

Combined use of basal insulin analog and acarbose reduces postprandial glucose in patients with uncontrolled type 2 diabetes

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Keywords

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ABSTRACT

Aims/Introduction: Early initiation of basal insulin therapy is recommended for normalizing fasting blood glucose in type 2 diabetes mellitus. However, basal insulin treatment might not adequately control postprandial glucose levels. The present study evaluated whether the combination of the α -glucosidase inhibitor, acarbose, and basal insulin improved blood glucose control under daily-life treatment conditions in a large sample of Korean patients.

Materials and Methods: The present study was a multicenter, prospective, observational study under daily-life treatment conditions. A total of 539 patients with type 2 diabetes who were treated with basal insulin and additional acarbose were enrolled and followed up for 20 weeks. Changes in hemoglobin A1c, fasting and postprandial blood glucose were evaluated at baseline and at the end of the observation period. The physician and patient satisfaction of the combination treatment and safety were assessed.

Results: Hemoglobin A1c decreased by $0.55 \pm 1.05\%$ from baseline ($P < 0.0001$). Fasting and postprandial blood glucose levels were reduced by 0.89 ± 3.79 and 2.59 ± 4.77 mmol/L (both $P < 0.0001$). The most frequently reported adverse drug reactions were flatulence (0.37%) and abnormal gastrointestinal sounds (0.37%), and all were mild in intensity and transient. In the satisfaction evaluation, 79.0% of physicians and 77.3% of patients were 'very satisfied' or 'satisfied' with the combined basal insulin and acarbose therapy.

Conclusions: Combination therapy of basal insulin and acarbose in patients with type 2 diabetes improved glucose control, and had no drug-specific safety concerns, suggesting that the treatment might benefit individuals who cannot control blood glucose with basal insulin alone.

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INTRODUCTION

Type 2 diabetes mellitus is an epidemic resulting in enormous human suffering, such as cardiovascular disease or renal failure, and economic costs. Much of the morbidity associated with long-term complications can be reduced by lowering blood glucose close to the range of a non-diabetic individual^{1–3}. Given the progressive nature of diabetes and the substantial evidence supporting insulin regimens, patients must utilize insulin therapy to maintain glycemic control, and reduce morbidity and mortality rates associated with diabetes and its related complications⁴.

Currently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend hemoglobin A1c (HbA1c) $\geq 7.0\%$ treated with insulin therapy to improve glycemic control⁵. Targeting fasting blood glucose (FBG) by injection basal insulin and monitoring blood glucose once per day often helps patients reach treatment goals, and is a recommended approach for early insulin initiation⁶.

However, using basal insulin alone might not be effective for the management of postprandial glucose levels in individuals with type 2 diabetes. Once FBG is under tight control with basal insulin, adding an oral hypoglycemic agent, such as an α -glucosidase inhibitor, that targets postprandial hyperglycemia helps reduce postprandial blood glucose excursions^{7,8}.

Several studies have evaluated the efficacy of acarbose when combined with insulin therapy, but most were carried out some time ago, therefore they utilized normal insulin^{9–11}. Recently, insulin analogs with quite a long half-life have become available, and are gaining the popularity. Therefore, in the present study, we collected the data from real-life practice from patients who were treated with basal insulin and who had started additional acarbose treatment.

MATERIALS AND METHODS

Participants

From September 2010 to July 2012, we enrolled Korean patients aged ≥ 18 years who had been diagnosed with type 2 diabetes for 6 months according to the 1999 World Health Organization criteria¹², had been treated with a stable dose of basal insulin (insulin glargine or insulin detemir) for ≥ 2 months, and had a verified HbA1c level between 7.5 and 10.0%.

Patients were excluded from study enrolment if they had a known allergy to acarbose, hepatic dysfunction or liver cirrhosis, a serious infection pre- or post-surgery, severe trauma, chronic intestinal disease related with digestive or absorption disorder, severe diabetic ketoacidosis, diabetic coma or precoma, biochemical evidence of severe renal impairment (creatinine clearance < 25 mL/min), or were pregnant or nursing at the time of the study. Patients who had aggravated symptoms related to an increase in intestinal gas development (Roemheld

syndrome, severe hernia, intestinal obstruction, intestinal ulcer, or inflammatory intestinal disease, etc.) were also excluded.

The study complied with the Declaration of Helsinki, and informed consent was obtained from all participants. The protocol was reviewed and approved by independent institutional review boards at the study sites.

