Regression of Carotid Atherosclerosis by Control of Postprandial Hyperglycemia in Type 2 Diabetes Mellitus

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Background—Postprandial hyperglycemia may be a risk factor for cardiovascular disease. We compared the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in type 2 diabetic patients.

Methods and Results—We performed a randomized, single-blind trial on 175 drug-naive patients with type 2 diabetes mellitus (93 men and 82 women), 35 to 70 years of age, selected from a population of 401 patients who participated in an epidemiological analysis assessing the relation of postprandial hyperglycemia to surrogate measures of atherosclerosis. Eighty-eight patients were randomly assigned to receive repaglinide and 87 patients to glyburide, with a titration period of 6 to 8 weeks for optimization of drug dosage and a subsequent 12-month treatment period. The effects of repaglinide (1.5 to 12 mg/d) and glyburide (5 to 20 mg/d) on CIMT were compared by using blinded, serial assessments of the far wall. After 12 months, postprandial glucose peak was 148 ± 28 mg/dL in the repaglinide group and 180 ± 32 mg/dL in the glyburide group ($P<0.01$). HbA_{1c} showed a similar decrease in both groups (-0.9%). CIMT regression, defined as a decrease of >0.020 mm, was observed in 52% of diabetics receiving repaglinide and in 18% of those receiving glyburide ($P<0.01$). Interleukin-6 ($P=0.04$) and C-reactive protein ($P=0.02$) decreased more in the repaglinide group than in the glyburide group. The reduction in CIMT was associated with changes in postprandial but not fasting hyperglycemia.

Conclusions—Reduction of postprandial hyperglycemia in type 2 diabetic patients is associated with CIMT regression. (***Circulation.*** 2004;110:214-219.)

Key Words: diabetes mellitus ■ atherosclerosis ■ interleukins ■ carotid arteries

Cardiovascular disease is the leading cause of death among type 2 diabetic subjects.[1] Recent epidemiological studies suggest that postprandial hyperglycemia might be an independent risk factor of cardiovascular disease beyond and more powerful than fasting hyperglycemia.[2] However, it is not clear whether pharmacological interventions that target postprandial hyperglycemia provide unique benefits relative to other pharmacological therapies that lower HbA_{1c} comparably.[3]

The Campanian Postprandial Hyperglycemia Study was conducted to assess the relation of postprandial hyperglycemia to carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point,[4–6] and circulating inflammatory markers (interleukin [IL]-6, IL-18, IL-10, and C-reactive protein [CRP]) in a population of patients with type 2 diabetes mellitus. Moreover, we compared the effects of two insulin secretagogues, repaglinide and glyburide, on CIMT and circulating markers of vascular inflammation. Repaglinide, a carbamoylmethyl benzoic acid derivative, is a rapid-onset/short-duration insulinotropic agent, whereas gly-

buride is a long-acting sulfonylurea. Repaglinide selectively increases meal-related early insulin secretion and may result in better control of postprandial hyperglycemia than glyburide.[7–9]

Methods

Epidemiological Study
We screened type 2 diabetic patients regularly attending 14 diabetes clinics located in the area of Naples and Caserta, two towns of the Campania county, South Italy. Among them, we selected those with a diagnosis of type 2 diabetes for ≥6 months but <10 years, 35 to 70 years of age, a body mass index (BMI) of ≥24, a value of HbA_{1c} of $\geq6.5\%$, and treated with diet or oral drugs. Criteria for exclusion were need for insulin use, concomitant chronic diseases, including kidney, liver, and cardiovascular diseases, recent acute illness, or change in diet, treatment, or lifestyle within the 3 months before the study. The 401 diabetic patients enrolled in the study were compared with 150 subjects recruited by newspaper advertisements among the population near the clinics. Criteria for inclusion were the absence of diabetes or glucose intolerance (assessed by an oral glucose tolerance test), apparent good health (assessed by absence of self-reported
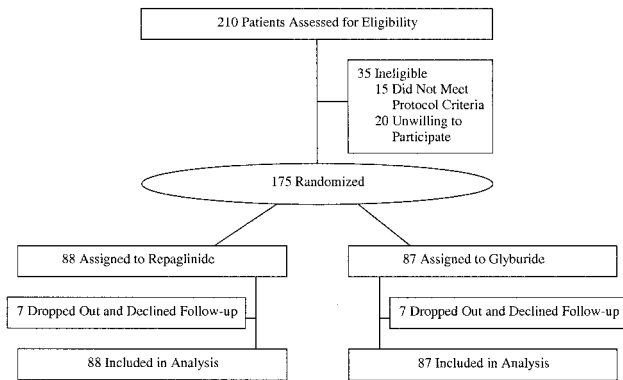
Figure 1. Flow of patients through the trial.

diseases, particularly cardiovascular diseases), similar sex, age, and BMI.

