Acarbose in NIDDM Patients With Poor Control on Conventional Oral Agents

A 24-week placebo-controlled study

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OBJECTIVE — To determine the efficacy of acarbose, compared with placebo, on the metabolic control of NIDDM patients inadequately controlled on maximal doses of conventional oral agents.

RESEARCH DESIGN AND METHODS — In this three-center double-blind study, 90 Chinese NIDDM patients with persistent poor glycemic control despite maximal doses of sulfonylurea and metformin were randomly assigned to receive additional treatment with acarbose 100 mg thrice daily or placebo for 24 weeks, after 6 weeks of dietary reinforcement. Efficacy was assessed by changes in HbA_{1c}, fasting and 1-h postprandial plasma glucose and insulin levels, and fasting lipid levels.

RESULTS — Acarbose treatment was associated with significantly greater reductions in HbA_{1c} (−0.5 ± 0.2% vs. placebo 0.1 ± 0.2% [means ± SEM], $P = 0.038$), 1-h postprandial glucose (−2.3 ± 0.4 mmol/l vs. placebo 0.7 ± 0.4 mmol/l, $P < 0.001$) and body weight (−0.54 ± 0.32 kg vs. placebo 0.42 ± 0.29 kg, $P < 0.05$). There was no significant difference between the two groups regarding changes in fasting plasma glucose and lipids or fasting and postprandial insulin levels. Flatulence was the most common side effect (acarbose vs. placebo: 28/45 vs. 11/44, $P < 0.05$). One patient on acarbose had asymptomatic elevations in serum transaminases that normalized in 4 weeks after acarbose withdrawal. Another patient on acarbose developed severe hypoglycemia; glycemic control was subsequently maintained on half the baseline dosage of sulfonylurea.

CONCLUSIONS — In NIDDM patients inadequately controlled on conventional oral agents, acarbose in moderate doses resulted in beneficial effects on glycemic control, especially postprandial glycemia, and mean body weight. Additional use of acarbose can be considered as a useful alternative in such patients if they are reluctant to accept insulin therapy.

NIDDM patients with persistent hyperglycemia despite dietary therapy are conventionally treated with oral hypoglycemic agents such as sulfonylurea, metformin, or both. However, secondary failure to oral agents commonly occurs, so that >25% of patients with NIDDM eventually require insulin to achieve glycemic control (1). In addition to the need for daily injections that most patients tend to resist, insulin therapy may promote weight gain and exacerbate insulin resistance (1). It is, therefore, worthwhile to explore the use of alternative treatment options in these patients.

Acarbose is an α-glucosidase inhibitor that, after oral administration, competitively and reversibly inhibits the intestinal α-glucosidases, resulting in dose-dependent reductions in postprandial plasma insulin and glucose peaks (2). It has been shown to be efficacious in improving HbA_{1c} and postprandial hyperglycemia in NIDDM patients, either as a monotherapy (3,4) or in combination with metformin, sulfonylurea, or insulin (5,6). Recent studies suggest that it is also useful in the treatment of IDDM (7). On the other hand, there is limited information on its efficacy in improving glycemic control in NIDDM patients who cannot be adequately controlled on maximal doses of sulfonylurea. Significant improvement in HbA_{1c} by acarbose has been observed in several open studies (8–10). However, in the only fully published placebo-controlled study (11), which involved 28 patients poorly controlled on diet and maximal oral treatment (sulfonylurea and biguanide), acarbose did not achieve any significant reduction in HbA_{1c}, although postprandial hyperglycemia was improved.

In this double-blind placebo-controlled study, we investigated the efficacy and tolerability of acarbose, given for 24 weeks, in 90 Chinese NIDDM patients with poor glycemic control despite diet and maximal doses of conventional oral agents (sulfonylurea and metformin).

RESEARCH DESIGN AND METHODS

— This is a randomized double-blind three-center study involving outpatient treatment with acarbose or placebo, in addition to maximal doses of conventional oral agents, for 24 weeks. All patients had previously been advised by a qualified dietitian on a diet consisting of 30 kcal/kg ideal body wt, 50% carbohydrate (at least 60% of which should be starch), 30% fat, and 20% protein, which was reinforced for 6 weeks before commencement of treatment with acarbose or placebo. Chinese men and women aged 35–70 years with NIDDM for over 6 months and with stable body weight (BMI <30 kg/m²) but high HbA_{1c} levels of 8.4–10.8% (normal ≤6%) on at least two occasions in the past 3 months despite maximal doses of glibenclamide (10 mg twice daily) or gliclazide (160 mg twice daily) and metformin (at the highest tolerable dose) for over 6 months were eligible for recruitment. Exclusion criteria were as follows: serum creatinine >200 μmol/l, serum transaminases two times the upper normal range; significant diseases or conditions, including emotional disorders

