Effect of Acarbose on Glycemic Variability in Patients with Poorly Controlled Type 2 Diabetes Mellitus Receiving Stable Background Therapy: A Placebo-Controlled Trial

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STUDY OBJECTIVE To evaluate the effect of acarbose on glycemic control and glycemic variability, using a continuous glucose-monitoring system, in patients with type 2 diabetes mellitus who were not well controlled on metformin and vildagliptin therapy.

DESIGN Multicenter, randomized, double-blind, placebo-controlled study.

SETTING Clinical research units at three hospitals in Italy.

PATIENTS Fifty-three patients with type 2 diabetes who were taking stable dosages of metformin 850 mg 3 times/day and vildagliptin 50 mg twice/day for at least 3 months and who were not adequately controlled with these therapies.

INTERVENTION Patients were randomized to either placebo or acarbose 100 mg 3 times/day to be added to their metformin-vildagliptin regimen.

MEASUREMENTS AND MAIN RESULTS Glycemic excursions were assessed by using a continuous glucose-monitoring system for 1 week. Glycemic control was estimated as the mean blood glucose (MBG) level, the area under the glucose concentration-time curve for a glucose level above 70 mg/dl (AUC above 70) or 180 mg/dl (AUC above 180), and the percentage of time that the glucose level was above 70 mg/dl (T above 70) or 180 mg/dl (T above 180). Intraday glycemic variability was assessed by the standard deviation of the blood glucose level, the mean amplitude of glycemic excursions (MAGE), the M value, and continuous overlapping net glycemic action. Day-to-day glycemic variability was assessed as the mean of daily difference (MODD). The MBG level was ~20 mg/dl lower in the acarbose group than in the placebo group (p<0.05), particularly during the postprandial period. The AUC above 70 did not significantly differ between the two groups, whereas the AUC above 180 was ~40% lower in the acarbose group than in the placebo group during the daytime (p<0.01). The T above 180 was significantly higher in the placebo group than in the acarbose group (31% vs 8%, p<0.01). Moreover, the standard deviation and MAGE values were significantly lower in the acarbose group. The MODD value was not significantly changed in either group, and no significant differences were recorded between groups. All adverse events were mild in both groups, with only a significantly greater frequency of flatulence noted in the acarbose group (5% with acarbose vs 0.5% with placebo, p<0.05).

CONCLUSION The addition of acarbose to metformin and vildagliptin background therapy in patients with inadequately controlled type 2 diabetes decreased intraday glycemic variability, especially post-
prandial variability, but it was not associated with a significant change in interday glycemic variability.

**Key Words** acarbose, continuous glucose-monitoring system, glycemic variability, vildagliptin.


Patients with type 2 diabetes mellitus are characterized by sustained chronic hyperglycemia and increased amplitude of glycemic excursions. Recent studies have identified postprandial glycemic excursions as risk factors for diabetes complications; however, the glycemic disorders in patients with type 2 diabetes are not solely limited to sustained chronic hyperglycemia but can be extended to glycemic variability that includes both upward (postprandial) and downward (interprandial) acute glucose level changes. Oxidative stress may be activated by both upward and downward acute fluctuations of glucose level around a mean value. There has been much debate about the need for treating inadequate glycemic control and increased glycemic variability in patients with type 2 diabetes. Previous reports showed that the relative contribution of postprandial glucose excursions is predominant in fairly controlled patients, closer to normal hemoglobin A1c (A1C), whereas the contribution of fasting hyperglycemia increases gradually as diabetes control worsens. One report demonstrated that postprandial hyperglycemia, specifically the 2-hour postprandial glucose level, is associated with high A1C levels. In addition, accumulating evidence suggests that causal relationships exist between glycemic excursions and excessive oxidative stress, increased carotid intima-media thickness, and endothelial dysfunction, all of which are markers of cardiovascular disease. In previous clinical trials, acarbose proved to reduce postprandial hyperglycemia effectively, but its effect on glycemic variability is not known. Acarbose belongs to the class of α-glucosidase inhibitors, and it inhibits carbohydrate absorption and reduces postprandial hyperglycemia without stimulating insulin secretion.