After the initial screening visit, all diabetic patients were requested to monitor home blood glucose on 3 nonconsecutive days during a period of 1 month. In particular, they assessed blood glucose just before and every 30 minutes after the main meal of the day (whether lunch or dinner) for 2 hours. Patients were also asked to follow their usual treatment and eat their usual diet during the month. After that, all patients were invited to the reference center (Department of Geriatrics and Metabolic Diseases at the Second University of Naples) for fasting blood sampling and assessment of CIMT.

Randomized Trial

This study was performed in the reference center only on drug-naive, type 2 diabetic patients with a duration of diabetes <3 years and inclusion criteria as described above, except for duration of diabetes. Exclusion criteria also included severe uncontrolled hypertension (blood pressure >200/100 mm Hg) and women who were pregnant or intended to become pregnant. Both the epidemiological study and the trial were approved by the ethics committee of our institution, and written informed consent was obtained by each patient. The trial was conducted from May 2001 to April 2003.

A total of 175 diabetic patients were randomly assigned to open-label treatment with either repaglinide or glyburide, through the use of a computer-generated random number sequence (Figure 1). Allocation was concealed in sealed study folders that were held in a central, secured location until after informed consent was obtained. The laboratory staff did not know the participants' group assignments. The study protocol comprised a screening visit to assess patient eligibility, a titration period of 6 to 8 weeks for optimization of drug dosage, and a subsequent 12-month treatment period on fixed optimal dosages. There were 4 dosage levels each for repaglinide and glyburide. In the repaglinide group, the daily dosages were 1.5, 3.0, 6.0, and 12 mg all in 3 identical dosages (0.5 to 4.0 mg) taken just before meals. In the glyburide group, daily dosages were 5.0, 10, 15, and 20 mg, equally divided before breakfast and dinner. The goals of the intervention were fasting blood glucose <110 mg/dL, postprandial glucose <140 mg/dL, and HbA$_{1c}$ <6.5%. All patients received standard dietary counseling by a study investigator in accord with the dietary recommendations of the American Diabetes Association.[10]

The 161 patients who completed the 12-month study demonstrated compliance with the treatment program through monthly return visit for prescription refills and clinic visits. Home blood glucose monitoring after the main meal of the day was repeated 3 times in a month, at 6 and 12 months of the study, and the results were averaged. Patients were asked to record all hypoglycemic symptoms in their diaries and if possible to measure their blood glucose at the time of symptoms.

Carotid B-Mode Ultrasound

Carotid sonography was performed on a single ultrasound machine (Aloka 5500) with a 7.5-MHz sector scanner probe. Baseline and

follow-up studies were performed in a standard fashion by a single specialist physician who was specifically trained to perform the prescribed study examination and blinded to treatment group. All images were electronically stored. The measurement was made in the 1-cm segment proximal to the dilation of the carotid bulb and always in plaque-free segments. For each patient, 3 measurements on both sides were performed on the anterior, lateral, and posterior projections of the far wall; the readings were then averaged. An independent observer who was blinded to treatment group and trained in the interpretation of CIMT images performed off-line analysis of B-mode ultrasound images. Both patients and providers were blinded to the CIMT results until 1-year follow-up examination was completed. Paired CIMT measurements in the same arteries showed a high degree of reproducibility, with a mean difference in CIMT of 0.020 mm, and an intraclass correlation coefficient of 0.97 ($P<0.001$). CIMT regression was defined as a decrease of >0.020 mm in mean CIMT at 12 months.

Laboratory Analysis

All analyses were performed in the reference center, except for postmeal blood glucose monitoring, which was performed at home with the same devices through the study (One Touch, Lifescan). Plasma glucose and serum lipids were measured by enzymatic assays in the hospital's chemistry laboratory, HbA$_{1c}$ by nephelometry, and serum insulin by radioimmunoassay (Pharmacia). Serum samples for inflammatory markers were stored at −80°C until assay. Serum concentrations of IL-6, IL-10, and IL-18 were determined in duplicate with commercially available kits (Quantikine HS, R&D Systems). All samples for the same patient were measured in the same assay. The interassay coefficient of variation was <6% for all kits. High-sensitivity CRP was assayed in duplicate by immunonephelometry on a Behring Nephelometer 2 (Dade Behring).