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and substance abuse; ketonuria or symptomatic hyperglycemia; gastrointestinal diseases likely to be associated with abnormal gut motility or absorption; known lactose intolerance; and other investigational drugs or medications known to affect glucose homeostasis (such as glucocorticoids) taken in the past 3 months; pregnant and nursing patients were also excluded. A total of 90 subjects (30 per center) fulfilled the recruitment criteria and, after 6 weeks of dietary reinforcement, were randomly assigned in blocks of six patients to receive treatment with either acarbose or placebo for 24 weeks. The investigations were performed in accordance with the principles of the Helsinki Declarations. All patients gave informed consent to a protocol that was approved by the local ethics committee.

Each patient was asked to take 3 tablets/day, one each with the first mouthful of each meal. For acarbose, the dose was 50 mg/tablet for 4 weeks and 100 mg/tablet for 20 weeks. Patients were followed up at 6-week intervals. At each visit, body weight (fasting) and blood pressure were measured; drug compliance was ascertained by counting the tablets returned; and side effects were assessed by history and physical examination and the checking of complete blood counts, urea, creatinine, and liver function. Efficacy was assessed on the basis of the following parameters: HbA_{1c}, fasting and postprandial plasma glucose and serum insulin, fasting cholesterol, triglyceride, and HDL cholesterol levels. Postprandial blood samples were taken 1 h after a standard breakfast that consisted of 369 kcal, 50.7% carbohydrates, 35.8% fat, and 13.6% protein.

Except for serum insulin, which was measured at the laboratory of the Queen Mary Hospital, all other assays were performed in each individual center. Plasma glucose was measured by the glucose oxidase method on a Beckman autoanalyzer (Beckman Instruments, Brea, CA). HbA_{1c} was measured using the DCA2000 Hemoglobin A1c System (Miles, Elkhart, IN), which used a specific immunochemical assay. Quality control checking using two standard reference samples was carried out at regular intervals in the three centers: between-run coefficients of variation were 5.6 and 3.3% at HbA_{1c} of 5.8 and 10.1%, respectively. Serum insulin was determined with a microparticle enzyme immunoassay on an Abbott IMx system (Abbott, Abbott Park, IL), using a monoclonal mouse anti-human insulin antibody. Intra- and interassay coefficients of variation were <4%. Plasma lipid levels and renal and liver function tests were measured using standard clinical laboratory methods as previously reported (12).

Student's *t* tests and Fisher's exact test were used for the comparison of continuous and categorical variables, respectively. All subjects who received study medications for >18 weeks were considered to be eligible for efficacy analysis (per protocol). The primary efficacy end point was defined to be the change in HbA_{1c} between week 0 and week 24; secondary efficacy end points included the corresponding fasting and 1-h postprandial glucose and insulin changes. For subjects who dropped out after 18 weeks, the values at 18 weeks were taken to calculate the changes from week 0. For safety analysis, all subjects who received at least one dose of study medications were included.

Table 1—*Baseline clinical characteristics*

	Acarbose	Placebo
n	45	44
Sex (M/F)	20/25	19/25
Age (years)	57.8 ± 1.3	56.9 ± 1.3
BMI (kg/m²)	24.8 ± 0.5	24.1 ± 0.4
Systolic blood pressure (mmHg)	135.9 ± 3.0	132.2 ± 2.9
Diastolic blood pressure (mmHg)	77.4 ± 1.7	76.4 ± 1.5
Duration of NIDDM (months)	122.0 ± 8.4	121.5 ± 9.9
HbA_{1c} (%)	9.5 ± 0.1	9.4 ± 0.1
Fasting plasma glucose (mmol/l)	11.1 ± 0.4	11.3 ± 0.5
1-h postprandial plasma glucose (mmol/l)	16.6 ± 3.2	16.9 ± 3.6
Use of metformin	41 (91)	40 (91)

Data are *n*, means ± SEM, or *n* (%).

