ORIGINAL ARTICLE

Nateglinide and Acarbose Are Comparably Effective Reducers of Postprandial Glycemic Excursions in Chinese Antihyperglycemic Agent–Naïve Subjects with Type 2 Diabetes

Jian Zhou, MD, PhD,^{1*} Hong Li, MD,^{2*} Xiuzhen Zhang, MD, PhD,^{3*}
Yongde Peng, MD, PhD,^{4*} Yifei Mo, MD,¹ Yuqian Bao, MD,¹ and Weiping Jia, MD, PhD¹

Abstract

Background: Recent studies have identified postprandial glycemic excursions as risk factors for diabetes complications. This study aimed to compare the effects of nateglinide and acarbose treatments on postprandial glycemic excursions in Chinese subjects with type 2 diabetes.

Subjects and Methods: This was a multicenter, open-label, randomized, active-controlled, parallel-group study. One hundred three antihyperglycemic agent–naïve subjects with type 2 diabetes (hemoglobin A1c range, 6.5–9.0%) were prospectively recruited from four hospitals in China. The intervention was nateglinide (120 mg three times a day) or acarbose (50 mg three times a day) therapy for 2 weeks. A continuous glucose monitoring system was used to calculate the incremental area under the curve of postprandial blood glucose (AUC_{pp}), the incremental glucose peak (IGP), mean amplitude of glycemic excursions, SD of blood glucose, the mean of daily differences, and 24-h mean blood glucose (MBG). Subjects' serum glycated albumin and the plasma insulin levels were also analyzed.

Results: Both agents caused significant reductions on AUC_{pp} and IGP. Similarly, both treatment groups showed significant improvements in the intra- and interday glycemic excursions, as well as the 24-h MBG and serum glycated albumin compared with baseline ($P < 0.001$). However, neither of the agents produced a significantly better effect ($P > 0.05$). Moreover, the nateglinide-treated group had significantly increased insulin levels at 30 min and at 120 min after a standard meal compared with baseline, whereas the acarbose-treated group decreased. No serious adverse events occurred in either group. The rates of hypoglycemic episodes were comparable in the two groups, and no severe hypoglycemic episode occurred in either group.

Conclusions: Nateglinide and acarbose were comparably effective in reducing postprandial glycemic excursions in antihyperglycemic agent–naïve Chinese patients with type 2 diabetes, possibly through different pathophysiological mechanisms.

Introduction

PATIENTS WITH TYPE 2 DIABETES mellitus (T2DM) are characterized by sustained chronic hyperglycemia and increased amplitude of glycemic excursions. Hypoglycemia induced by various reasons and postprandial (post-loading) hyperglycemia are major components of abnormal glycemic excursions in patients with T2DM.¹ Epidemiological studies have revealed that acute postprandial hyperglycemia is significantly correlated with increased cardiovascular events.^{2,3}

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.^{4–6} Therefore, the therapeutic strategies used to achieve optimal blood glucose control should also aim to reduce glycemic excursions.⁷

Continuous glucose monitoring (CGM) technology based on implantable sensors and wireless transmission of measurement data has rapidly become a widespread application

¹Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Diabetes Institute, Shanghai, China.

²Department of Endocrinology and Metabolism, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

³Department of Endocrinology and Metabolism, Tongji University Affiliated Tongji Hospital, Shanghai, China.

⁴Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai, China.

*The first four authors contributed equally to this work.

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due to its convenience and accuracy for recording multiday glycemic values and trends. This device also represents a useful tool for researchers to obtain robust, quantitative data from human subjects.^{8,9} However, few studies to date have used the CGM system to evaluate the effects of oral antidiabetes drugs on glucose variability. Nateglinide and acarbose are two of the oral antidiabetes drugs that preferentially affect postprandial hyperglycemia and are widely used to treat T2DM patients in China. Previous studies have demonstrated that both nateglinide and acarbose can reduce postprandial hyperglycemia,^{10,11} but their effects on glycemic excursions have not been well studied in antihyperglycemic agent-naïve T2DM patients, although the results of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial showed that nateglinide was not effective in decreasing both the new cases of diabetes and the new cardiovascular events in a population at high risk.¹² Therefore, this study was designed to compare the efficacies of nateglinide and acarbose for reducing postprandial glycemic excursions in antihyperglycemic agent-naïve Chinese patients with T2DM.