Study Design

The present study was a single-country, prospective, observational, non-interventional study of patients who had been treated with basal insulin and started acarbose under daily-life treatment conditions. A total of 30 medical centers and diabetes clinics in Korea participated in this clinical trial. All patients who fulfilled the inclusion criteria and had been prescribed acarbose by their physician were eligible to participate. Study-related procedures were not defined because of the non-interventional nature of the study, and the selection of which patients received acarbose and the dose they took were left to the physician's discretion.

The patients were treated with 50- or 100-mg acarbose (Glucobay; Bayer HealthCare, Leverkusen, Germany) two or three times per day with meals and followed up for 20 weeks after the initial visit. The decision on the treatment duration was solely at the discretion of the attending physician. The medication was prescribed within the regular practice of the physician. During that timeframe, at least two follow-up visits were documented. Basic assessments and blood samples were carried out at baseline, two follow-up visits and the final visit 20 weeks after the patients commenced taking the study medications. All patients were advised to continue with their usual diet, physical activity and medications. All medications taken during the study were documented (trade name, start and stop date, and daily dose), as were concomitant therapies (e.g., radiotherapy).

All study participants underwent anthropometric measurements, including height; weight and body mass index (BMI); and blood chemistry analysis including FBG, postprandial blood glucose, HbA1c, liver function tests and lipid profiles. Weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.5 cm without shoes and in light clothing on each visit. BMI was calculated as bodyweight (in kg) divided by the square of the height (in m). All blood samples were drawn after an overnight 12-h fast.

Based on a statistical power of 90%, a sample size of 1,400 was required to detect a significant difference between a null hypothesis mean HbA1c change of 0.4 and an alternative mean change of 0.6 from baseline to last follow up, assuming a standard deviation of 2.1, using a paired *t*-test with a 0.025 one-sided significance level, and predicting a 20% dropout rate.

Study Evaluations

The primary efficacy outcome was the change in baseline HbA1c from the initial stage to the end of the observation

period. Secondary efficacy end-points included the change in baseline FBG, postprandial blood glucose and weight over the course of the observation period. Clinician and patient satisfaction of the combined basal insulin and acarbose treatment were also assessed. Patients were monitored throughout for the occurrence of drug reactions and serious adverse events.

A full analysis set (FAS) was defined as data obtained from those who took acarbose more than once and had efficacy outcomes evaluated at least one more time after their baseline assessment. All enrolled patients were included in safety set.

Analysis and Statistics

Efficacy

The results were expressed as the mean ± standard deviation and/or median value (range) for continuous variables. All background data, such as patient demographics, diagnosis, prior antidiabetic treatment, concomitant diseases and concomitant medication, were described by using absolute and relative frequencies, and/or basic summary statistics. Duration and dose of acarbose treatment during the observation period were calculated for each patient. Analyses were carried out on medically relevant subgroups, such as concomitant antidiabetic medication, diabetes duration and acarbose dose. The differences between baseline and last follow up were assessed using paired *t*-tests (Wilcoxon signed-rank test). In addition, subgroup analysis was carried out according to the quartile of baseline postprandial glucose levels. The time-based sequential change of HbA1c, fasting blood glucose and 2-h postprandial glucose levels were analyzed by using the Kruskal–Wallis test under stratifying with quartile group.

Physician and patient satisfaction of basal insulin and acarbose combination therapy was presented using absolute and relative frequencies. The data were analyzed using SAS (version 9.1; SAS Institute, Cary, NC, USA), and statistical significance was set at *P* < 0.05.

Safety and Tolerability

Adverse events were coded by MedDRA version 14.0, and physicians were requested to assess whether adverse events were drug (acarbose)-related and serious or non-serious. All safety results were summarized in a descriptive manner.

RESULTS

Patients Disposition and Characteristics

Of the 539 enrolled patients, 406 (75.3%) patients completed the 20-week observational study period. A total of 539 patients were included in the safety set and 494 patients (83.3%) were in the FAS, which enabled them to be analyzed for all of the end-points (Figure 1).

The patient characteristics are summarized in Table 1. The mean age of the 494 FAS group was 60.3 ± 11.5 years, with 306 patients (61.9%) aged <65 years, 140 patients (28.3%) aged between 65 and 75 years, and 48 patients (9.7%) aged >75 years. BMI was 24.2 ± 3.2 kg/m², duration of diabetes was 12.8 ± 7.7 years and basal insulin therapy period was 2.5 ± 2.6 years. The baseline characteristics of patients in the safety analysis were similar to that of the patients in the FAS group.