RESULTS — Of the 90 subjects recruited, one patient in the placebo group dropped out after randomization without receiving any medication. The clinical characteristics at recruitment (week −6) of the remaining 89 subjects are summarized in Table 1. There was no significant difference between the acarbose and placebo groups in any of the clinical parameters, including HbA_{1c} and fasting and postprandial glucose levels. Of the subjects in each group, 91% were on metformin, in addition to maximal doses of glibenclamide or gliclazide; the others were intolerant to metformin. Mean dosage of metformin was (mean ± SD) 1.79 ± 0.75 (*n* = 41) and 1.79 ± 0.78 gm/day (*n* = 40) in the acarbose and placebo groups, respectively.

Drug compliance was similar between the two groups, being satisfactory (consuming >80% of the prescribed medications) in 89 and 93% of the acarbose and placebo groups, respectively. The dosage of all concurrent medications remained unchanged throughout the study period except in one patient on acarbose in whom the dosage of sulfonylurea had to be reduced because of hypoglycemia. The dropout rate was also similar in the two groups, with five patients on acarbose and four patients on placebo withdrawn from the study before 24 weeks. The reasons for withdrawal were as follows: gross drug noncompliance (*n* = 3), intercurrent illness (*n* = 3), and adverse events (*n* = 2 in the placebo group and *n* = 1 in the acarbose group because of raised serum transaminases). Thus, 83 and 80 patients received 18 and 24 weeks of medications, respectively. Because of missing data from two patients (one on acarbose and one on placebo), the efficacy analysis was based on data from 81 patients (representing 91% of patients treated with either acarbose or placebo).

As shown in Table 2, mean HbA_{1c} decreased in the acarbose group but increased in the placebo group during the treatment period so that the change in HbA_{1c} was significantly different between the two groups ($P < 0.05$). There was no significant difference in the change in fasting plasma glucose levels, but the reduction in 1-h postprandial plasma glucose was significantly greater in the acarbose group ($P < 0.001$ vs. placebo) (Fig. 1). Changes in plasma insulin levels, either fasting (acarbose vs. placebo: 0.4 ± 0.4 vs. −0.1 ± 0.5 mU/l or 5 ± 5% vs. −1 ± 7%) or 1-h postprandial (acarbose vs. placebo: −3.8 ± 1.3 vs. −1.7 ± 1.3 mU/l or −21 ± 7% vs. −10 ± 8%), were not significantly different between the two groups. When the acarbose-treated patients were

Table 2—*Analysis of efficacy: HbA_{1c}*

	Acarbose	Placebo
n	41	40
Week 0	9.3 ± 0.2	9.3 ± 0.2
Week 18/24	8.8 ± 0.2	9.4 ± 0.2
Change between week 0 and week 18/24	−0.5 ± 0.2*	0.1 ± 0.2

Data are *n* or means ± SEM. *P = 0.038 vs. placebo.

divided into responders (reduction in HbA_{1c} ≥0.5%) and nonresponders (reduction in HbA_{1c} <0.5%), there was no significant difference between responders (n = 20) and nonresponders (n = 21) with respect to age, sex distribution, BMI, known duration of diabetes, use of metformin, dosage of metformin, or baseline HbA_{1c} and fasting or 2-h plasma glucose levels.

The mean body weight showed a reduction in the acarbose group but increased in the placebo-treated patients (Table 3), so that the change in body weight over the treatment period was significantly different between the two groups (P < 0.05). No significant difference was observed between the two groups regarding the changes in fasting plasma triglyceride, total cholesterol, or HDL cholesterol levels (Table 3).

Gastrointestinal symptoms, especially flatulence, were the most common side effects experienced (Fig. 2). The symptoms were usually mild in nature, and were considered to be of moderate severity only in three patients in the acarbose group who complained of flatulence. One patient in the acarbose group had severe hypoglycemia that required treatment with intravenous glucose in the emergency room; his glycemic control was subsequently maintained on half of the baseline dosage of sulfonylurea. Another patient in the acarbose group was found at 6 weeks to have persistently increased transaminase levels up to three times the upper normal range that were not accompanied by changes in other liver function tests. He was completely asymptomatic, and transaminase levels normalized within 4 weeks after withdrawal of acarbose. No rechallenge with acarbose was performed. Liver ultrasonogram was normal and serologies for hepatitis A, B, and C were negative.