Subjects and Methods

Study design

This study was designed as a prospective, randomized, open-label, and active-controlled 2-week assessment of nateglinide and acarbose therapy. Between December 2009 and February 2011, four medical centers in China participated in this clinical trial: Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai; Sir Run Run Shaw Hospital, Hangzhou; Tongji University Affiliated Tongji Hospital, Shanghai; and Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai. The protocol was approved by the independent Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth

People's Hospital, in accordance with the principle of the Helsinki Declaration II. All study participants provided written informed consent.

Inclusion and exclusion criteria

Adult patients (age range, 18–75 years) were recruited for the study according to T2DM diagnosis (hemoglobin A1c range, 6.5–9.0%) and no treatment with antihyperglycemic agents for at least 3 consecutive months prior to study enrollment (designated as antihyperglycemic agent-naïve patients). Patients were excluded from study enrollment according to known allergies to nateglinide or acarbose and hepatic or renal dysfunction. Following study enrollment (visit 1), the subjects were given a CGM system from Medtronic MiniMed Inc. (Northridge, CA) and instructions for use (visit 2; analysis Day 1). After 3 days of CGM (detailed below) with no therapeutic intervention, the subjects were given a standard meal test in the fasting state (visit 3; analysis Day 4), which consisted of 70 g of bread/instant noodles eaten within a 15-min period. Then, the subjects were randomized (1:1) to receive 2 weeks of either nateglinide (120 mg three times a day; Novartis Pharma Ltd., Beijing, China) or acarbose (50 mg three times a day; Bayer HealthCare Pharmaceuticals Inc., Montville, NJ). The subjects performed CGM from visit 4 (Day 18) to visit 5 (Day 21), at which a final standard meal test in the fasting state was conducted. The treatment group strategy is illustrated in Figure 1.

CGM

The CGM system obtained 288 continuous sensor values per day. Daily calibration of the device was carried out by entering a minimum of four capillary blood glucose measurements made by a SureStep[®] blood glucose meter (LifeScan, Milpitas, CA).

FIG. 1. Study design and clinic visit schedule. CGMS, continuous glucose monitoring system; TID, three times a day.

Efficacy parameters

The incremental area under the curve of postprandial blood glucose (AUC_{pp}) during CGM was the primary efficacy measure. AUC_{pp} was calculated as the area between the sensor glucose concentration–time curve and the preprandial baseline glucose value measured at 4 h after each meal. The following six secondary efficacy measures were taken:

1. The incremental glucose peak (IGP), which was calculated as the maximal incremental increase in blood glucose obtained at any point after the meal.
2. The intraday glycemic variability, which included the mean amplitude of glycemic excursions (MAGE) and the SD of blood glucose (SDBG) readings. The MAGE value was obtained by calculating the arithmetic mean of the differences between consecutive peaks and nadirs; measurement in the peak-to-nadir direction was determined by the first excursion more than 1 SD. Intraday glycemic variability was based on the mean values taken on two successive 24-h periods.
3. The interday glycemic variability, which was calculated as the mean of daily differences (MODD) using the absolute difference between paired CGM values obtained during two successive 24-h periods.
4. The 24 h mean blood glucose (24-h MBG), which was calculated as the average of 288 readings collected during a 24-h CGM period.
5. The serum glycated albumin (GA), which was measured by a liquid enzymatic assay kit (Lucica® GA-L; Asahi Kasei Pharma, Tokyo, Japan). The normal GA reference range was 11–17%.
6. The plasma insulin levels, which were detected at the 0-, 30-, and 120-min time points of the standard meal test by using the standard radioimmunoassay procedure (Linco Research, St. Charles, MO), with intra- and inter-assay coefficients of variation of <10%. The normal plasma insulin reference range in the fasting state was 3.42–16.44 μ U/mL.

Safety parameters

Throughout the study, any hypoglycemia events and adverse events were recorded. In addition, results of physical examination, including vital signs, were recorded.

Diet and exercise during the CGM period

Patients were instructed to adhere to a standard diet during the 3-day period of CGM sensor monitoring. The diet was designed to ensure a total daily caloric intake of 25 kcal/kg/day, with 55% of calories coming from carbohydrates, 17% from proteins, and 28% from fats. Written instructions were provided to achieve the appropriate caloric content and to guide the consumption times, which included breakfast (20% of daily calories, 06:30–07:30 h), lunch (40%, 11:30–12:30 h), and dinner (40%, 18:00–19:00 h). Meanwhile, each patient exercised according to doctors' personalized instruction.