Of the 494 patients in the FAS group, 396 (80.2%) had concomitant diseases. The concomitant diseases that occurred at a

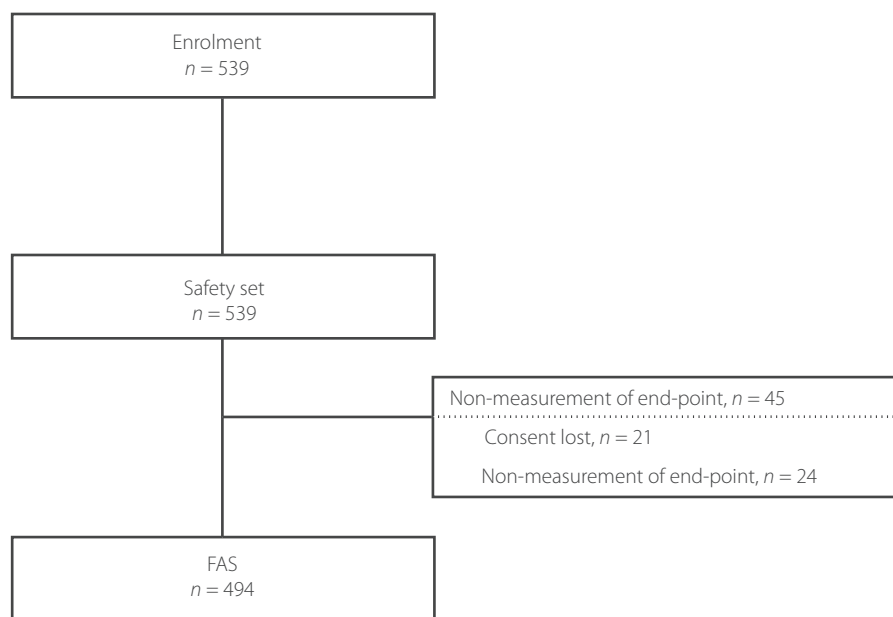


Figure 1 | Patient disposition. FAS, full analysis set.

frequency over 10% were hypertension (58.5%), dyslipidemia (43.1%), diabetic neuropathy (22.7%) and diabetic retinopathy (16.4%). The acarbose dose was 198.5 ± 73.9 mg/day and treatment duration was 194.6 ± 98.9 day. The daily dose of basal insulin was 25.0 ± 10.6 IU. The percentage of patients treated with antidiabetic drugs in addition to basal insulin and acarbose was 71.1%. The most common antidiabetic drugs used were biguanides (52.6%) and sulfonylurea (16.4%). Baseline demographics and efficacy-related characteristics of FAS were generally similar to those of the safety set.

Efficacy Outcome

The primary efficacy outcome was that HbA1c decreased significantly over the course of the observation period ($0.55 \pm 1.05\%$; $P < 0.0001$). FBG decreased by 0.89 ± 3.79 mmol/L.

Postprandial glucose was reduced by 2.59 ± 4.77 mmol/L ($P < 0.0001$; Table 2).

For the satisfaction analysis, 21.38% of physicians and 15.31% of patients were 'very satisfied,' and 57.64% of physicians and 62.04% of patients were 'satisfied' with the basal insulin and acarbose combination therapy (Table 3).

Analysis of Subgroups

Subgroup analyses were carried out to determine whether other antidiabetic drugs, mean daily dose of acarbose, duration of diabetes and duration of basal insulin use, weight, sex, and presence of concomitant disease influenced primary and secondary efficacy outcome measures. Patients taking other antidiabetic drugs showed less of a decrease in FBG (0.75 ± 3.96 vs 1.47 ± 2.97 mmol/L, $P = 0.0312$), and more of a decrease