CONCLUSIONS — In this double-blind controlled study, acarbose, given at a moderate dose of 100 mg thrice daily for 24 weeks (18 weeks in three patients) in NIDDM patients with poor control on maximal conventional oral agents, resulted in significantly greater improvement in HbA_{1c} and postprandial glucose levels when compared with treatment with placebo. The improvement in glycemic control was accompanied by a significant reduction in body weight relative to placebo treatment. In a previous multicenter study, a beneficial effect of acarbose was also reported, in that the weight gain associated with tolbutamide treatment can be attenuated by concomitant use of acarbose (6). The small weight loss in the acarbose-treated patients may be related to a reduction in postprandial hyperinsulinemia, consequent to the reduction in postprandial glycemia.

The discrepancy between this and a previous placebo-controlled study that failed to demonstrate an improvement in HbA_{1c} in NIDDM patients with oral drug failure can probably be explained by the shorter treatment duration and much smaller sample size of the other study (11). The improvement in both HbA_{1c} and postprandial hyperglycemia in these patients with oral drug failure and long-standing diabetes was in fact comparable to that observed in patients with dietary failure and considerably shorter mean duration of known diabetes (13,14). This is probably not surprising because the major difference between the two categories of NIDDM patients lies in the level of their residual β-cell function, which should not affect their response to acarbose, a drug that works largely by altering intestinal carbohydrate digestion and absorption. This mechanism of action is reflected by the highly significant reduction in postprandial glycemia but much less impressive change in fasting plasma glucose, any reduction of which probably results from decreased glucose toxicity consequent to the overall improvement in glycemic control. Whether the better response to acarbose, compared with that found in the North American study (11), could be explained by the higher content of complex carbohydrates in the traditional Chinese diet remains to be determined by comparative studies involving both ethnic groups.

The improvement in glycemic control observed in the acarbose-treated patients was not accompanied by changes in basal or meal-stimulated insulin levels, in agreement with previous studies using similar or higher doses of acarbose (5,6,8,14). Acarbose has also been shown to have no significant effect on insulin sensitivity, as reflected by insulin-stimulated glucose utilization (8,15), or basal hepatic glucose output (15). There have been isolated reports of reductions in fasting (8) or post-meal triglyceride (13) levels, which have been attributed to improvements in glycemic control and reduction in postprandial hyperinsuline-

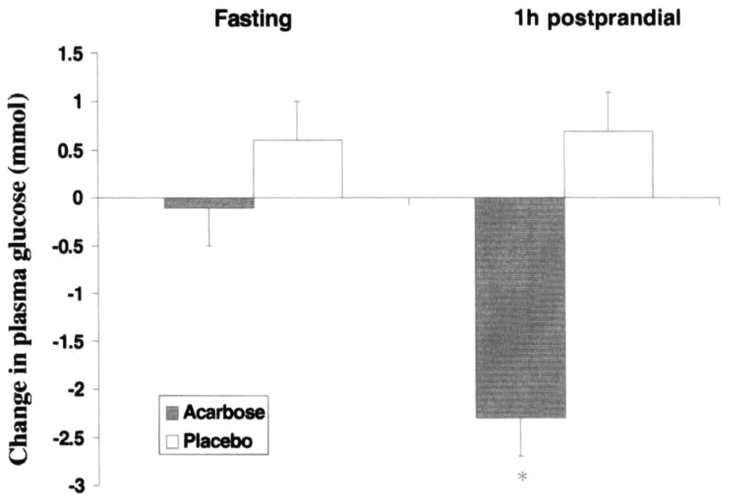

Figure 1—*Changes from baseline in fasting and 1-h postprandial plasma glucose levels (means ± SEM) after 18–24 weeks of treatment with acarbose* (n = *41) or placebo* (n = *40). *P < 0.001 vs. placebo.*

Table 3—*Changes from baseline in body weight and plasma lipid levels*

	Acarbose	Placebo
n	41	40
Body weight (kg)	−0.54 ± 0.32*	0.42 ± 0.29
Triglyceride (mmol/l)	0.16 ± 0.26	−0.22 ± 0.17
Cholesterol (mmol/l)	−0.09 ± 0.13	−0.05 ± 0.13
HDL cholesterol (mmol/l)	−0.06 ± 0.04	−0.06 ± 0.03

Data are *n* or means ± SEM. *$P < 0.05$ vs. placebo.

mia, respectively. However, significant reductions in fasting lipid levels, relative to placebo, have not been observed in most multicenter long-term studies on acarbose treatment (5,6). In this study, the use of acarbose was also not associated with any significant change in fasting lipid levels.

