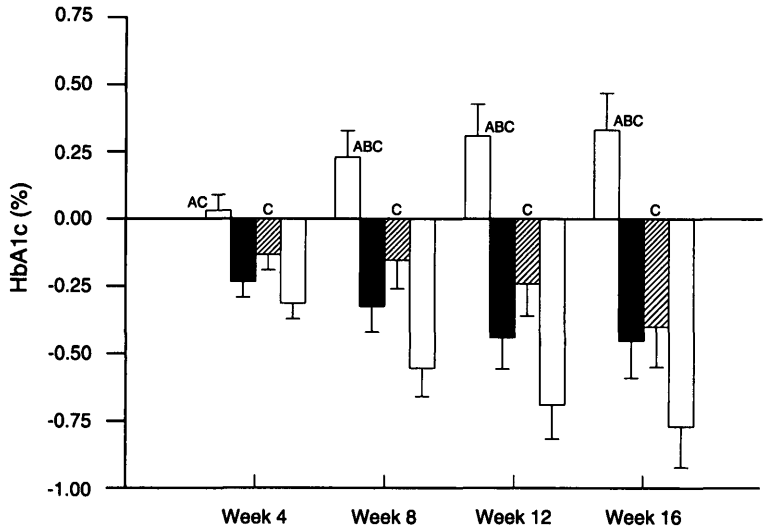

Figure 2—*Mean change in HbA_{1c} levels from baseline during the study. HbA_{1c} levels were determined using the Diamat HPLC method. □ above 0.0, placebo; ■, 100 mg acarbose; ▨, 200 mg acarbose; □ below 0.0, 300 mg acarbose. A, significantly different from 100 mg acarbose t.i.d.; B, significantly different from 200 mg acarbose t.i.d.; C, significantly different from 300 mg acarbose t.i.d.*

and 19% in the 100-, 200-, and 300-mg groups, respectively) compared with placebo group (5%). Neither the incidence of specific gastrointestinal side effects nor the incidence of any other adverse events appeared to be related to the dose of acarbose. The incidence of premature discontinuation from the study due to adverse events was significantly higher in the acarbose treatment groups than in the placebo group (16, 21, and 19% vs. 4% in the 100-, 200-, and 300-mg groups vs. placebo).

The results of the liver function tests were monitored during the course of the study and if severe abnormalities occurred, the patient was withdrawn from the study. Three patients had serum transaminase levels (AST and/or ALT) greater than three times the upper limit of normal. Two of these patients were withdrawn from the study. The third patient continued in the study with complete resolution of the liver function abnormalities. Two additional patients had elevated serum transaminase levels considered serious by the investigator and were withdrawn from the study. All five patients were taking acarbose, 200 or 300 mg t.i.d. Except for the one patient who had a transient increase in bilirubin and alkaline phosphatase, there were no associated laboratory findings of cholestasis. In all cases, patients were asymptomatic and the serum transaminase elevations reversed on discontinuation of treatment.

CONCLUSIONS — Between 85 and 90% of all diagnosed cases of diabetes in the U.S. are classified as NIDDM. Depending on the disease severity, therapy for NIDDM patients consists of diet, exercise, weight reduction, sulfonylurea drugs, and/or insulin therapy. The primary therapeutic endpoint in the treatment of diabetes has been to maintain near-normal levels of glycemia with the goal of reducing microvascular and macrovascular complications.

Over the past 10 years, reports from numerous clinical studies have demonstrated a strong association between hyperglycemia and an increased risk of microvascular tissue damage (15–17). HbA_{1c} has been used as a surrogate long-term measure of glycemic control. Klein et al. (18) demonstrated that HbA_{1c} was a more significant predictor of the onset or progression of retinopathy in NIDDM diabetic patients than blood glucose concentration. From this study, it was also shown that patients with mean HbA_{1c} levels of 11% had two times the 4-year risk of proliferative retinopathy than did patients with HbA_{1c} levels of 9%. Data from the recently published Diabetes Control and Complications Trial

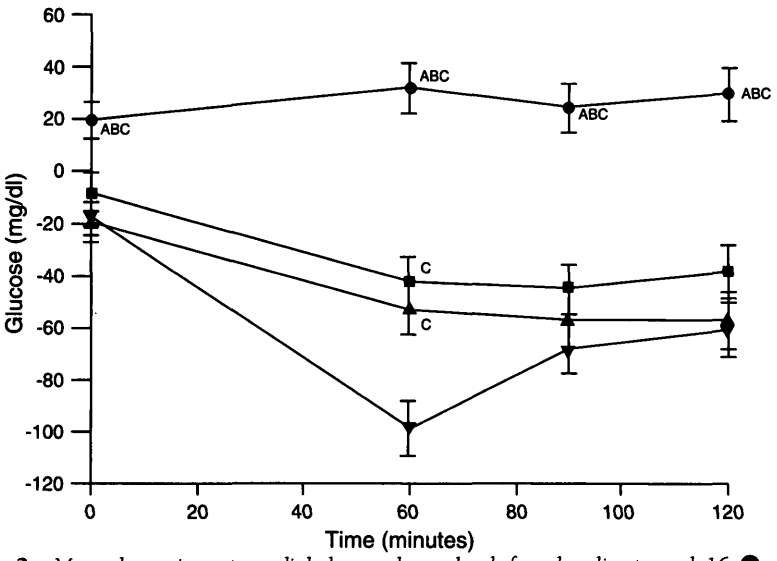

Figure 3—*Mean change in postprandial plasma glucose levels from baseline to week 16. ●, placebo; ■, 100 mg acarbose; ▲, 200 mg acarbose; ▼ 300 mg acarbose. A, significantly different from 100 mg acarbose t.i.d.; B, significantly different from 200 mg acarbose t.i.d.; C, significantly different from 300 mg acarbose t.i.d.*

