Treating Postprandial Hyperglycemia Does Not Appear to Delay Progression of Early Type 2 Diabetes

The Early Diabetes Intervention Program

M. Sue Kirkman, md[1,2]
R. Ravi Shankar, md[1]
Sudha Shankar, md[1]
Changyu Shen, phd[1]
Edward Brizendine, ms[1]
Alain Baron, md[1,3]
Janet McGill, md[4]

OBJECTIVE — Postprandial hyperglycemia characterizes early type 2 diabetes. We investigated whether ameliorating postprandial hyperglycemia with acarbose would prevent or delay progression of diabetes, defined as progression to frank fasting hyperglycemia, in subjects with early diabetes (fasting plasma glucose [FPG] <140 mg/dl and 2-h plasma glucose ≥200 mg/dl).

RESEARCH DESIGN AND METHODS — Two hundred nineteen subjects with early diabetes were randomly assigned to 100 mg acarbose t.i.d. or identical placebo and followed for 5 years or until they reached the primary outcome (two consecutive quarterly FPG measurements of ≥140 mg/dl). Secondary outcomes included measures of glycemia (meal tolerance tests, HbA_{1c}, annual oral glucose tolerance tests [OGTTs]), measures of insulin resistance (homeostasis model assessment [HOMA] of insulin resistance and insulin sensitivity index from hyperglycemic clamps), and secondary measures of β-cell function (HOMA-β, early- and late-phase insulin secretion, and proinsulin-to-insulin ratio).

RESULTS — Acarbose significantly reduced postprandial hyperglycemia. However, there was no difference in the cumulative rate of frank fasting hyperglycemia (29% with acarbose and 34% with placebo; $P = 0.65$ for survival analysis). There were no significant differences between groups in OGTT values, measures of insulin resistance, or secondary measures of β-cell function. In a post hoc analysis of subjects with initial FPG <126 mg/dl, acarbose reduced the rate of development of FPG ≥126 mg/dl (27 vs. 50%; $P = 0.04$).

CONCLUSIONS — Ameliorating postprandial hyperglycemia did not appear to delay progression of early type 2 diabetes. Factors other than postprandial hyperglycemia may be greater determinants of progression of diabetes. Alternatively, once FPG exceeds 126 mg/dl, β-cell failure may no longer be remediable.

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Type 2 diabetes is a progressive disease, often with an inexorable rise in HbA1c (A1C) over time and the need for increasingly aggressive multidrug therapy (1). Insulin resistance is a fundamental abnormality in type 2 diabetes that appears to develop long before the development of hyperglycemia. However, many obese subjects never develop hyperglycemia despite significant insulin resistance. β-Cell dysfunction, with progressive loss of the capacity to hypersecrete insulin to compensate for insulin resistance, seems to be required for the development of impaired glucose tolerance (IGT) or diabetes (2,3). Several abnormalities have been described as part of the syndrome of β-cell dysfunction, including loss of first-phase insulin secretion, a defect in conversion of proinsulin to insulin, decreasing maximal capacity of glucose to potentiate nonglucose signals, and eventually loss of adequate basal insulin secretion (2–5). The causes of β-cell dysfunction and failure are unknown but may include genetic factors, glucose toxicity, lipotoxicity, or some combination thereof.

Most patients in whom type 2 diabetes is diagnosed in clinical practice do not actually have "new-onset" diabetes; on average, diabetes has been present for 9–12 years at the time of clinical diagnosis (6). During the pre-diabetic state of IGT and the early years of diabetes, hyperglycemia is primarily postprandial in nature (7–9), asymptomatic, and difficult to detect, leading to delay in diagnosis. With time, as the β-cell defect becomes more severe, impaired basal insulin secretion leads to fasting hyperglycemia, more severe postprandial hyperglycemia, hyperglycemic symptoms, and a clinical diagnosis. At this point, the U.K. Prospective Diabetes Study Group (UKPDS) data suggest that β-cell decline may not be remediable (1).