Table 1 | Baseline characteristics of the study participants

Parameters	Category	Safety set ($n = 539$) n (%)	FAS ($n = 494$) n (%)			
Age (years)	n	539	494			
	Mean \pm SD	60.1 ± 11.3	60.3 ± 11.5			
	Median (range)	60 (22–83)	61 (22–83)			
Sex	n	539	494			
	Male	258 (47.87)	239 (48.38)			
	Female	281 (52.13)	255 (51.62)			
BMI (kg/m^2)	n	454	417			
	Mean \pm SD	24.3 ± 3.2	24.2 ± 3.2			
	Median (range)	23.9 (17.2–37.9)	23.8 (17.2–36.6)			
Weight (kg)	n	457	420			
	Mean \pm SD	63.6 ± 11.0	63.4 ± 11.1			
	n	510	470			
Height (cm)	Mean \pm SD	161.7 ± 8.6	161.7 ± 8.5			
	n	522	479			
	Mean \pm SD	12.8 ± 7.7	12.8 ± 7.7			
Duration of diabetes (years)	n	517	473			
	Mean \pm SD	2.4 ± 2.6	2.5 ± 2.6			
	No. patients with concomitant diseases, n (%)	435 (80.71)	396 (80.16)			
Hypertension		319 (59.18)	289 (58.50)			
	Dyslipidemia		237 (43.97)	213 (43.12)		
		Diabetic neuropathy		127 (23.56)	112 (22.67)	
			Diabetic retinopathy		90 (16.70)	81 (16.40)
				Microalbuminuria		49 (9.09)
Acarbose (glucobay [®])					n	525
	Mean \pm SD				200.6 ± 74.3	198.5 ± 73.9
	Median (range)	200.0 (50.0–300.0)			200.0 (50.0–300.0)	
Duration of treatment (days)	n	525	494			
	Mean \pm SD	190.7 ± 98.0	194.6 ± 98.9			
	Median (range)	178 (15–575)	180 (15–575)			
	Basal insulin (lantus [glargine] + levemir [detemir])	n	525	494		
Mean \pm SD		25.0 ± 10.6	25.0 ± 10.6			
Median (range)		23.0 (5.0–70.0)	22.8 (6.0–70.0)			

BMI, body mass index; FAS, full analysis set; IU, international units; SD, standard deviation.

Table 2 | Change in hemoglobin A1c, glucose and weight from baseline to week 20

Parameters	Baseline	20 weeks	Change	P-value
HbA1c (%) (n = 387)	8.55 ± 0.83	7.99 ± 1.24	-0.55 ± 1.05	<0.0001
Fasting blood glucose (mmol/L) (n = 293)	8.00 ± 3.46	7.14 ± 2.47	-0.89 ± 3.79	<0.0001
Postprandial glucose (mmol/L) (n = 384)	13.54 ± 4.18	10.95 ± 3.41	-2.59 ± 4.77	<0.0001
Weight (kg) (n = 329)	63.41 ± 11.10	63.61 ± 11.06	-0.23 ± 2.21	0.0805

Data are mean ± SD. Change: final visit – baseline. HbA1c, hemoglobin A1c.

in postprandial glucose (3.00 ± 4.78 vs 1.52 ± 4.60 mmol/L, $P = 0.0227$) than patients who did not take these drugs. FBG was also significantly lower in patients with dyslipidemia compared with patients without dyslipidemia (1.62 ± 4.37 vs 0.45 ± 3.33 mmol/L, $P = 0.0244$) (data are not shown). HbA1c, FBG and postprandial glucose changes over the 20 weeks were not significantly different among any of the other subgroups. In a result of subgroup analysis according to baseline 2-h postprandial glucose levels, the upper quartile group (higher baseline postprandial glucose level) showed a significantly more decreased pattern of postprandial glucose levels than that of the lower quartile groups at 20 weeks ($P < 0.0001$). However, the change of HbA1c and FBG did not show a difference between or within quartile groups (Table 4).

Safety and Tolerability

A total of 33 adverse events from 22 patients (4.08%) were reported during the study period. Nine cases of adverse events related to the acarbose developed in eight patients (1.48%) and included gastrointestinal disorders, such as flatulence (two patients), abnormal gastrointestinal sounds (two patients), abdominal discomfort (one patient), abdominal distension (one patient), abdominal pain upper (one patient) and elevated liver function test (one patient). A total of 10 serious adverse events occurred in six patients (1.11%), although they were reported

by hospital admission and were confirmed to be unrelated to the study drug. There was no case of hypoglycemia in the present study.

DISCUSSION

The present study showed that combined basal insulin, and acarbose therapy decreased HbA1c, FBG and postprandial blood glucose levels in Korean patients with type 2 diabetes without a change in bodyweight. Adding acarbose helped type 2 diabetes patients achieve glycemic control when basal insulin and other antidiabetic drugs did not work under routine clinical practice conditions.