Table 5—*Incidence rates of the most frequently occurring (≥5%) adverse events significantly different between treatment groups*

Adverse event	Placebo	Acarbose 100 mg	Acarbose 200 mg	Acarbose 300 mg
Overall incidence of adverse events	59/73 (81)*†‡	70/73 (96)	69/72 (96)	70/72 (97)
Flatulence	18/73 (25)*†‡	56/72 (78)	62/71 (87)	57/72 (79)
Diarrhea	7/73 (10)*†‡	26/73 (36)	24/72 (33)	25/72 (35)
Nausea	0/73†	4/73 (5)	6/72 (8)	1/72 (1)
Abdominal pain	4/73 (5)*‡	13/73 (18)	11/72 (15)	14/72 (19)
Headache	5/73 (7)‡	11/73 (15)†	3/72 (4)‡	13/72 (18)
Hyperglycemia	8/73 (11)*	1/73 (1)	3/72 (4)	3/72 (4)

Data are number of patients reporting the event during treatment/number of patients who, during pretreatment, either did not report the event or reported the event with less severe intensity (%). * Significantly different from 100-mg group. † Significantly different from 200-mg group. ‡ Significantly different from 300-mg group.

(DCCT) demonstrated that improved glycemic control in IDDM patients is associated with a reduced incidence and progression of retinopathy, nephropathy, and neuropathy (19). This study also indicated a linear relationship between HbA_{1c} levels and the incidence of diabetic retinopathy, suggesting that even small elevations in HbA_{1c} levels are associated with an increased risk of microvascular complications. Similar results were obtained from the Stockholm Diabetes Intervention Study (20) in which IDDM patients in whom tight glycemic control was maintained had a slower development of microvascular complications than patients receiving standard insulin regimens. Because the mechanisms responsible for the pathological consequences of hyperglycemia are presumed to be the same for both IDDM and NIDDM (21), tight glycemic control should be of benefit to both populations of diabetic patients.

The results of the present study indicate that acarbose at doses of 100, 200, and 300 mg t.i.d. significantly reduced HbA_{1c} levels in NIDDM patients maintained on dietary therapy alone. The magnitude of the treatment effect steadily increased during the 16 weeks of active treatment; at the end of treatment period, mean reductions in HbA_{1c} levels (placebo-subtracted) ranged from 0.73 to 1.10%. From the relationship derived from the DCCT between HbA_{1c} and the rate of progression of sustained retinopathy, a reduction of this magnitude would be expected to reduce the risk of retinopathy by ~30–35% (19).

Concomitant with reduced HbA_{1c} levels were reductions in postprandial glucose concentrations (at 60, 90, and 120 min after test meal challenge), glucose AUC, and glucose C_{max} in the acarbose treatment groups. In contrast, in placebo-treated patients, for all glucose variables that were measured (including HbA_{1c}), there was a steady deterioration in glycemic control. It is likely that this deterioration is a reflection of an increasing lack of compliance to the dietary regimen instituted at the beginning of treatment.

Although there were no statistically significant differences between treatment groups in postprandial serum insulin levels, in the acarbose-treatment groups there were reductions for all insulin variables that were measured (i.e., 60-, 90-, and 120-min postprandial serum insulin levels, serum insulin AUC, and serum insulin C_{max}). Hoffman and Spengler (22), Hanefeld et al. (12), and Hillebrand et al. (11) have recently described a similar reduction in postprandial hyperinsulinemia in acarbose-treated patients.

For all postprandial plasma glucose variables that were measured (i.e., 60-, 90-, and 120-min postprandial plasma glucose levels, glucose AUC, and glucose C_{max}), there appeared to be a dose-related response, with the greatest reductions evident in the 300-mg dose group. For HbA_{1c}, however, there was a greater reduction in the 200-mg dose group than in the 300-mg dose group. This lack of a clear dose response for HbA_{1c} may reflect either the inadequate sizing of this study to enable comparisons between the various acarbose dose levels (i.e., the primary comparison was between the acarbose and placebo treatment groups) or the effect of variables influencing HbA_{1c} that were inadequately controlled in the study design.

The side effects occurring in the acarbose-treated groups consisted primarily of gastrointestinal symptoms, such as flatulence and diarrhea, attributable to the undigested complex carbohydrate delivered to the large intestine. Subsequent fermentation by colonic bacteria can result in cramping, abdominal pain, increased gas production, flatulence, and diarrhea. The occurrence of these side effects was tolerated by the majority of the patients. Significant elevations in serum transaminases (AST and ALT greater than three times the upper limit of normal) were observed in three patients at the 200- and 300-mg dose levels. These patients were asymptomatic and their serum transaminase levels rapidly returned to normal on discontinuation of acarbose.

In this study, we have demonstrated that treatment of NIDDM patients with acarbose significantly reduced the HbA_{1c} levels. There was also a trend for a dose-dependent reduction in postprandial glucose concentrations, glucose AUC, and glucose C_{max}. These results were obtained without many of the side effects characteristic of treatment with insulin or sulfonylurea drugs (e.g., weight gain, hypoglycemia, and hyperinsuline-

mia). Acarbose represents a novel therapeutic alternative for treatment of NIDDM patients that is associated with a low risk of serious side effects.

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