Because postprandial hyperglycemia is an early abnormality in type 2 diabetes, the resultant glucose toxicity is a potential mediator of progressive β-cell dysfunction (10–13). We hypothesized that ameliorating postprandial hyperglycemia in subjects with early type 2 diabetes (primarily postprandial hyperglycemia and found by screening asymptomatic individuals) would prevent or delay β-cell failure, manifested by progression to frank fasting hyperglycemia. We used acarbose, a drug known to primarily af-

From the [1]Indiana University School of Medicine, Indianapolis, Indiana; the [2]Roudebush VA Medical Center, Indianapolis Indiana; [3]Amylin Pharmaceuticals, San Diego California; and the [4]Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to M. Sue Kirkman, MD, 545 Barnhill Dr., EH 421, Indianapolis, IN 46202. E-mail: mkirkman@iupui.edu.

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Abbreviations: AUC, area under the curve; DPP, Diabetes Prevention Program; EDIP, Early Diabetes Intervention Program; FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of of insulin resistance; IGT, impaired glucose tolerance; MPS, meal profile study; OGTT, oral glucose tolerance test; STOP-NIDDM, Study to Prevent NIDDM; UKPDS, U.K. Prospective Diabetes Study Group.

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

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fect postprandial hyperglycemia and to have little effect on fasting glucose (14), to test this hypothesis in a randomized, double-blind placebo-controlled clinical trial.

RESEARCH DESIGN AND METHODS

— The Early Diabetes Intervention Program (EDIP) was a 5-year trial carried out at Indiana University School of Medicine and Washington University School of Medicine. The study was approved by the institutional review boards of both institutions, and all subjects provided informed consent for screening and for the trial.

Recruitment for EDIP paralleled recruitment for the Diabetes Prevention Program (DPP) trial (15) at both institutions and has been described previously (16). Individuals at least 25 years of age with obesity, a history of gestational diabetes, or a family history of diabetes were targeted. After informed consent, subjects underwent fasting plasma glucose (FPG) measurement using a glucose analyzer (YSI, Yellow Springs, OH). Subjects with FPG measurements between 105 mg/dl (5.5 mmol/l) and 140 mg/dl (7.8 mmol/l, the diagnostic FPG cutoff for diabetes at the time of study initiation) underwent a 75-g oral glucose tolerance test (OGTT). Those with a 2-h postload plasma glucose measurement ≥200 mg/dl (11.1 mmol/l) along with FPG <140 mg/dl were considered to have early diabetes and screened for enrollment. Exclusion criteria included BMI <24 kg/m^2, cancer within 5 years, infectious disease including HIV infection, a cardiac event within the previous 6 months, uncontrolled hypertension or hypertension that could not be controlled with agents other than β-blockers or thiazide diuretics, elevated aspartate aminotransferase or alanine aminotransferase, serum creatinine >1.4 mg/dl in men or 1.3 mg/dl in women, fasting plasma triglycerides >600 mg/dl despite treatment, any significant disease or medication that could interfere with medication tolerance or with outcomes, suspected inability to adhere to the protocol, or inability to give informed consent.

Within 6 weeks of the qualifying OGTT, subjects were admitted for a 2-day study initiation visit. All subjects had a medical history taken and underwent physical examination, electrocardiogram, seven-field fundus photography, 24-h urine collection for creatinine clearance and microalbumin, and a 9-h meal profile study (MPS; described below). Half of the subjects were randomly assigned to undergo a hyperglycemic clamp procedure, described below. A registered dietitian counseled subjects on an appropriate diet for type 2 diabetes. At the end of the admission, subjects began either acarbose or an identical placebo based on a blinded randomization stratified by site and by randomization to the clamp. Study drug was initiated at a dose of 25 mg once daily with the evening meal, then titrated at weekly intervals by 25 mg daily to the maximum dose of 100 mg t.i.d. with meals. Study drug was down-titrated as needed in subjects who complained of gastrointestinal side effects. Efforts were made to reach a daily dosage of at least 50 mg t.i.d.

The primary outcome was development of frank fasting hyperglycemia (defined a priori as two consecutive quarterly FPG measurements ≥140 mg/dl or 7.8 mmol/l). Subjects visited the study clinic at 3-month intervals and had FPG measured by the YSI glucose analyzer, among other measurements. Subjects whose FPG was ≥140 mg/dl had intensified dietary counseling. If the next quarterly FPG was <140 mg/dl, the subject continued in the study. If the next FPG again was >140 mg/dl, the subject was considered to have reached the primary end point and was asked to complete a closeout visit; this visit was equivalent to what would have been the next annual visit.