Thus the purpose of this study was to compare the effect of acarbose on glycemic variability, using a continuous glucose-monitoring system (CGMS), in patients with type 2 diabetes who were not well controlled on metformin and vildagliptin therapy. The primary objective was to compare the change in glycemic control with acarbose or placebo with CGM, using the mean of the continuous 24-hour mean blood glucose (MBG) levels; area under the glucose concentration-time curve (AUC) for a glucose level above 70 and 180 mg/dl; and the percentage of time that the glucose level was above 70 mg/dl (T above 70) or 180 mg/dl (T above 180). The secondary objective was to compare the change in glycemic variability, which was assessed by the standard deviation (SD) of the blood glucose level, mean of daily differences (MODD), continuous overlapping net glycemic action (CONGA), mean amplitude of glycemic excursions (MAGE), and the M value from the baseline to the end point of the study.

**Methods**

**Study Design and Setting**

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia, and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy (coordinating site); the Metabolic Unit, S. Antonio Abate Hospital, Gallarate, Varese, Italy; and at the Ospedale Pesenti Fenaroli, Alzano Lombardo, Bergamo, Italy.

The study protocol was approved by each institutional review board and was conducted in accordance with the Declaration of Helsinki and its amendments. All eligible study candidates had to provide signed informed consent before enrolling in the study.

**Patients**

We enrolled white patients of either sex, older than 18 years, with a diagnosis of type 2 diabetes according to the European Society of Cardiology and European Association for the Study of Diabetes guidelines’ criteria and who were taking a stable dosage of metformin 850 mg...
3 times/day and vildagliptin 50 mg twice/day for at least 3 months. Patients had to be inadequately controlled by their current antidiabetic therapy; inadequate glycemic control was defined as an A1C of 7.5% or higher and 9.0% or lower.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or \( \gamma \)-glutamyltransferase levels higher than 3 times the upper limit of normal [ULN] for age and sex), impaired renal function (defined as a serum creatinine level higher than the ULN for age and sex); or severe anemia (hemoglobin 10.5 g/dl or higher). Patients with serious cardiovascular disease (e.g., New York Heart Association classes I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment also were excluded.

Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded. Suitable subjects, identified from review of case notes and/or computerized clinic registers, were contacted personally or by telephone.

Study Drug Protocol

At the study entry, patients were instructed to follow a controlled-energy diet and were randomized to add placebo or acarbose 50 mg 3 times/day to their metformin-vildagliptin regimen. After 2 weeks, acarbose was up-titrated to 100 mg 3 times/day with forced titration. After 1 month of placebo or acarbose at the stable dosage, CGM was performed. Both acarbose and placebo were supplied as identical opaque white capsules in coded bottles to ensure the blind status of the study. Randomization was performed by using envelopes containing randomization codes prepared by a statistician that were randomly drawn. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Throughout the study, patients were instructed to take their first dose of new medication in the evening. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge. A compliance rate of 80% or higher was required for patients to continue in the study.

Diet and Exercise

At the study entry, patients were instructed to follow a controlled-energy diet (near 600-kcal daily deficit) based on American Heart Association recommendations\(^\text{12}\) that included 50% of calories from carbohydrates, 30% from fat (6% saturated fat), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and fiber content of 35 g/day. Patients were not treated with vitamins or mineral preparations during the study.

Standard diet advice was provided by a dietician and/or specialist doctor. The dietician and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the patient’s food diaries for counseling. Patients were also encouraged to increase their physical activity by walking briskly or by cycling for 20–30 minutes, 3–5 times/week. The recommended changes in physical activity throughout the study were not assessed.