Similar to findings in studies in Caucasians, the side effects observed in these Chinese subjects were mainly gastrointestinal. Flatulence and diarrhea were the most common complaints, and two patients had mild nonspecific abdominal pain. The incidence of all three abdominal side effects was considerably lower than that reported in the multicenter studies, which used higher doses of up to 200 mg thrice daily (5,6), suggesting that the occurrence of such side effects is likely to be dose-dependent. On the other hand, allowing for the difference in patient characteristics, the improvement in HbA_{1c} in the present study was similar to that reported using the higher doses (5,6), suggesting that at least in this Chinese population, 100 mg thrice daily may be the optimal dose. The incidence of gastrointestinal side effects was also lower than that reported in a study on Caucasians treated with the same dose (14). This difference may be explained, at least in part, by the use of a lower dose of 50 mg thrice daily in the initial 4 weeks. Whether there is any ethnic difference in drug reaction with regard to acarbose cannot be concluded from the present study.

Systemic side effects due to acarbose are rarely encountered (4–6,13,14), since only ~1% of the dose is absorbed into the systemic circulation after oral administration (2). The incidence of elevated transaminase levels up to three times the upper normal range, asymptomatic and reversible with drug withdrawal, varied from 0 (5,13) to 4% (6,14) in reported series, and were usually observed with the higher doses of 200 or 300 mg thrice daily (6,14). It has been suggested that nutritional alterations induced by acarbose may play a role in this phenomenon (6,16). In this study, elevated transaminase levels were observed in one patient on acarbose despite the use of a lower dose of 100 mg thrice daily. Although rechallenge with acarbose was not performed, our observation suggested that mild and asymptomatic disturbance in liver function may occur even with lower doses of acarbose. Indeed, it has recently been reported that clinically significant hepatotoxicity may be induced by acarbose at the dose used in this study (17). Monitoring of serum transaminase levels during acarbose treatment may be warranted.

Although acarbose alone is not expected to appreciably lower fasting glucose levels, hypoglycemic episodes were shown to be increased when acarbose was used together with tolbutamide (6). In this study, despite prior advice to reduce the sulfonylurea dosage in case of symptoms of hypoglycemia, one patient developed severe hypoglycemia requiring emergency treatment, and with the concurrent use of acarbose, glycemic control could be maintained on half of the previous dosage of sulfonylurea. Considering that the mean reduction in HbA_{1c} was 0.5% and mean fasting glucose was not significantly reduced for the group as a whole, the observation in this patient provided a good illustration of the large individual variation in the clinical response to acarbose. In an open study on 12 patients with sulfonylurea failure (8), considerable individual variation in the response to acarbose has also been observed, with dramatic reductions in both fasting and postprandial glucose concentrations observed in four patients. Although the possibility of hypoglycemia occurring as a result of better compliance to diet could not be excluded, its occurrence was more likely the effect of acarbose treatment, since, in this double-blind placebo-controlled study, all patients underwent 6 weeks of dietary reinforcement before commencement of treatment with acarbose or placebo.

The present study has demonstrated the efficacy of the additional use of acarbose in NIDDM patients who cannot be adequately controlled on maximal doses of conventional oral agents. This can be considered as an alternative to insulin therapy and may be more advantageous than insulin therapy with regard to weight gain and hyperinsulinemia.

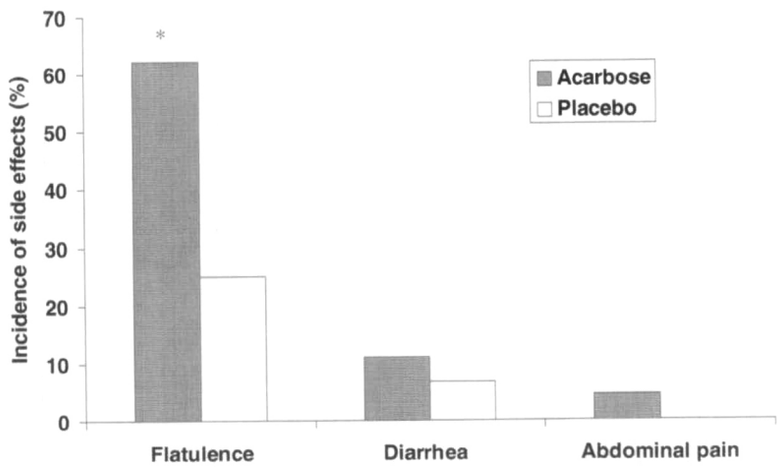

Figure 2—*Gastrointestinal side effects of acarbose* (n = *41*) *or placebo* (n = *40*). *P < *0.05 vs. placebo.*

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