Annually, each subject completed a visit at which multiple measures were done (OGTT, history, and physical examination, seven-field fundus photographs, electrocardiogram, and laboratory tests for renal and hepatic function). At years 1 and 2, MPS studies and hyperglycemic clamps were repeated, as detailed below.

Meal profile studies

Subjects underwent MPS at the initiation visit (before beginning the study drug) and at years 1 and 2, when the study drug was taken with the MPS. For each subject, a standardized isocaloric meal plan composed of 55% carbohydrate, 30% fat, and 15% protein was provided, with one-third of calories at each of three meals. Each breakfast or lunch consisted of the same food items from subject to subject and from year to year. Test meals were consumed within 20 min starting at 8:00 A.M. and 12:00 P.M., with the final (nontest) meal consumed after the 5:00 P.M. sampling. Blood samples for plasma glucose and insulin were obtained at 7:30 A.M. and then hourly from 8:00 A.M. through 5:00 P.M. Fasting samples for proinsulin were obtained at 7:30 and 8:00 A.M.

Hyperglycemic clamp

Of the subjects at each site, 50% were randomly assigned to undergo hyperglycemic clamp testing at the initiation visit and at years 1 and 2. Studies were done in the fasting state with no study medication. At −10 and 0 min, samples were obtained for plasma glucose and insulin. A priming and then a maintenance rate of glucose, calculated by modification of the Andres method (17), was infused to rapidly bring the plasma glucose to 200 mg/dl and "clamp" it there for 4 h. To prevent hypokalemia, potassium phosphate was infused. Samples for plasma glucose and insulin were obtained every 2 min for the first 10 min of glucose infusion, then at 15 and 30 min, and then every 30 min for 4 h.

Other measurements

A1C was measured every 6 months by immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN). Total and HDL cholesterol and triglycerides were measured annually by the enzymatic end point assay (Roche Diagnostics). LDL cholesterol was calculated by the Friedewald calculation (18) if the value for triglycerides was <400 mg/dl. Insulin and proinsulin were measured by radioimmunoassay (Linco Research), with fasting values being the mean of −30 and 0 min samples. Early insulin secretion in the clamp was defined as the incremental area under the curve (AUC) for insulin over the first 10 min, with late-phase insulin secretion defined as incremental AUC for insulin for 30–240 min. All AUC measurements were calculated using the trapezoid rule. The insulin sensitivity index was assessed from the clamp by calculating (glucose infusion rate over final 30 min) divided by (mean insulin level over final 30 min). Peak postprandial glucose was calculated as the highest plasma glucose measurement after each test meal in the MPS, and glucose incremental AUC was calculated for each meal and for the entire 9 h. Homeostasis model assessments of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated as described by Matthews et al. (19). All laboratory assays for both sites, other than the YSI plasma glucose measurements, were done at the central study laboratory at the Indiana University School of Medicine.

Table 1—*Baseline characteristics*

	Overall	Acarbose	Placebo
n	219	109	110
Sex			
Male	74 (33.8)	36 (33.0)	38 (34.6)
Female	145 (66.2)	73 (67.0)	72 (65.4)
Race			
White	171 (78.1)	84 (77.1)	87 (79.1)
African American	41 (18.7)	21 (19.3)	20 (18.2)
Asian	3 (1.4)	2 (1.8)	1 (0.9)
Hispanic	4 (1.8)	2 (1.8)	2 (1.8)
Family history of diabetes	153 (79.3)	74 (77.9)	79 (80.6)
Women with history of gestational diabetes mellitus	17 (11.7)	14 (19.2)	3 (4.2)
Age (years)	53.7 ± 11.4	53.7 ± 11.0	53.7 ± 11.7
Weight (kg)	98.6 ± 21.2	97.4 ± 19.1	99.9 ± 23.1
BMI (kg/m^2)	35.2 ± 7.1	35.1 ± 7.2	35.2 ± 7.1
Waist circumference (inches)	41.2 ± 5.1	41.2 ± 5.6	41.2 ± 4.6
% body fat by dual-energy X-ray absorptiometry	42.7 ± 9.0	42.2 ± 9.5	43.2 ± 8.5
FPG (mg/dl)	121.4 ± 13.7	122.1 ± 13.9	120.8 ± 13.4
2-h plasma glucose (dl)	236.2 ± 31.0	236.5 ± 31.8	235.8 ± 30.4
A1C (%)	6.34 ± 0.64	6.35 ± 0.65	6.33 ± 0.63
Diagnosis of hypertension	107 (49.8)	54 (50.5)	53 (49.1)
Systolic blood pressure (mmHg)	132.6 ± 17.3	133.3 ± 16.4	132.0 ± 18.2
Diastolic blood pressure (mmHg)	75.4 ± 11.0	75.6 ± 11.1	75.2 ± 11.0
Lipids (mg/dl)			
Total cholesterol	195.0 ± 38.7	195.1 ± 37.4	195.0 ± 40.0
HDL cholesterol	38.4 ± 8.6	38.2 ± 8.4	38.5 ± 8.8
LDL cholesterol	118.1 ± 36.1	117.7 ± 36.2	118.4 ± 36.1
Triglycerides	192.9 ± 102.0	195.5 ± 113.9	190.3 ± 89.3
Retinopathy present	25 (12.7)	11 (11.7)	14 (13.6)
Microalbuminuria present	6 (2.8)	3 (2.8)	3 (2.8)
Sensory neuropathy present	33 (15.5)	15 (14.2)	18 (16.7)