Type 2 diabetes mellitus is a progressive disease characterized by insulin insufficiency and resistance along with chronic hyperglycemia¹³, and its prevalence is projected to increase in Korea. However, only approximately 40% of diabetic patients in Korea achieve a HbA1c <7.0%, a common goal of diabetes treatment¹⁴. The patients in the present study had a baseline HbA1c 8.5% using basal insulin therapy, and adding acarbose treatment reduced it by 0.55% and postprandial glucose by 2.6 mmol/L. Although the mean HbA1c after 20 weeks treatment of acarbose (7.99%) was somewhat still higher than the treatment target of <7%, it should be noted that acarbose had a neutral effect on bodyweight, and did not trigger any severe adverse events or hypoglycemia, two common side-effects of diabetes treatments, in particular insulin treatment. These two aspects (hypoglycemia and bodyweight) are supported by recent several meta-analyses^{15,16}, and might be explained by the insulin-sparing mechanism of acarbose^{17,18}. As acarbose is a drug that targets postprandial glucose levels, a significant declined-pattern of postprandial glucose level after additional acarbose treatment was shown in a group of higher baseline postprandial glucose levels.

The majority of physicians and patients that participated in the present study were 'very satisfied' or 'satisfied' with this combined acarbose and basal insulin therapy, further supporting its usefulness in controlling hyperglycemia in the daily-life treatment of Korean patients.

Early insulin initiation is the recommended initial treatment for targeting FBG, and helps reach glycemic control treatment

Table 3 | Satisfaction of the combined basal insulin and acarbose treatment

Evaluator	Category	Total (n = 494) n (%)
Investigator	Very satisfied	105 (21.38)
	Satisfied	283 (57.64)
	Unsatisfied	86 (17.52)
	Very unsatisfied	17 (3.46)
Patient	Very satisfied	75 (15.31)
	Satisfied	304 (62.04)
	Unsatisfied	95 (19.39)
	Very unsatisfied	16 (3.27)

Table 4 | Change in blood glucose levels according to patient postprandial blood glucose at baseline

Outcome measurement	Visit	2-h postprandial blood glucose at baseline (mmol/L)				Between P-value
		≤10.9 (n = 84)	>10.9 and ≤12.6 (n = 85)	>12.6 and ≤16.0 (n = 83)	>16.0 (n = 83)	
HbA1c (%)	Baseline	8.30 ± 0.70	8.02 ± 0.48	8.48 ± 0.67	8.88 ± 0.81	0.7770
	Final visit	7.91 ± 1.25	7.59 ± 0.72	7.96 ± 0.94	8.28 ± 1.13	
	Change	-0.40 ± 1.07	-0.43 ± 0.60	-0.52 ± 0.80	-0.60 ± 1.17	
	P-value	0.0055	<0.0001	<0.0001	0.0012	
Fasting blood glucose (mmol/L)	Baseline	6.14 ± 1.47	7.04 ± 1.26	8.04 ± 2.02	8.39 ± 3.92	0.0318
	Final visit	6.38 ± 1.65	6.35 ± 1.08	7.16 ± 1.84	7.15 ± 3.38	
	Change	0.24 ± 1.18	-0.68 ± 1.45	-0.88 ± 2.55	-1.23 ± 3.64	
	P-value	0.3873	<0.0001	0.1039	0.2653	
Postprandial glucose (mmol/L)	Baseline	9.01 ± 1.82	11.81 ± 0.47	14.22 ± 0.86	18.80 ± 3.06	<0.0001
	Final visit	10.38 ± 2.92	10.20 ± 1.95	10.59 ± 3.08	11.74 ± 4.19	
	Change	1.38 ± 3.29	-1.61 ± 1.98	-3.63 ± 3.01	-7.06 ± 5.17	
	P-value	0.0019	<0.0001	<0.0001	<0.0001	

Data are mean ± SD. Change: final visit – baseline. HbA1c, hemoglobin A1c.

goals. A once-daily injection of basal insulin and fewer hypoglycemic events provide a simple-to-manage therapy^{5,6,19,20}, and improve quality of life and treatment satisfaction^{21,22}. A long-acting basal insulin analog plus oral antidiabetic drugs could be beneficial for patients who have problems with hypoglycemic episodes and insulin injection number²³.