Statistical methods

Statistical analyses were performed by the SAS version 9.1 software package (SAS Institute Inc., Cary, NC). Normally distributed data are presented as mean $\pm$ SD; data with non-normal distribution are presented as median and interquartile range. The significance of intergroup differences between

AUC_{pp} from baseline was analyzed by analysis of covariance. The intragroup differences of parameters before and after treatment were analyzed by *t* test or paired *t* test, as appropriate. Analyses for primary and secondary end points were performed on the intent-to-treat population.

Determination of sample size

Because comparative data about effects of nateglinide and acarbose on PPGE have not yet been published, the estimate of sample size was based on the feasibility of conducting a clinical trial. A total sample size of 84 randomized patients with primary assessment during the open-label treatment period of the trial is required. After adjustments for an estimated 20% of dropouts without any primary efficacy assessments after baseline, approximately 108 patients (54 patients each group) were to be enrolled in this study at the four centers. Patients were to be assigned to receive nateglinide or acarbose by random allocation at a 1:1 ratio.

Results

Characteristics of study subjects

In total, 103 patients with T2DM met the enrollment criteria and were randomized into the two treatment groups, with 51 (49.51%) receiving the nateglinide therapy and 52 (50.49%) receiving the acarbose therapy. In total, 98 patients (95.15%) completed the study. Of the five patients who did not complete the study, two (1.94%) were from the nateglinide group

TABLE 1. BASELINE CHARACTERISTICS OF ENROLLED PATIENTS

	Nateglinide group	Acarbose group
Enrolled (<i>n</i>)	51	52
Analyzed (<i>n</i>)	49	49
Age (years)	53.4 $\pm$ 10.3	53.7 $\pm$ 9.4
Male/female ratio	31/20	29/23
Duration since diagnosis of diabetes (years)	0.20 (0.07–0.73)	0.19 (0.09–1.02)
BMI (kg/m^2)	25.02 $\pm$ 2.98	25.18 $\pm$ 2.76
Waist circumference (cm)	86.1 $\pm$ 10.2	86.8 $\pm$ 8.4
Total cholesterol (mmol/L)	4.82 $\pm$ 0.79	5.13 $\pm$ 0.96
Triglyceride (mmol/L)	1.71 $\pm$ 1.05	1.81 $\pm$ 0.75
LDL-C (mmol/L)	2.80 $\pm$ 0.86	2.95 $\pm$ 1.07
HDL-C (mmol/L)	1.20 $\pm$ 0.47	1.17 $\pm$ 0.37
Blood pressure (mm Hg)		
Systolic	126.5 $\pm$ 12.1	131.2 $\pm$ 16.0
Diastolic	77.7 $\pm$ 7.9	79.5 $\pm$ 10.2
HbA1c (%)	7.46 $\pm$ 0.75	7.53 $\pm$ 0.56
GA (%)	20.77 $\pm$ 3.99	20.69 $\pm$ 3.28
MBG (mmol/L)	8.78 $\pm$ 1.94	8.86 $\pm$ 1.71
SDBG (mmol/L)	1.80 $\pm$ 0.67	1.90 $\pm$ 0.60
MAGE (mmol/L)	5.27 $\pm$ 2.09	5.03 $\pm$ 1.82
MODD (mmol/L)	1.31 (0.68–1.85)	1.51 (0.56–2.01)

The demographic and baseline characteristics of the study participants were well matched between the two treatment groups (all *P* > 0.05).

BMI, body mass index; GA, glycated albumin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MAGE, mean amplitude of glycemic excursions; MBG, mean blood glucose; MODD, mean of daily differences; SDBG, SD of blood glucose.

FIG. 2. Average continuous glucose monitoring tracings from baseline (red curve) and after 2 weeks of treatment (green curve) with either **(A)** nateglinide or **(B)** acarbose.

(one withdrew informed consent, and one withdrew for an unstated reason), and three (2.91%) were from the acarbose group (one was lost to follow-up, one was excluded because of major protocol deviation, and one withdrew for an unstated reason). Among these 98 patients, the number of patients who completed the entire clinical trial according to the protocol was 85. The demographic and baseline characteristics of the 103 study participants were well matched between the two treatment groups (Table 1).

Blood glucose regulation and CGM-detected excursions (Fig. 2)

Therapy-mediated effects on postprandial blood glucose excursions. Both treatment groups showed a significant decrease in the AUC_{pp} of treatment (vs. baseline, $P < 0.001$), but the decrease achieved by the two therapies was not sig-

nificantly different (nateglinide vs. acarbose, $P = 0.691$). A similar trend in therapy-induced reduction of mean IGP was also observed for both agents (vs. baseline, $P < 0.001$; nateglinide vs. acarbose, $P = 0.192$) (Table 2).