Data are *n* (%) or means ± SD.

Sample size

The conversion rate from postprandial diabetes to frank fasting hyperglycemia is unknown but was estimated to be from 4 to 14% per year. We assumed a 10% annual rate of reaching the primary end point in the placebo arm. A sample size of 100 per group would provide 80% power to detect a decrease from 34% at 4 years to 18% and a difference of 7 mg/dl in FPG. With allowance for a 10% drop-out rate, the target sample size was 220 subjects.

Analyses

The primary outcome, time to development of frank fasting hyperglycemia, was assessed using Kaplan-Meier product-limit estimation. Cumulative probability curves were compared using the log-rank test. Repeated-measures ANOVA and random-effects models were used to analyze other longitudinal outcomes, with assumptions of normally distributed errors and subject-specific random effects. Tukey's correction was used to adjust significance levels of multiple tests. Results are presented as means ± SD.

RESULTS — To screen for the study, 454 subjects underwent OGTT testing. Of these, 246 had early diabetes by OGTT criteria, met entry criteria, and provided informed consent. Twenty-seven subjects subsequently did not complete the baseline testing, which took place during an initiation admission up to 6 weeks after the OGTT. In total, 219 subjects (160 at Indiana University and 59 at Washington University) completed the initiation visit, received the study drug, returned for at least one follow-up visit, and are included in the intention-to-treat analysis. (More details on subject flow are available in an online appendix at http://care.diabetesjournals.org.) After study drug titration, 91% of subjects receiving acarbose had achieved the full dose (97% of placebo subjects). Compliance was assessed by pill counts; mean pill consumption was 79.5% of prescribed dose in the acarbose group at year 1 and 84.6% in the placebo group, with little change in compliance over time (year 5 means 79.0 and 83.8%, respectively).

Table 1 shows demographic and clinical characteristics of the study population. On average, subjects were obese with a high prevalence of hypertension and diabetic dyslipidemia. Race and ethnicity reflected the populations of Indianapolis and St. Louis in the late 1990s. Retinopathy (Early Treatment of Diabetic Retinopathy Study [ETDRS] score ≥20 on fundus photographs) was present in 12% of subjects, whereas 14% had evidence of peripheral neuropathy (inability to sense a 10-g monofilament on two or more sites on the foot). There were no significant differences in any baseline variable between subjects randomly assigned to acarbose and those randomly assigned to placebo.

Over the course of the 5-year trial, a total of 95 subjects terminated follow-up prematurely. In the acarbose group (53 subjects), reasons for early termination included drug side effects (13), loss to follow-up (14), withdrawal of consent (11), prescription of other diabetes medications by outside physicians (5), and other (10). In the placebo group (42 subjects), reasons included drug side effects (5), loss to follow-up (10), withdrawal of consent (12), prescription of other diabetes medications (9), and other (6).