Although basal insulin treatment is a simple and effective method to initiate, and is frequently used to control FBG, controlling postprandial glucose can be challenging. The postprandial phase might comprise 60–70% of the day²⁴, and postprandial hyperglycemia is an important component of abnormal glycemic excursions in patients with type 2 diabetes²⁵. The blood glucose fluctuation associated with postprandial hyperglycemia increases oxidative stress, and could influence the onset and progression of cardiovascular complications in patients with type 2 diabetes^{25–28}. Postprandial hyperglycemia is also associated with microvascular complications of diabetes independent of HbA1c or FBG²⁹. Control of postprandial glucose, as well as FBG, are also important in addition to HbA1c, the main glycemic parameter for glucose control³⁰. Furthermore, the majority of patients with type 2 diabetes do not achieve the target range of HbA1c levels for a considerable period of time, which might make them vulnerable to diabetic complications later in life^{31,32}. Therefore, therapeutic strategies to achieve optimal blood glucose control should also reduce glycemic excursions³³. However, the best way to do this is still unclear.

Postprandial glucose targeting drugs, such as α -glucosidase inhibitors, meglitinides or dipeptidyl peptidase-4 inhibitors, might be used in the treatment of type 2 diabetes, and basal insulin therapy combined with oral antidiabetic drugs are particularly safe and effective for managing type 2 diabetes^{34–36}. The addition of oral hypoglycemic agents to only one injection of basal insulin increases the treatment compliance and induces further control over postprandial glycemic excursions²⁰. Similar previous studies also show that combining basal insulin

injection and antidiabetic drugs, such as sulfonylurea and/or metformin, improved postprandial glycemic control^{35–38}.

In the present study, 384 patients (71.2%) were taking other oral antidiabetic drugs and 281 patients (52.1%) were taking metformin. If diabetes control is not improved with these therapies, additional treatment strategies might be considered to include the addition of preprandial rapid acting insulin, injection of premixed insulin two times per day or administration of other preprandial oral antidiabetic drugs. Preprandial rapid acting insulin therapy might be most effective for controlling postprandial glucose, but multiple insulin injections are not easy in a routine clinical setting because of complexity and time-consuming inconvenience. Premixed insulin injections are also more difficult than basal insulin, and they increase the risk of hypoglycemia³⁹. Therefore, adding antidiabetic drugs with different pharmacokinetics or mechanism of action could help patients manage their diabetes more easily.

Asian people, including Koreans, generally eat a relatively high proportion of carbohydrates in their diet, which increases postprandial glucose more rapidly than a low carbohydrate diet does⁴⁰. Asian populations predominantly have an insulin-insufficiency type of type 2 diabetes, whereas Western populations tend to have an insulin-resistance type, which might be related to differences in body anthropometry and insulin secretion capability in the two ethnic groups^{23,34,38,41,42}. Acarbose slows the breakdown of dietary carbohydrates, thereby improving postprandial glycemic control, particularly for Asian people with type 2 diabetes⁴³. In one study of Korean patients with diabetes, nateglinide and acarbose both decreased postprandial glucose levels to target levels after FBG control was established by basal insulin²⁰, showing that acarbose combined with basal insulin could be effective for overall blood glucose control.

The present study had some limitations. This was a non-interventional study, and we did not have a group treated with placebo or another class of antidiabetic drug to compare with. Therefore, there could have been confounding effects in the

interpretation of the present results. Also, this study was carried out under a real clinical environment, permitting combined treatment of other antidiabetic drugs or drugs for dyslipidemia. Although we could assume the effect of these drugs on blood glucose levels, we could not make a conclusion about it in the present study. Nevertheless, we can assume that the confounding effect of these drugs on the results could be minimized, because most of the combined other drugs had been taken before enrolment in the present study.

Although an observational study assesses the effectiveness and safety of treatments under clinical practice conditions, it does not establish causality. A large prospective controlled clinical study should be carried out to elucidate the exact effects of specific oral antidiabetic drugs on postprandial glycaemic control. Furthermore, the present study was carried out over a relatively short-term period, so the results might not represent the long-term efficacy of the treatment.

However, the present study highlights the effectiveness of acarbose when combined with basal insulin in a large sample of Korean patients in a real clinical practice setting. Combined use is gradually increasing as the treatment strategy focused on basal insulin becomes more prevalent. The present findings show that combined insulin and acarbose therapy improves glucose control among different subgroups of patients with type 2 diabetes, and that the majority of clinicians and patients are satisfied with the treatment.

In conclusion, data from a real-life treatment setting in Korea for the combination therapy of basal insulin and acarbose showed it was effective and safe, with high satisfaction both from physicians and patients.

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