Statistical Analysis

Data are presented as mean±SD unless stated otherwise. Baseline comparison was made by means of a *t* test and Wilcoxon test as appropriate. Glucose peak was defined as the maximal increase in blood glucose obtained at any point after the meal. The incremental area under the curve (AUC) for glucose was calculated by the trapezoidal method. The correlation of selected variables to CIMT was assessed by using Pearson or Spearman correlation coefficients, as appropriate, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with CIMT. In the randomized trial, data were analyzed by intention-to-treat on all randomly assigned subjects, by imputing no change in CIMT or any other variable to the dropouts. Changes in glucose, HbA$_{1c}$, lipids, IL-6, IL-18, IL-10, and CRP over time were evaluated by using either a paired *t* test or Wilcoxon signed-rank test, as appropriate. Comparison of the treatment effect between experimental groups for the changes in the primary outcome at 12 months was performed with a *t* test for independent groups. The χ^2 test was used for comparing proportions of patients in the two groups that demonstrated regression of mean CIMT. A value of $P<0.05$ was considered significant. All statistical analyses were performed with the use of SPSS software (version 10.05, SPSS Inc).

Results

The baseline characteristics of type 2 diabetic patients and control subjects are given in Table 1. Forty-eight percent of diabetic patients were treated with oral drugs, including a sulfonylurea (16%), metformin (10%), or combined therapy (22%). Moreover, statins, ACE inhibitors, and aspirin were used in 8%, 18%, and 15% of patients, respectively.

The mean value of postmeal incremental glucose peak was 70±42 mg/dL, with a wide range (0 to 213 mg/dL). The interclass correlation coefficient between the 3 postmeal glucose curves obtained in the same patient was 0.85 ($P<0.001$). In univariate analysis adjusted for sex and age,

TABLE 1. Clinical Characteristics of Study Participants

Variable	Diabetic Patients (n=401)	Control Subjects (n=150)	P
Sex, M/F, n	240/161	90/60	0.70
Age, y	56±8.9	55±7.6	0.65
BMI, kg/m^2	29.3±5.2	28.7±4.8	0.75
Plasma glucose, mg/dL	154±41	98±12	<0.001
HbA$_{1c}$, %	7.7±1.3	4.9±0.6	<0.001
Plasma insulin, μU/mL	14±7	12±6	0.10
Serum lipids, mg/dL			
Total cholesterol	201±30	195±35	0.52
HDL cholesterol	42±11	46±12	0.03
Triglycerides	149±80	132±65	0.25
Systolic blood pressure, mm Hg	143±16	139±17	0.03
Diastolic blood pressure, mm Hg	88±9	85±8	0.02
IL-6, pg/mL*	2.4 (0.5/3.8)	2.0 (0.4/3.6)	0.02
IL-18, pg/mL*	216 (172/268)	141 (107/184)	0.015
IL-10, pg/mL*†	1.8 (0.6/4.0)	2.5 (0.8/4.9)	0.035
CRP, mg/L*	3.5 (0.5/6.1)	1.4 (0.4/2.7)	0.02
CIMT, mm	0.867±0.231	0.741±0.192	0.01

Data are presented as mean±SD except where otherwise indicated.

*Data are presented as median (interquartile range).

†Serum concentrations of IL-10 were detectable in 196 diabetic patients and 108 control subjects.

TABLE 2. Baseline Characteristics of Diabetic Subjects Assigned to Either Repaglinide or Glyburide

Variable	Repaglinide (n=88)	Glyburide (n=87)	P
Sex, M/F, n	47/41	46/41	0.80
Age, y	52±6.4	51.3±5.9	0.67
BMI, kg/m^2	28.5±4.3	28.3±4.1	0.75
Current smoker (No.)	10	11	0.57
Glucose, mg/dL			
Fasting	159±32	163±30	0.68
Peak	224±47	231±45	0.51
AUC, mg/dL · 2 h	6375±1053	6165±995	0.47
HbA$_{1c}$, %	7.5±1.1	7.4±1.1	0.73
Serum insulin, μU/mL	13±6	14±7	0.45
Serum lipids, mg/dL*			
Total cholesterol	197±34	201±36	0.38
HDL cholesterol	44±12	43±11	0.65
Triglycerides	156±71	160±73	0.19
Systolic blood pressure, mm Hg†	142±17	143±16	0.59
Diastolic blood pressure, mm Hg	87±9	86±9	0.61
IL-6, pg/mL	2.3 (0.5/3.8)	2.4 (0.5/4.2)	0.24
IL-18, pg/mL	216 (172/268)	224 (164/270)	0.35
IL-10 pg/mL‡	1.8 (0.5/4.0)	1.8 (0.5/3.8)	0.74
CRP, mg/L	3.3 (0.5/6.1)	3.2 (0.5/5.9)	0.45
CIMT, mm	0.849±0.208	0.850±0.210	0.39