As shown in Table 2, acarbose significantly reduced peak postprandial glucose after both meals at year 1 and at year 2 compared with baseline, whereas there was no significant reduction with placebo; the difference between groups was highly significant at both time points. In addition, compared with placebo, acarbose significantly reduced the AUC curve for glucose after the second meal at year 1 and year 2 and for the entire 9-h MPS at year 2. Acarbose lowered AIC slightly at year 1 and significantly at year 2, whereas there was no significant improvement with placebo. For the OGTT, there was improvement in both fasting and 2-h glucose over the first 2–3 years in both groups, with a subsequent increase in both variables back to baseline. The difference from baseline was significant for FPG at year 1 and at year 2 for acarbose, whereas the 2-h values were significantly reduced from baseline in both groups at

Table 2—*Postprandial glucose, glucose tolerance, measures of insulin resistance, and β-cell function by treatment group and visit*

	Acarbose		Placebo	
Visit	*n*	Mean ± SD	*n*	Mean ± SD
Peak postprandial glucose, first meal (mg/dl)				
Baseline	108	189.8 ± 33.4	110	189.5 ± 30.5
Year 1	81	164.6 ± 28.6*	82	183.5 ± 29.7
Year 2	63	164.7 ± 25.1*	62	184.2 ± 29.7
Peak postprandial glucose, second meal (mg/dl)				
Baseline	108	141.6 ± 27.5	110	140.9 ± 25.5
Year 1	81	122.3 ± 16.9*	82	136.5 ± 21.3
Year 2	63	119.6 ± 14.5*	61	133.4 ± 17.8
AUC plasma glucose, first meal ($mg \cdot h^{-1} \cdot dl^{-1}$)				
Baseline	108	148.1 ± 75.5	109	129.8 ± 70.5
Year 1	81	97.4 ± 51.3	82	117.6 ± 62.6
Year 2	62	94.5 ± 51.6	61	124.4 ± 70.1
AUC plasma glucose, second meal ($mg \cdot h^{-1} \cdot dl^{-1}$)				
Baseline	108	66.1 ± 64.8	109	65.9 ± 69.7
Year 1	81	31.1 ± 52.0*	82	70.0 ± 71.7
Year 2	63	29.2 ± 53.4*	61	76.2 ± 58.4
AUC plasma glucose, both meals ($mg \cdot h^{-1} \cdot dl^{-1}$)				
Baseline	106	206.2 ± 135.4	106	164.5 ± 135.7
Year 1	81	105.0 ± 98.0	82	143.6 ± 109.2
Year 2	62	90.1 ± 100.2†	60	154.7 ± 133.1
A1C (%)				
Baseline	106	6.35 ± 0.64	106	6.32 ± 0.62
Year 1	81	6.16 ± 0.74	76	6.22 ± 0.60
Year 2	63	6.02 ± 0.49‡	63	6.26 ± 0.62
Year 3	45	6.17 ± 0.60	49	6.24 ± 0.56
Year 4	41	6.44 ± 0.72	40	6.40 ± 0.64
Year 5	15	6.03 ± 0.71	16	6.41 ± 0.89
FPG in OGTT (mg/dl)				
Baseline	109	122.1 ± 13.9	110	120.8 ± 13.4
Year 1	74	114.3 ± 16.2§	78	116.2 ± 16.8
Year 2	60	112.7 ± 16.9§	59	116.9 ± 15.7
Year 3	50	115.7 ± 15.0	52	115.4 ± 13.1
Year 4	39	124.4 ± 20.1	45	118.2 ± 18.2
Year 5	20	123.6 ± 19.8	29	124.1 ± 22.8
2-h PG in OGTT (mg/dl)				
Baseline	109	236.5 ± 31.8	110	235.8 ± 30.4
Year 1	74	202.9 ± 45.5§	78	211.9 ± 50.4§
Year 2	60	201.1 ± 47.2§	59	204.3 ± 45.2§
Year 3	50	202.3 ± 50.1§	52	206.0 ± 51.7§
Year 4	39	224.6 ± 61.4	45	223.1 ± 52.4
Year 5	20	222.2 ± 35.7	29	237.0 ± 55.4
HOMA-IR				
Baseline	104	5.4 ± 3.6	103	5.9 ± 4.1
Year 1	63	5.5 ± 5.5	72	5.4 ± 4.3
Year 2	52	5.4 ± 3.7	50	5.4 ± 3.0
Year 3	44	5.2 ± 3.0	46	5.7 ± 5.1
Year 4	42	5.5 ± 3.0	46	4.4 ± 2.6
Year 5	32	6.6 ± 5.0	36	5.8 ± 3.4
HOMA-β				
Baseline	104	114 ± 76	103	124 ± 85
Year 1	63	143 ± 129	72	127 ± 91
Year 2	52	153 ± 135	50	142 ± 115
Year 3	44	133 ± 112	46	159 ± 179
Year 4	42	112 ± 70	46	104 ± 55
Year 5	32	122 ± 77	36	133 ± 125