Clinical Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history evaluation, physical examination, vital signs, 12-lead electrocardiogram, body mass index measurement, and A1C. After 1 month of acarbose or placebo at the stable dosage, all patients underwent CGM with the iPro Digital Recorder (Medtronic MiniMed, Northridge, CA) for 1 week. Glycemic control was estimated as the MBG level, AUC above 70 and AUC above 180, and the \( T \) above 70 and \( T \) above 180. Intraday glycemic variability was assessed as the SD, M value, MAGE, and CONGA. Day-to-day glycemic variability was assessed as the MODD. All parameters were evaluated on the third and fourth day of CGM, when the sensor was more stable, to ensure the reliability of data.

Variables of Glycemic Control

MBG level was used as a measure of quality of glycemic control.

Variables of Intraday Glycemic Variability

From a statistical point of view, the SD around a mean glucose value measured over a 24-hour period using the CGMS is probably the most appropriate method for assessing intraday
glycemic variability. Such a method integrates both minor and major fluctuations; however, it does not allow differentiation of the major from the minor ones. For this reason, the MAGE is the most comprehensive index for assessing the intraday glycemic variability. MAGE is obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs provided the differences are greater than one SD of the mean glucose value. The M value is a logarithmic transformation of the deviation of glycemia from an arbitrary assigned “ideal” glucose value. The M value attempts to provide, in a single numerical value, an expression of both the mean glucose value and the effect of glucose swings. Finally, CONGA evaluates intraday glycemic variation. It was calculated after different hourly intervals of observations called n (n=1, 2, 3….). For each observation or glucose value after n hours of observations, the difference between the current observation and the previous observation at n hours was calculated.

Variables of Day-to-Day Glycemic Variability

The MODD currently remains the sole index for estimating day-to-day glycemic variability. This parameter is calculated as the mean of the absolute differences between glucose values at the same time on two consecutive days.

Laboratory Procedures

All blood samples were obtained after a 12-hour overnight fast. Venous blood samples were collected from all patients between 8 and 9 A.M. We used plasma obtained by the addition of ethylenediaminetetraacetic acid disodium salt 1 mg/ml, and it was centrifuged at 3000 g for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C for not more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. A1C was measured by a high-performance liquid chromatography method (Diamat; Bio-Rad, Hercules, CA [normal values 4.2–6.2%]), with intraassay and interassay coefficients of variation less than 2%.

Adverse Events

To evaluate the tolerability assessments, all adverse events were recorded.

Statistical Analysis

The sample size was determined based on the assumption that an expected change in AUC if 270 mg/dl or above was 270 ± 743 mg/dl. Based on this assumption, 50 evaluated subjects allowed us to reject the hypothesis of no change with 80% power and 1% level of significance. Descriptive statistics were calculated for baseline demographic and clinical characteristics of all study patients. Paired differences between treatments in evaluated variables were analyzed. A hypothesis of no difference in evaluated variables was tested. Normal distribution of all tested continuous variables was assessed by means of the Shapiro-Wilks test. Normal distributed variables were tested by a parametric test (unpaired t test) and not normally distributed variables by a nonparametric test (Wilcoxon signed rank test). For all statistical tests and confidence intervals, the significance level (α) was fixed at p<0.05. The primary analyzed variable was glucose level measured by CGMS and evaluated using AUC. Percentage of time spent (based on CGMS records) in these ranges of glucose was also analyzed. These two variables were analyzed by using the Wilcoxon signed rank test, and the step-down Bonferroni (Holm) correction of p values was applied to adjust p values for multiple testing. The following variables were analyzed by using the Wilcoxon signed rank test: M value, A1C, MBG level, number of hypoglycemic events during CGM (blood glucose level of 59 mg/dl or lower), and SD of glucose level measured by CGM. MAGE measured by CGM was analyzed by using a t test. All variables derived from glucose values recorded by CGM were derived from records over the evaluable 48 hours during the third and fourth day of CGM, when the sensor was more reliable, to ensure the reliability of data. Statistical analysis of data was performed by using the Statistical Package for Social Sciences software v.11.0 (SPSS Inc., Chicago, IL).