Data are presented as mean±SD except where otherwise indicated.

*Cholesterol-lowering drugs were being taken by 7% of patients in the repaglinide group and 6% of patients in the glyburide group.

†Antihypertensive drugs were being taken by 30% of patients in the repaglinide group and 31% of patients in the glyburide group (ACE inhibitors or angiotensin receptor blockers by 22% and 21%, respectively).

‡Serum concentrations of IL-10 were detectable in 50 patients of the repaglinide group and 48 patients of the glyburide group.

glucose parameters were significantly correlated to CIMT: HbA$_{1c}$, $r=0.19$, $P=0.02$; glucose peak, $r=0.21$, $P=0.01$; and fasting glucose, $r=0.12$, $P=0.04$. There was a significant correlation between CMIT and IL-6 ($r=0.31$, $P=0.002$), CRP ($r=0.24$, $P=0.01$), and IL-18 ($r=0.16$, $P=0.04$). In a multivariate analysis including CIMT as a dependent variable and candidate risk factors (age, sex, BMI, smoking, blood pressure, lipid and glucose parameters, IL-6, IL-18, and CRP) as independent variables, we found that glucose peak, IL-6, and CRP were significant independent determinants of CIMT and explained 49% of the variability (20%, 12%, and 17%, respectively, $P<0.05$).

Intervention Study

The two experimental groups (repaglinide and glyburide) had similar baseline characteristics (Table 2). At the end of the trial, 19% of patients were at dose level 1, 12% were at dose level 2, 10% were at dose level 3, and 59% were at dose level 4; this distribution was not significantly different between the two treatments. There was a similar course in HbA$_{1c}$ concentration during the study in both treatment groups; the fasting glucose concentration decreased significantly more among patients in the glyburide group, whereas the glucose peak and AUC decreased significantly more among the patients in the repaglinide group (Table 3 and Figure 2). AUC for glucose at the end of the study was 2370±565 mg/dL · 2 h in the repaglinide group and 4020±790 mg/dL · 2 h in the glyburide group ($P=0.01$). Twenty-four percent of patients in the repaglinide group and 48% of patients in the glyburide group achieved a fasting glucose level <110 mg/dL ($P=0.01$); by contrast, 43% of patients in the repaglinide group and 21% of

patients in the glyburide group achieved a glucose peak <140 mg/dL ($P=0.01$).

Compared with glyburide, repaglinide resulted in significantly greater reductions in IL-6 and CRP concentrations (Table 3). Changes in IL-6 and CRP concentrations after treatment were related to reductions in postprandial glucose peaks ($r=0.35$, $P<0.001$, $r=0.26$, $P=0.01$, respectively) in both groups but not to changes in fasting glucose or HbA$_{1c}$. Repaglinide induced progressive mean CIMT regression over 12 months, whereas mean CIMT was stable in the glyburide group (Table 3 and Figure 3). CIMT regression was observed in 52% of diabetic patients receiving repaglinide and in 18% of diabetic patients receiving glyburide ($P=0.01$). There was no difference observed between treatment groups in any of the 6-month CIMT measurements. No significant changes from baseline in lipid and blood pressure parameters occurred in either group (Table 3).