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Table 2—*Continued*

Visit	Acarbose		Placebo	
	n	Mean ± SD	*n*	Mean ± SD
Insulin sensitivity index				
Baseline	47	0.076 ± 0.047	49	0.091 ± 0.101
Year 1	30	0.102 ± 0.085	29	0.094 ± 0.063
Year 2	24	0.089 ± 0.047	24	0.094 ± 0.058
Insulin AUC early phase ($\mu U \cdot min^{-1} \cdot ml^{-1}$)				
Baseline	41	44.2 ± 73.6	46	72.1 ± 150.0
Year 1	28	100.2 ± 155.6	28	104.6 ± 130.8
Year 2	25	91.3 ± 139.3	21	73.0 ± 118.8
Insulin AUC late phase ($\mu U \cdot min^{-1} \cdot ml^{-1}$)				
Baseline	43	7,264 ± 4,510	42	10,722 ± 15,547
Year 1	27	7,031 ± 5,950	26	6,383 ± 4,248
Year 2	22	7,696 ± 6,912	21	8,622 ± 10,341
Insulin AUC during MPS ($\mu U \cdot h^{-1} \cdot ml^{-1}$)				
Baseline	99	377.2 ± 281.3	100	435.1 ± 369.0
Year 1	72	268.3 ± 223.7	72	300.2 ± 241.2
Year 2	62	235.1 ± 207.3	52	309.0 ± 227.0
Proinsulin-to-insulin ratio				
Baseline	68	1.8 ± 1.5	70	1.5 ± 1.0
Year 1	41	1.7 ± 1.3	38	1.7 ± 1.1
Year 2	48	1.5 ± 0.9	44	1.6 ± 0.7

*$P < 0.01$, †$P < 0.05$ for difference from placebo at time point. ‡$P < 0.05$, §$P < 0.01$ for difference from baseline.

years 1–3. However, there were no differences between acarbose and placebo for either variable at any time point.

Figure 1 shows the cumulative probability curves for the primary outcome, progression to frank fasting hyperglycemia (two consecutive quarterly FPG measures of at least 140 mg/dl). Subjects with at least two consecutive quarterly visits after the baseline visit ($n = 196$) were included in the analysis. The outcome was reached by 28 of 96 acarbose subjects (29%) and by 34 of 100 placebo subjects (34%), with no difference between groups in the survival analysis ($P = 0.65$). The results were no different when adjusted for body weight; there were no significant changes in mean weight in either