Results

Study Sample

Fifty-three patients were enrolled in the study, with 28 patients randomized to acarbose and 25 to placebo; of the 53 patients, 50 patients completed the study. Three patients did not complete the study for the following reasons:
flatulence (one man in the acarbose group) and low quality of the recording during CGMS (one man in the acarbose group and one woman in the placebo group). To be considered adequate, CGMS needed to record at least 80% of the total amount of time (1 wk). For two patients, the total time recorded was below that threshold, and for this reason, these subjects were excluded from the analysis. The sample enrolled was predominantly a group of middle-aged overweight white subjects with type 2 diabetes mellitus. Table 1 provides a full description of the study population.

Glycemic Control

The MBG level, as calculated from CGM values, was $\sim 20$ mg/dl lower in the acarbose group than in the placebo group (p<0.05) (Figure 1). The AUC above 70 did not significantly differ between the two groups, whereas AUC above 180 was $\sim 40\%$ lower in the acarbose group than in the placebo group during the daytime (p<0.01) (Figure 2). The T above 180 was significantly higher in the placebo group than in the acarbose group (31\% vs 8\%, p<0.01) (Figure 3).

Glycemic Variability

The SD was $\sim 12$ mg/dl lower in the acarbose group than in the placebo group (p=0.05) (Figure 1). Figure 4 shows the M values on days 3 and 4 of CGM. The M value was generally 20–25 mg/dl lower in the acarbose group compared with the placebo group (p<0.05 for M values of 7–8, 10–11, and 23–24, and p<0.01 for M values of 17–18). Moreover, the CONGA value was $\sim 5$ mg/dl lower in the acarbose group than in the placebo group, although this difference was not statistically significant. The MAGE value was $\sim 20$ mg/dl lower in the acarbose group than in the placebo group (p<0.05). The MODD value was not significantly changed in either group, and no significant differences were recorded between groups.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acarbose group (n=28)</th>
<th>Placebo group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>15 (54)/13 (46)</td>
<td>12 (48)/13 (32)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>57.5 ± 9.3</td>
<td>55.8 ± 8.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td>11 (39) [5/6]</td>
<td>7 (28) [4/3]</td>
</tr>
<tr>
<td>Diabetes duration, yrs</td>
<td>6.8 ± 2.1</td>
<td>6.3 ± 1.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.4 ± 6.1</td>
<td>75.8 ± 5.4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.68 ± 0.04</td>
<td>1.67 ± 0.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 ± 2.3</td>
<td>27.2 ± 2.1</td>
</tr>
<tr>
<td>Hemoglobin A1C, %</td>
<td>8.2 ± 0.7</td>
<td>8.3 ± 0.7</td>
</tr>
<tr>
<td>Concomitant conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>24 (86) [14/10]</td>
<td>20 (80) [8/12]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (61) [9/8]</td>
<td>14 (56) [7/7]</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>9 (32) [4/5]</td>
<td>7 (28) [4/3]</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>7 (25) [4/3]</td>
<td>6 (24) [3/3]</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>4 (14) [3/1]</td>
<td>3 (12) [1/2]</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (4) [1/0]</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (4) [1/0]</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (7) [1/1]</td>
<td>1 (4) [0/1]</td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypercholesterolemic agents</td>
<td>24 (86) [14/10]</td>
<td>20 (80) [8/12]</td>
</tr>
<tr>
<td>Statins</td>
<td>22 (79) [10/12]</td>
<td>16 (64) [7/9]</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>8 (29) [5/3]</td>
<td>5 (20) [3/2]</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>4 (14) [2/2]</td>
<td>2 (8) [1/1]</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>3 (11) [1/2]</td>
<td>1 (4) [0/1]</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>17 (61) [9/8]</td>
<td>14 (56) [7/7]</td>
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<tr>
<td>Angiotensin II receptor blockers</td>
<td>7 (25) [3/4]</td>
<td>8 (32) [5/3]</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>5 (18) [2/3]</td>
<td>4 (16) [3/1]</td>
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<tr>
<td>β-Blockers</td>
<td>2 (7) [1/1]</td>
<td>1 (4) [0/1]</td>
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<tr>
<td>Diuretics</td>
<td>4 (14) [2/2]</td>
<td>3 (12) [2/1]</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>14 (50) [6/8]</td>
<td>12 (48) [7/5]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10 (36) [5/5]</td>
<td>11 (44) [6/9]</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>1 (4) [0/1]</td>
<td>0</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>3 (11) [1/2]</td>
<td>1 (4) [1/0]</td>
</tr>
</tbody>
</table>

