Safety and efficacy of acarbose in the treatment of diabetes in Chinese patients

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Abstract: Acarbose is an α-glucosidase inhibitor that is commonly used to control postprandial blood glucose. It functions as a competitive and reversible inhibitor of small intestinal brush border glucosidase, blocks the degradation of starch and sucrose, and delays the absorption of glucose and fructose in the alimentary tract. The starch content of a diet might alter the hypoglycemic effects of acarbose because of its mechanism of action. Chinese individuals consume a typical Eastern diet, which is characterized by a high intake of whole grains, legumes, vegetables, fruits, and fish. These dietary habits allow acarbose to be used extensively in the People’s Republic of China. Several Chinese-based studies have demonstrated that the use of acarbose as a monotherapy had similar effects on other anti-diabetes agents in decreasing glycosylated hemoglobin (HbA1c) and blood glucose levels, and acarbose in combination with other anti-diabetic drugs could further reduce blood glucose and decrease the mean amplitude of glycemic excursions. Importantly, acarbose is safe and well tolerated, with a low incidence of adverse effects. This article provides a comprehensive review of the safety and efficacy of acarbose for the treatment of diabetes in Chinese patients.

Keywords: acarbose, α-glucosidase inhibitor, efficacy, safety

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem, and an increasing cause of morbidity and mortality. However, the etiology and pathogenesis of T2DM are not fully understood. Controlling blood glucose in diabetic patients continues to be a major therapeutic strategy. Accumulating evidence has revealed that the effective control of blood glucose could reduce various diabetic complications.1–4 Furthermore, the UK Prospective Diabetes Study reported that the benefits of tight blood glucose control extended well beyond the end of the study, and even persisted for 10 years.5 Postprandial glucose is a key predictor of premature death6–8 that contributes to hyperglycemia and elevated glycosylated hemoglobin (HbA1c) levels.9–12 Therefore, controlling post-prandial glucose is very important for reducing HbA1c levels and preventing diabetic complications in patients with T2DM.

Alpha-glucosidase inhibitors (AGIs), such as acarbose, are commonly used oral hypoglycemic agents in the People’s Republic of China. AGIs primarily target α-glucosidase in the small intestine, where α-glucosidase catabolizes non-absorbable complex carbohydrates into absorbable monosaccharides. Acarbose is a competitive and reversible inhibitor of small intestinal brush border glucosidase, which blocks the degradation of starch and sucrose, and delays the absorption of glucose and fructose in the upper small bowel (Figure 1).13 This reduces blood glucose concentrations, particularly postprandial levels.14–16
Dietary starch content might alter the hypoglycemic effect of acarbose because of its mechanism of action. A meta-analysis was performed to compare the differences in the hypoglycemic effect of acarbose in Eastern and Western individuals according to the starch content of their diets. The results suggested that acarbose exerts more potent hypoglycemic effects in T2DM patients who consume an Eastern diet than those consuming a Western diet; its effects were similar to sulfonylureas, metformin, and glinides.

Dietary patterns evolve over time, and income, food prices, individual preferences and beliefs, and cultural traditions, as well as geographical, environmental, social, and economic factors, all interact in a complex way to shape dietary habits. Food consumption in Eastern individuals is characterized by a higher intake of whole grains, legumes, vegetables, fruits, and fish, whereas a Western diet is characterized by a higher intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains. Although Asian diets in recent years have shifted away from cereals and toward a more typical Western pattern of animal and dairy products, fats, and oils concurrent with rapid economic growth, urbanization, and globalization in this region, at least 50%–60% of the total calories in Asians are still obtained from cereals.

Acarbose was first marketed in the People’s Republic of China in 1995 as an oral agent used mainly to regulate postprandial glucose in patients with T2DM. A lot of clinical evidence has suggested that acarbose is an effective drug for controlling postprandial glucose in Chinese patients with T2DM. Recently, a study based in Chinese patients with T2DM demonstrated that acarbose had a similar efficacy to metformin, and that more bodyweight was lost in the acarbose-treated group. The authors concluded that acarbose is a viable choice for initial therapy in Chinese patients with newly diagnosed T2DM.

This review summarizes the efficacy and safety of acarbose for treating Chinese patients with T2DM.

### Therapeutic efficacy

#### Monotherapy

The efficacy of acarbose in Chinese patients with T2DM has been confirmed in a number of controlled trials. Most of these studies were designed to assess the potential non-inferiority of acarbose compared with other therapeutic agents. These data confirmed that acarbose had similar efficacy to other anti-diabetic drugs, including vildagliptin, nateglinide, and metformin, in terms of reducing HbA1c and fasting and postprandial glucose levels. Furthermore, acarbose was more effective at decreasing bodyweight than was vildagliptin and metformin in Chinese T2DM patients (Table 1). However, changes in bodyweight were not evaluated in three