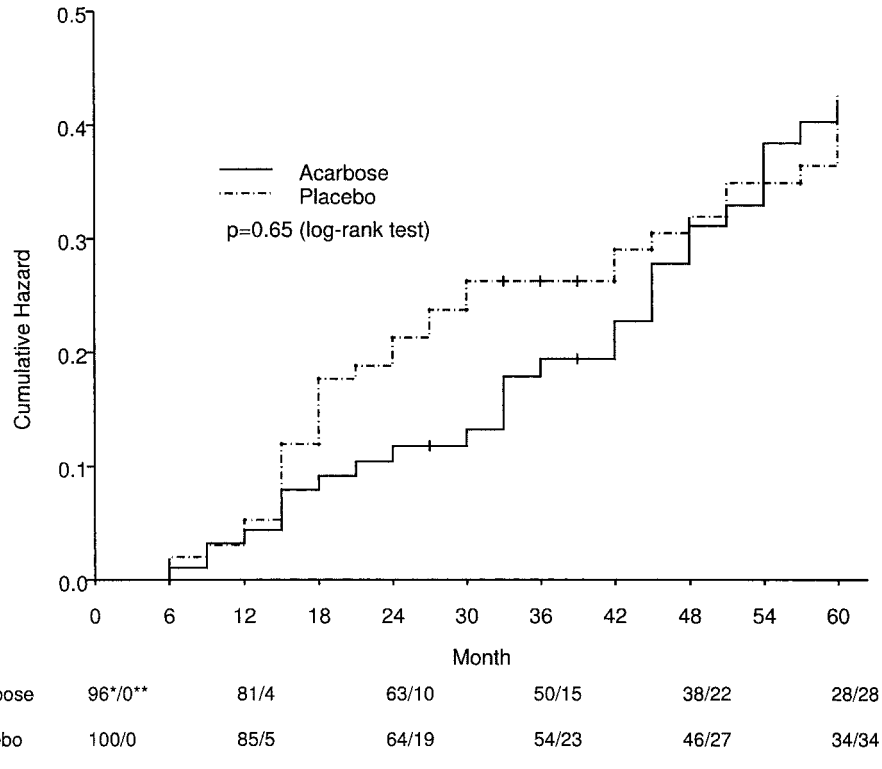

Figure 1—*Cumulative probability of reaching the end point of frank fasting hyperglycemia (two consecutive quarterly FPG measurements ≥140 mg/dl or 7.8 mmol/l). For each group, the first number (*) represents the number of subjects not at the end point at that time period, and the second number (**) represents the number of subjects at the end point at that time period.*

group. During the study, some subjects were treated for diabetes with other medications by outside physicians and therefore withdrawn from the study. Assuming that these subjects had more significant hyperglycemia, we did an analysis defining progression to frank fasting hyperglycemia as either reaching the primary end point or starting diabetes medication by another physician. There was no difference between groups in this analysis (33 of 96 acarbose subjects and 43 of 100 placebo subjects; $P = 0.41$ for the difference in survival curves). Although the survival curves appear to diverge until month 42, there was no statistical difference between groups at any time point, whether frank fasting hyperglycemia was defined as initially planned or whether we included the subjects treated by their primary care physicians. In a post hoc analysis of subjects with FPG measurements <7.0 mmol/l (126 mg/dl) at randomization, significantly fewer acarbose subjects (13 of 48) than placebo subjects (31 of 62) reached a FPG of ≥126 mg/dl ($P = 0.04$ for survival analysis).

As shown in Table 2, there were no significant differences in measures of insulin resistance (HOMA-IR or insulin sensitivity index) over time or between groups. Despite the differences in postprandial hyperglycemia between treatment groups, at least over the first 2 years, there were no significant differences over time or between groups for other measures of β-cell function: HOMA-β, early- or late-phase insulin secretion during hyperglycemic clamps, proinsulin-to-insulin ratio, or AUC for insulin during the MPS.

CONCLUSIONS — We assessed whether ameliorating postprandial hyperglycemia in subjects with early diabetes might delay or prevent β-cell failure, defined as progression to frank fasting hyperglycemia. We used acarbose, a drug known to directly reduce postprandial glucose without direct effects on β-cell function, insulin resistance, or fasting glucose. During the course of our study, the Study to Prevent NIDDM (STOP-NIDDM) trial showed that acarbose delayed the progression of IGT to diabetes (20). Because IGT is characterized primarily by mild postchallenge hyperglycemia, these findings seemed to strengthen our hypothesis.

As expected, acarbose significantly reduced postprandial hyperglycemia when compared with placebo, at least over the first 2 years of therapy. Despite this amelioration of postprandial hyperglycemia, we found no difference in the rate of progression to frank fasting hyperglycemia in acarbose-treated subjects compared with those treated with placebo. We also found no differences between treatment groups in other measures of β-cell function, including HOMA-β, early and late insulin secretion, proinsulin-to-insulin ratio, or AUC for insulin during the MPS.

There are several possible explanations for our results and for the discrepancy between our results in early diabetes and those of STOP-NIDDM for IGT. One must always consider whether a negative study was underpowered. In fact, the rate of reaching the primary outcome in the placebo arm was lower than predicted (34% over 5 years instead of 41%), and the drop-out rate was higher than expected. The latter was probably due to the length and complexity of our trial; additionally, the changing definition of fasting hyperglycemia and treatment standards since 1997 led to more aggressive treatment of diabetes by some subjects' primary care physicians. However, the 34% cumulative incidence rate observed in the placebo arm is a conservative estimate, because it assumes that no subject who terminated early would have reached the end point. In addition, the results are no different if we include subjects who began diabetes therapy outside of the protocol in the primary end point, and results of all secondary outcomes related to β-cell function were similarly negative.