Data are total no. (%) of patients [no. of males/no. of females] or mean ± SD values.
Adverse Events

In the acarbose group, a significantly greater frequency of flatulence was noted (5% with acarbose vs 0.5% with placebo, \( p < 0.05 \)); however, all adverse events were mild in both groups, and only one patient discontinued the study because of flatulence.

Discussion

Our study confirmed what has already been reported in larger and longer clinical trials: acarbose was effective at reducing MBG during the postprandial period. The novel finding of our study, however, is the positive effect of acarbose on glycemic variability when added to metformin.
and vildagliptin therapy. Our results are in line with the findings of a study in which 103 anti-hyperglycemic agent–naive patients with type 2 diabetes were prospectively randomized to nateglinide 120 mg 3 times/day or acarbose 50 mg 3 times/day for 2 weeks. Both agents caused significant reductions on the incremental AUC of the postprandial glucose level and the incremental glucose level peak. Similarly, both treatment groups showed significant improvements in the intraday and interday glycemic excursions, as well as the 24-hour MBG level and serum glycated albumin compared with baseline. This was also confirmed in another study in which the same dosages of acarbose and nateglinide were used. In that study, patients underwent a 70-g carbohydrate-standardized meal and a consecutive 3-day mixed meal (consisting of 55% of calories from carbohydrates, 25% from fat, and 20% from proteins). Both nateglinide and acarbose effectively improved postprandial glycemic control, although acarbose was shown to be more efficient in controlling early postprandial glucose excursions during the carbohydrate meal test and nateglinide was shown to be superior to acarbose in controlling postprandial glucose excursions during the mixed-meal test. The positive effects of acarbose on glycemic variability were confirmed in another study conducted in
120 patients with type 1 diabetes mellitus. The control group received preprandial ultrashort-acting insulin and long-acting insulin before bedtime, whereas the observation group received acarbose 50 mg in addition to the medication taken by the control group. The average blood glucose level, the largest amplitude of glycemic excursions, hyperglycemia-AUC, MAGE, M value, and insulin dosage with acarbose were significantly lower than with insulin. To the best of our knowledge, however, we are the first to report the effects of acarbose on glycemic variability in a European population.

Regarding the clinical application of our findings, we think that the ability of a drug to lower glycemic variability is important in reducing microvascular complications linked to diabetes because it has been reported that causal relationships exist between glycemic excursions and excessive oxidative stress. This was demonstrated in a study in which a multivariable analysis showed that a high MAGE level was significantly associated with the occurrence of a major adverse cardiac event.

Finally, we believe the role of CGM in managing patients with diabetes should be stressed because it provides much more information compared with the measurement of capillary glycaemia and A1C.

Our study has some limitations. The first is the limited sample size, despite the sample being large enough to reach adequate statistical power. Moreover, it would be interesting to determine whether the effects observed in our study would be maintained after acarbose was stopped; to evaluate this, a crossover study design would be appropriate. In addition, because our study population was overweight, it would be interesting to see if our results would be applicable to a lean white population with type 2 diabetes mellitus. Finally, we did not assess if the recommended changes in physical activity were followed; however, this would likely only minimally influence the study results.

Conclusion

The addition of acarbose to metformin and vildagliptin background therapy in patients with inadequately controlled type 2 diabetes mellitus decreased intraday glycemic variability, especially postprandial variability, but it was not associated with a significant change in interday glycemic variability.

References