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**Table 1** Comparison of effects of acarbose and other anti-diabetic agents

| Study     | Duration (weeks) | Drugs/comparators   | Patients (n) | Main outcomes                                                                 | Other outcomes                                                                 |
|-----------|------------------|---------------------|--------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Pan et al24 | 24               | Acarbose/vildagliptin | 441/220      | Decreased HbA1c and fasting plasma glucose were similar in both groups         | Bodyweight was decreased more in the acarbose group than in the vildagliptin group |
| Gao et al27 | 9                | Acarbose/nateglinide  | 16/16        | Postprandial glucose was decreased to a similar extent in both groups         | Nateglinide significantly increased postprandial insulin release and decreased FFA concentrations |
| Lu et al28 | 4                | Acarbose/nateglinide  | 80/80        | Postprandial glucose was decreased to a similar extent in both groups         | Nateglinide improved lipid metabolism under postprandial conditions more than acarbose |
| Zhou et al29 | 2               | Acarbose/nateglinide  | 52/51        | AUCpp and IGP were decreased to a similar extent in both groups               | Both treatment groups exhibited significantly improved intra- and inter-day glycemic excursions  |
| Yang et al26 | 48              | Acarbose/metformin    | 391/393      | HbA1c was decreased to a similar extent in both groups                        | Bodyweight was decreased more in the acarbose group than in the metformin group |

Abbreviations: AUCpp, area under the curve of postprandial blood glucose; FFA, free fatty acid; HbA1c, glycosylated hemoglobin; IGP, incremental glucose peak.
Acarbose as an add-on therapy to sulfonylureas

In a multicenter, randomized, double-blinded study performed in the People's Republic of China, patients with insufficiently controlled blood glucose who received a fixed dose of sulfonylureas for 4 weeks before the study exhibited significantly reduced HbA1c and blood glucose levels after 12 weeks of add-on treatment with acarbose 50 mg tid. An additional study of acarbose in Asian patients with T2DM.
that was inadequately controlled by diet and sulfonylureas revealed that treatment with acarbose 100 mg tid for 24 weeks was associated with significantly greater reductions in HbA1c (0.9% vs 0.13%, \(P=0.0018\)) and 1-hour postprandial blood glucose levels (2.84 mmol/L vs 0.28 mmol/L, \(P=0.002\)) compared with placebo.\(^ \text{38} \) These studies suggest that the use of acarbose in Asian patients with T2DM that is inadequately controlled by diet and sulfonylureas improves metabolic control and is safe and well tolerated.

### Acarbose as an add-on therapy to metformin

The use of acarbose as an add-on therapy to sulphonylureas and/or metformin could further reduce blood glucose and HbA1c levels in Chinese T2DM patients.\(^ \text{38} \) Acarbose (50 mg tid) or glibenclamide (2.5 mg tid) were used as add-on drugs for 4 weeks in a population of adult Taiwanese patients with T2DM that was inadequately controlled by metformin monotherapy (1,500 mg od); the doses were then doubled in the subsequent 12 weeks. Although both agents could significantly reduce HbA1c levels, the mean amplitude of glycemic excursions (MAGE) (5.6 mmol/L vs 4.0 mmol/L, \(P<0.001\)), bodyweight (69.8 kg vs 68.3 kg, \(P<0.01\)), and serum triglycerides (1.2 mmol/L vs 0.9 mmol/L, \(P<0.01\)) decreased only in patients treated with acarbose.\(^ \text{39,40} \) A subsequent study, also performed in Taiwanese T2DM patients, suggested that 16 weeks of fixed-dose combination therapy with acarbose (50 mg tid) plus metformin (500 mg tid) resulted in significantly more T2DM patients reaching their HbA1c goal compared with those receiving acarbose 50 mg tid monotherapy (the proportion of patients who achieved HbA1c <7.0% was 47.8% vs 10.7%, respectively; \(P<0.0001\)). Combination therapy also further reduced bodyweight compared with monotherapy (1.7 kg vs 1.0 kg, respectively, \(P<0.01\)). The authors concluded that acarbose/metformin fixed-dose combination therapy was well tolerated, with no significant risk of hypoglycemia; therefore, it might be a useful treatment for T2DM.\(^ \text{41} \)

### Acarbose as an add-on therapy to insulin

A study was performed to evaluate the characteristics of glycemic variability in Chinese T2DM patients with HbA1c <6.5%. All patients were administered premixed insulin twice daily; 86 patients were also treated with acarbose 50 mg tid for 2 weeks. A continuous glucose monitoring system was used to assess all patients. After combination therapy with acarbose, MAGE, and the mean of daily differences were decreased significantly compared with the insulin monotherapy group (40%, \(P<0.01\) and 15%, \(P<0.05\), respectively). In addition, the incidence of hypoglycemic events was decreased significantly (2% vs 24%, \(P<0.01\)). This study concluded that combination therapy with premixed insulin bid with acarbose could reduce glycemic variability and decrease hypoglycemic events.\(^ \text{42} \)

Consistent with the above study, adjunctive therapy with acarbose 100 mg tid provided an efficacious and safe method for improving glycemic control in Asian patients with T2DM that was insufficiently controlled with insulin. Specifically, combination therapy with acarbose caused greater reductions in HbA1c (0.5% vs 0.2%, \(P=0.008\)) and 1-hour postprandial glucose levels (1.33 mmol/L vs 0.67 mmol/L, \(P=0.029\)) compared with placebo.\(^ \text{43} \)