It is possible that the dietary suggestions provided to both groups were potent and overwhelmed any effects of acarbose on β-cell function. However, postprandial glucose was significantly lower in the acarbose group, and acarbose lowered A1C slightly but significantly over the first several years, suggesting that the drug itself had a superior effect on glycemia. In addition, the dietary intervention was no more potent than that provided to the placebo arms in studies such as the DPP and STOP-NIDDM.

Another possible explanation is that our subjects, like those in the UKPDS and in clinical practice, were "too far gone" along the path of β-cell failure for the intervention to affect progression. This would require us to believe that early diabetes is quite different from IGT, a condition in which controlling postprandial hyperglycemia seems to preserve β-cell function or at least delay onset of diabetes (20). Our post hoc analysis of subjects who entered with FPG <126 mg/dl (presumably with even earlier diabetes) suggested that the rate of progression to FPG ≥126 mg/dl may have been reduced by acarbose. This would support the argument that once FPG exceeds 126 mg/dl, it may be too late to significantly affect β-cell function.

It is also possible that EDIP truly disproved our hypothesis and that postprandial hyperglycemia is not the primary driver of β-cell failure. Other factors such as genetics, lifestyle factors, or postprandial free fatty acids (lipotoxicity) may be more important. Examining the determinants of progression to frank fasting hyperglycemia in our population may help answer these questions. The results of our study would seem to support those of a smaller trial in which acarbose or placebo was given for 6 weeks to subjects with IGT. Despite significant reductions in postprandial hyperglycemia with acarbose in that trial, there were no differences in insulin secretion rates by glucose ramp clamp nor in the acute insulin response to intravenous glucose by frequently sampled intravenous glucose tolerance tests (21).

Our results lend further support to efforts to prevent diabetes. It is unlikely that diabetes could be easily diagnosed in stages earlier than that of our subjects, a group in whom treating postprandial hyperglycemia did not seem to delay β-cell failure. Subjects at high risk for diabetes should be offered interventions known to delay the onset of early diabetes, such as acarbose (20), metformin (15), or intensive lifestyle interventions (15,22).

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References

1. UK Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
2. Polonsky KS, Sturis J, Bell G: Non-insulin-dependent diabetes mellitus: a genetically programmed failure of the β cell to compensate for insulin resistance. *N Engl J Med* 334:777–783, 1996
3. Kahn SE: The importance of β-cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 86:4047–4058, 2001
4. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
5. Porte DL, Kahn SE: β-Cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 50:S160–S163, 2001
6. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 years before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
7. Kanauchi M, Nakajima M, Saito Y, Kanauchi K: Pancreatic β-cell function and insulin sensitivity in Japanese subjects with impaired glucose tolerance and newly diagnosed type 2 diabetes mellitus. *Metabolism* 52:476–481, 2003
8. Harris M, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 20:1859–1862, 1997
9. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
10. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A: β-Cell adaptation and decompensation during progression of diabetes. *Diabetes* 50:S154–S159, 2001
11. Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H: Glucose toxicity in β-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes* 52:581–587, 2003
12. Ryan EA, Imes S, Wallace C: Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 27:1028–1032, 2004
13. Park S, Choi SB: Induction of long-term normoglycemia without medication in Korean type 2 patients after continuous subcutaneous insulin infusion therapy. *Diabetes Metab Res Rev* 19:124–130, 2003
14. Precose package insert. West Haven, CT, Bayer, 2004
15. The Diabetes Prevention Program Research Group: The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 22:623–634, 1999
16. Perry RC, Shankar RR, Fineberg N, McGill J, Baron AD: HbA_{1c} measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). *Diabetes Care* 24:465–471, 2001
17. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 273:E214–E223, 1979
18. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
20. Chaisson J-L, Josse RG, Gomis R, Hanefield M, Karasik A, Laakso M, the STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM trial. *Lancet* 359–2072-2077, 2002
21. Chang AM, Smith MJ, Bloem CJ, Galecki AT, Halter JB: Effect of lowering postprandial hyperglycemia on older people with impaired glucose tolerance. *Am J Physiol* 287:E906–E911, 2004
22. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, the Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001