Therapy-mediated intra- and interday variations in blood glycemic excursions. Both treatment groups showed significant improvements in the intraday glycemic excursions over treatment duration, as indicated by reduced MAGE and SDBG (vs. baseline, $P < 0.001$). Neither of the agents produced a significantly better effect (nateglinide vs. acarbose: MAGE, $P = 0.985$; SDBG, $P = 0.379$). A similar trend in therapy-induced reduction of the MODD was also observed for both agents (vs. baseline, $P < 0.001$; nateglinide vs. acarbose, $P > 0.05$).

Therapy-mediated effects on MBG levels. Both treatment groups showed significant decreases in the 24-h MBG

TABLE 2. INTRA- AND INTERDAY VARIATIONS IN BLOOD GLYCEMIC EXCURSIONS FROM BASELINE IN THE NATEGLINIDE AND ACARBOSE GROUPS

	Nateglinide group	Acarbose group	P value
<i>n</i>	51	52	
MBG (mmol/L)	-1.08 (-1.76, -0.51)	-0.88 (-1.91, -0.10)	0.183
SDBG (mmol/L)	-0.43 (-0.93, -0.08)	-0.49 (-1.14, -0.29)	0.379
MAGE (mmol/L)	-1.50 (-3.07, -0.72)	-1.67 (-3.20, -0.86)	0.985
MODD (mmol/L)	-0.24 (-0.55, 0.74)	-0.10 (-0.74, 0.21)	0.455
IGP (mmol/L)	-2.70 (-4.40, -0.90)	-2.10 (-4.40, -0.50)	0.321

IGP, incremental glucose peak; MAGE, mean amplitude of glycemic excursions; MBG, mean blood glucose; MODD, mean of daily differences; SDBG, SD of blood glucose.

($P < 0.001$), but there was no significant difference between the reductions induced by the two agents (nateglinide vs. acarbose, $P = 0.183$).

Therapy-mediated effects on GA. Both treatments groups showed a significant reduction in GA (vs. baseline, $P < 0.001$; nateglinide, $2.22 \pm 1.90\%$ reduction; acarbose,

$1.74 \pm 1.50\%$ reduction) (Fig. 3), but there was no significant difference between the reductions induced by the two agents (nateglinide vs. acarbose, $P = 0.908$).

Therapy-mediated effects on insulin levels. At baseline, there was no significant difference in insulin concentrations between the acarbose and nateglinide groups at 0 min, 30 min, or 120 min. However, after up to 2 weeks of treatment, the insulin concentrations in the nateglinide group dramatically increased at 30 min ($P < 0.0001$) and at 120 min ($P = 0.0012$), with statistical differences between pretreatment and post-treatment. In contrast, compared with baseline, the insulin concentrations at the end point in the acarbose group decreased at 30 min and at 120 min with statistical differences between pretreatment and post-treatment (both $P < 0.0001$) (Fig. 4).

Safety of the two therapeutic agents

The 2-week regimens of nateglinide and acarbose were well tolerated by the T2DM patients. No adverse events were reported that required clinical care or hospital admission. Eight adverse events were reported for seven of the subjects in the nateglinide group, and 16 adverse events were reported for 20 of the subjects in the acarbose group. The intergroup difference reached statistical significance (nateglinide; 13.73%; acarbose, 30.77%; $P = 0.038$). Among the adverse events, four for four subjects in the nateglinide group and 16 for 12 subjects in the acarbose group were drug-related (nateglinide, 7.84%; acarbose, 23.08%; $P = 0.033$). The most frequently reported adverse event was gastrointestinal-related, and these were only experienced by subjects in the acarbose group. Hypoglycemic episodes were experienced by three subjects (four events total) in the nateglinide group and one subject (one event) in the acarbose group, but the intergroup difference was not significant (nateglinide, 5.88%; acarbose, 1.92%; $P = 0.596$).

Discussion

Glucose management is the key to preventing the development of chronic complications in T2DM, as demonstrated in several large-scale clinical trials.¹³ Maintaining MBG levels within the narrow normoglycemic range and reducing episodes of glycemic excursions are two major aims of glucose control. An important component of dysglycemia is postprandial hyperglycemia, which has been extensively studied in both clinical and laboratory settings. The postprandial phase can cover 60–70% of the day in T2DM patients.¹⁴

FIG. 3. Comparison of mean changes in (A) postprandial blood glycemic excursions (incremental area under the curve of postprandial blood glucose [AUCpp]) and (B) serum glycated albumin (GA) in the nateglinide and acarbose groups. Data are mean $\pm$ SD values. * $P < 0.001$ versus baseline.