For evaluating the independent association of changes in CIMT with changes in glucose parameters and inflammatory markers, a multivariate analysis was performed in which CIMT was the dependent variable and fasting glucose, glucose peak, HbA$_{1c}$, IL-6, IL-18, and CRP were the inde-

TABLE 3.   Changes in Selected Variables and Carotid Intima-Media Thickness From Baseline in Repaglinide and Glyburide Groups

Variable	Repaglinide (n=88)		Glyburide (n=87)		
	Mean±SD	95% CI	Mean±SD	95% CI	P
BMI, kg/m²	0.3±0.4	−0.2 to 0.7	0.4±0.4	−0.1 to 0.6	0.22
Glucose, mg/dL					
Fasting	−24±18	−38 to −10	−32±25	−42 to −22	<0.001
Peak	−70±58	−98 to −42	−51±43	−75 to −27	<0.001
AUC, mg/dL · 2 h	−3998±1035	−5340 to −2450	−2090±670	−3100 to 980	0.01
HbA$_{1c}$, %	−0.9±0.5	−1.1 to −0.7	−0.8±0.5	−1.1 to −0.5	0.13
Serum lipids, mg/dL					
Total cholesterol	−5±10	−12 to 3	−1±2	−4 to 3	0.18
HDL cholesterol	3±4	−2 to 8	1±2	−1 to 3	0.28
Triglycerides	−15±19	−39 to 10	−10±20	−26 to 7	0.34
Blood pressure, mm Hg					
Systolic	−2±2	−5 to 3	−1±2	−2 to 1	0.17
Diastolic	−1±2	−3 to 2	0.5±2	−2 to 2	0.20
Serum cytokines, pg/mL					
IL-6	−0.5±0.8	−0.9 to −0.1	−0.2±0.3	−0.3 to −0.1	0.04
IL-18	−17±27	−35 to 1	−14±25	−30 to 2	0.09
IL-10	0.4±0.5	−0.1 to 0.9	0.5±0.6	−0.2 to 1.2	0.15
CRP, mg/L	−0.7±0.7	−1.2 to −0.2	−0.2±0.3	−0.4 to 0	0.02
CIMT, mm	−0.029±0.021	−0.041 to −0.017	−0.005±0.01	−0.010 to 0.005	0.02

A total of 14 patients withdrew from the study, 7 in each group.
Probability values were determined by 2-tailed *t* test for difference between groups.

pendent variables. The model explained 60% of variability in the change of CIMT with changes of glucose peak (28%, $P=0.002$), HbA$_{1c}$ (15%, $P=0.03$), and CRP (17%, $P=0.01$) concentrations.

The number of patients who had hypoglycemic events was similar in the repaglinide and glyburide groups (9% and 13% of patients, respectively). During the study, 14 patients (8%) withdrew (7 patients in each group). Of these patients, 10 withdrew for personal reasons, 2 withdrew because of severe illness, and 2 could not be contacted.

Discussion

This study provides evidence that progression of carotid atherosclerosis can be prevented by the control of postprandial hyperglycemia in type 2 diabetic patients. In particular, at the same level of HbA$_{1c}$, amelioration of postprandial glucose peaks was more effective in reducing CIMT than amelioration of fasting hyperglycemia. Although a nonglycemic effect (yet unknown) of repaglinide on CIMT regression cannot be
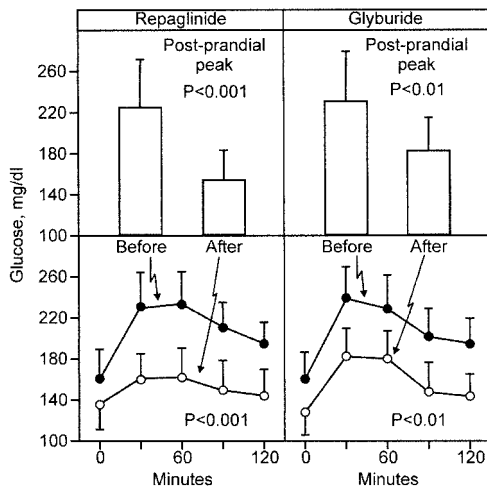

Figure 2. Glucose peaks (top) and glucose curves (bottom) after main meal of the day according to assigned treatment (repaglinide or glyburide) in diabetic patients of the intervention study.
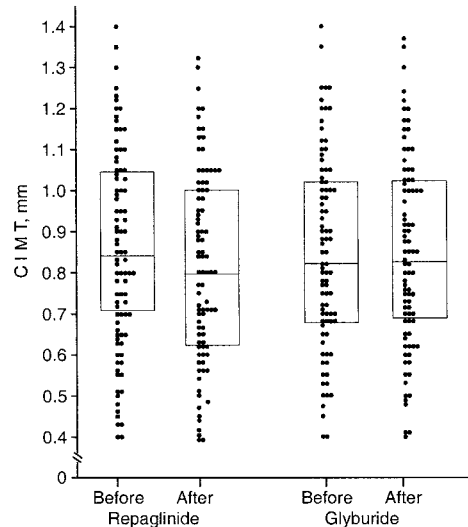

Figure 3. Individual CIMT measurements in diabetic patients assigned to repaglinide or glyburide treatment. Box plots indicate median and interquartile range.

ruled out, these results suggest that excessive excursions of plasma glucose in the postprandial state are harmful for the vascular tree and that postprandial hyperglycemia should be considered a treatment target of therapy.