### Effects of acarbose on cardiovascular disease

Epidemiological data have suggested that hyperglycemia is a continuous risk factor for CVD, and that 2-hour postprandial glucose levels are more strongly associated with CVD than fasting glucose. Postprandial hyperglycemia plays a major role in vascular damage, particularly via non-traditional risk factors such as oxidative stress and subclinical inflammation. Data have suggested that acarbose could prevent this damage and reduce the risk of CVD.\(^ \text{44} \)

Acarbose can decrease the activity of the transcription factor nuclear factor kappa B (NF-kB) in the peripheral blood mononuclear cells of T2DM patients. NF-kB activation is associated with inflammation, which leads to the development of endothelial dysfunction and atherosclerosis.\(^ \text{45} \) Acarbose can also reduce the levels of coagulation markers and postprandial fibrinogen, reduce the circulating levels of cell adhesion molecules, and delay the thickening of the intima-media in patients with T2DM.\(^ \text{46,47} \) Acarbose could also improve lipid profiles by reducing low-density lipoprotein (LDL) levels, leading to a significantly improved high-density lipoprotein (HDL)/LDL ratio, and also by reducing postprandial hyperglycemia. In addition, acarbose reduces oxidative stress, endothelial dysfunction, dyslipidemia, and thrombosis in individuals with dysglycemia.\(^ \text{48} \)

The effects of acarbose on vascular damage translate into improved clinical outcomes in patients with both pre-diabetes and established T2DM. In the Study to Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM), acarbose reduced the risk of any cardiovascular event by 49% and absolute risk by 2.5% compared with placebo.\(^ \text{48} \) In a sub-study of STOP-NIDDM, acarbose treatment was associated with a –50% reduction in the annual mean increase
in intima-media thickness. Furthermore, a meta-analysis of studies assessing the use of acarbose in patients with T2DM suggested a significant reduction in CVD-related events.

Although there is no direct evidence that acarbose could reduce the risk of CVD in Chinese T2DM patients, it could effectively reduce many CVD risk factors in this patient population, including postprandial hyperglycemia, MAGE, HbA1c, lipid parameters, and bodyweight.

Safety and tolerability

Side effects

Clinical and surveillance studies have revealed that acarbose treatment is associated with very few serious side effects. The most common side effects reported to date are mild-to-moderate gastrointestinal disorders, such as flatulence, abdominal distension, diarrhea, and dyspepsia, which arise from the fermentation of undigested carbohydrates by colonic bacteria in the large intestine. These disorders usually subside as treatment continues, which might be due to increased α-glucosidase activity in the lower segments of the small intestine. Gastrointestinal disorders are always transient and moderate if treatment is started at low doses and then increased gradually.

Following oral administration, acarbose is only absorbed into the systemic circulation to a very minor extent (<2%); consequently, systemic side effects are not normally anticipated. Indeed, no systemic side effects of acarbose have been reported in the clinical studies performed to date. Specifically, there were no significant changes in complete blood counts, urine analysis, and blood chemistry values over time. Acarbose was well tolerated irrespective of patient age, pre-treatment, or the number of concomitant diseases. Moreover, clinical trials assessing acarbose revealed that it was well tolerated, and that the adverse experience profile was clinically acceptable. A dose of acarbose 100 mg tid, alone or in combination with other anti-diabetic drugs, was safe and well tolerated in Chinese T2DM patients. Nevertheless, the dose might need to be reduced in patients with troublesome gastrointestinal symptoms.

Risk of hypoglycemia

The current approach to diabetes treatment consists of multi-drug regimens. However, concerns have been raised regarding intensive glucose control and the possibility that the rapid reduction in HbA1c levels might result in increased mortality, possibly as a result of increased hypoglycemia. Therefore, it is important to recognize that acarbose is associated with a low incidence of hypoglycemia in Chinese or Asian individuals, suggesting that it is suitable for use in combination therapy. If blood glucose falls into the hypoglycemic range when acarbose is prescribed with other agents such as sulphonylureas, metformin, or insulin, the prescribed dose of the co-administered agent might need to be decreased.

Contraindication

AGIs are contraindicated in patients with known hypersensitivity to the drug, in individuals with diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction as well as those predisposed to intestinal obstruction. They are also contraindicated in patients with chronic gastrointestinal diseases associated with marked digestion or absorption disorders and those with conditions that might deteriorate as a result of increased gas formation in the intestine.

Conclusion

Acarbose is a potential option for the treatment of Chinese T2DM patients. It is effective, safe, and well tolerated, both as a monotherapy and as an add-on to additional anti-diabetic agents in patients with uncontrolled T2DM. The hypoglycemic effects of acarbose are similar to those of sulfonylureas, metformin, and glinides. However, it elicits superior effects on reducing bodyweight and glycemic variability in Chinese T2DM patients. Acarbose is safe and well tolerated, and is associated with a low incidence of gastrointestinal adverse effects; it is well accepted for the treatment of diabetes in Chinese patients. Acarbose is a viable choice for use as an initial therapy in Chinese patients with newly diagnosed T2DM.

Disclosure

The authors report no conflicts of interest in this work.

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