FIG. 4. Change in insulin levels from baseline in the nateglinide and acarbose groups. The nateglinide-treated group had a significantly larger change in insulin levels than the acarbose-treated group ($P < 0.001$).

Postprandial hyperglycemia has been implicated as a contributing factor to both chronic increases and acute fluctuations in blood glucose levels, suggesting that prognosis of T2DM may not only rely on increased blood glucose levels but also the duration of chronic hyperglycemia and blood glucose excursions per unit time. In addition, clinical observations have indicated that the 2-h postprandial (post-loading) blood glucose level is not the peak postprandial blood glucose, and the hyperglycemic state may persist and not resolve when duration between meals is too short. Finally, the evidence supports the notion that postprandial hyperglycemia may induce further metabolic disorders and abnormal cellular function.¹⁵

Unfortunately, very few studies to date have evaluated the overall blood glycemic excursions experienced by T2DM patients during the course of oral antihyperglycemic agents. This type of study has been restricted by the challenges associated with blood glucose monitoring using a traditional electronic device and disposable test strip. The advent of CGM with an implantable sensor has overcome this challenge, so that a comprehensive assessment of postprandial hyperglycemia may be performed with little inconvenience to the study participants. The present study was designed to investigate the effectiveness of nateglinide and acarbose on improvement of blood glycemic excursions in antihyperglycemic agent-naïve T2DM patients using CGM technology.

Postprandial hyperglycemia remains a prominent feature in the early stage of diabetes, and this has been demonstrated in T2DM patients of Chinese ethnicity.¹⁶ In fact, a recent study of Chinese patients with newly diagnosed T2DM showed that 49% of the patients experienced isolated episodes of postprandial hyperglycemia each day, whereas only 12% experienced isolated episodes of fasting hyperglycemia.¹⁷ Besides facilitating progression and deterioration of the diabetes state, sustained postprandial hyperglycemia is an independent risk

factor for cardiovascular complications and death. The current study found that monotherapy with either nateglinide or acarbose reduced postprandial blood glycemic excursions in T2DM patients, which may lower a patient's risk of such complications. Furthermore, these findings are consistent with those of previous studies that have indicated the additive effect of supplementing the insulin glargine therapy with a nateglinide or acarbose regimen to further reduce postprandial blood glucose.^{18–20} It is possible that either of these agents may also help to further control postprandial glycemic excursions in insulin glargine-treated patients.

Many of the pathophysiological mechanisms that cause postprandial hyperglycemia in patients with T2DM have been elucidated. Among these are the loss of early-phase insulin secretion, perturbed rhythm of insulin secretion (such as abnormal reduction in peak frequency and amplitude of pulsatile secretion of postprandial insulin), insulin resistance due to inappropriate glucagon levels or reduced insulin action, and increased secretion of the insulin precursor, which results in excessive output of hepatic glucose at the beginning of a meal.^{21–25} The mechanisms by which nateglinide and acarbose reduce postprandial blood glucose are different. Nateglinide, an insulinotropic agent with rapid action on β -cells, enhances early-phase insulin secretion,^{26,27} whereas acarbose represents a pharmacologic approach for modifying the digestion and absorption of dietary carbohydrates as an adjunct to dietary changes. Moreover, a recent study found that treatment with repaglinide and nateglinide reconstructed postprandial ghrelin secretion patterns in diabetes, and thus nateglinide may help to improve the control of feeding behavior in patients with T2DM.²⁸

A few limitations to our study design should be considered when interpreting our results. In particular, the study population was relatively small, and the observation time was

relatively short. Because the data in our study show that, although acarbose is solely a postprandial agent, nateglinide has an effect on fasting plasma glucose as well; thus a longer study may demonstrate further a hemoglobin A1c benefit for nateglinide. In addition, the open-label feature may have influenced our findings with either or both of the drugs evaluated. Finally, we did not include a control group in which the patients only received lifestyle intervention without medication. In the future, a large-scale clinical study should be conducted to further assess the effects of specific oral antihyperglycemic drugs on postprandial glycemic excursions.

In conclusion, both nateglinide and acarbose can effectively improve postprandial glycemic excursions in Chinese T2DM patients, possibly through different pathophysiological mechanisms.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Weiping Jia, MD, PhD

Department of Endocrinology and Metabolism

Shanghai Jiao Tong University Affiliated Sixth People's Hospital

600 Yishan Road

Shanghai 200233, China

E-mail: wpjia@sjtu.edu.cn