We found that postprandial hyperglycemia assessed at home in a free-living condition was more strongly associated with CIMT than fasting glucose and HbA$_{1c}$. A similar association was reported with the plasma glucose peak after an oral glucose tolerance test.[11] Several experimental studies provide a plausible pathophysiological explanation for this association. In diabetic patients, hyperglycemia after meals causes an overproduction of free radicals and thrombin proportional to blood glucose levels.[12] Moreover, acute elevations of glucose levels in both normal subjects and type 2 diabetic patients induce vasoconstriction[13] and increase the circulating levels of some cellular adhesion molecules[14] and proinflammatory cytokines.[15] Baseline concentrations of the proinflammatory cytokines IL-6 and IL-18 were higher, whereas those of the antiinflammatory cytokine IL-10 were lower in diabetic patients as compared with control subjects. Such a profile of circulating cytokine concentration may be dangerous for cardiovascular health because elevated circulating concentrations of IL-6 predict future myocardial infarction among apparently healthy men[16] and elevated IL-18 concentrations predict future cardiovascular events and death in patients with documented coronary artery disease,[17] whereas lower serum IL-10 concentrations have been found in patients with unstable angina compared with those who had chronic stable angina.[18]

Although several epidemiological studies have found associations of cardiovascular disease with glycemia over a broad range of glucose tolerance, from normal to diabetic,[19] interventional studies have not demonstrated a convincing beneficial effect of glucose lowering on cardiovascular outcomes.[20] In those studies, however, no attention was paid to control of postprandial hyperglycemia, which also contributes to HbA$_{1c}$. Moreover, the majority of patients with diabetes fail to achieve their glycemic goals.[3] In our study, most of the drug-naive, diabetic patients assigned to treatment obtained HbA$_{1c}$ values below the recommended value of 7%. Moreover, patients who had the greatest reduction of postprandial hyperglycemia had the largest regression of CIMT.

In our study, diabetic patients had higher values of CIMT than did nondiabetic subjects; this was associated with higher serum concentrations of proinflammatory cytokines and CRP. CRP has been directly related to the rate of progression of carotid atherosclerosis.[21] Emerging data suggest that besides being a marker of cardiovascular risk, CRP may be a mediator of atherogenesis by quenching nitric oxide.[22] Interestingly enough, acute hyperglycemia also reduces nitric oxide bioavailability,[13] pointing to the intriguing possibility that the combined effect of raised CRP concentrations and increased postprandial glucose levels in diabetic patients may act synergistically to diminish nitric oxide bioactivity. A positive association between dietary glycemic load and circulating CRP levels has been reported,[23] suggesting that a high intake of rapidly digested and adsorbed carbohydrates, which leads to larger postprandial glycemic excursions, may exacerbate the inflammatory process.[24]

This study does have limitations. First, because the epidemiological study is cross-sectional, the directionality of associations cannot be conclusively explained. However, the results of the intervention study shows that near-normalization of glucose control with optimal sulfonylurea dosages causes CIMT regression or stabilization. Second, the randomized clinical trial used open-label administration of the study drug; however, the concealment of allocation and the use of an objective, blinded, end point assessment strengthened the significance of results. Finally, because of the limited follow-up, we could not evaluate clinical events. However, decreasing postprandial hyperglycemia with the α-glucosidase inhibitor acarbose, even at a much lower level than that obtained in the present study, is associated with a significant reduction in the incidence of cardiovascular disease and hypertension in patients with impaired glucose tolerance characterized by moderate postprandial hyperglycemia.[25]

In type 2 diabetic patients, amelioration of postprandial hyperglycemia provides superior efficacy for atherosclerosis regression in the distal common carotid artery at 1 year compared with amelioration of fasting hyperglycemia. These results suggest that control of excessive glucose excursions, especially in the postprandial state, may provide clinical benefit in type 2 diabetic patients.

Acknowledgments

Appendix

The Campanian Postprandial Hyperglycemia Study Group

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