

Acarbose Reduces Low-Grade Albuminuria Compared to Metformin in Chinese Patients with Newly Diagnosed Type 2 Diabetes

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Purpose: To assess the effect of acarbose in lowering low-grade albuminuria compared to metformin in newly diagnosed Chinese type 2 diabetes (T2DM) patients.

Patients and Methods: The Metformin and AcaRbose Clinical Trial was a randomized, open-label trial in newly diagnosed T2DM patients. Participants received 48 weeks of monotherapy with acarbose (100 mg three times a day) or metformin (1500 mg once a day). As the hypoglycemic effect of acarbose and metformin has been evaluated in previous reports. This analysis studied the effect of the two antidiabetic drugs on reducing urinary albumin. The percent change in the urinary albumin/creatinine ratio (uACR) from baseline to week 48 was analyzed, and ANCOVA was employed to establish whether the effect in decreasing uACR was mediated by metabolic improvement.

Results: Acarbose reduced the adjusted mean percent uACR by -31.5% (95% confidence interval [CI] -48.4 to -7.5) compared with metformin. When adjusting for changes in glycated hemoglobin, body weight, systolic blood pressure and triglycerides or changes in area under the curve of glucagon-like peptide 1 (AUCGLP-1) in the standard meal test, the uACR-lowering effect was not attenuated. If stratified by eGFR, blood glucose level, sex or uACR level, the effect of acarbose versus metformin was consistent across subgroups. The proportion of patients with a reduction in uACR of at least 70% was 48.6% in the acarbose group and 34.1% in the metformin group.

Conclusion: Acarbose lowered the uACR compared to metformin in newly diagnosed T2DM patients independent of improvements in hyperglycemia, blood pressure, body weight and triglycerides.

Keywords: diabetes mellitus, type 2, diabetic nephropathies, hypoglycemic agents

Introduction

Microalbuminuria, defined as a urinary albumin/creatinine ratio (uACR) higher than 30 mg/g, is believed to be an important marker of early-stage diabetic nephropathy.¹⁻⁵ In particular, microalbuminuria predicts renal structural damage in patients with early diabetes mellitus when the glomerular filtration rate (GFR) is preserved (higher than 60 mL/min).⁶ However, the normal range of the uACR has been challenged during the past decade. Recent studies have shown that even mild urinary albumin excretion, such as uACR <30 mg/g, also named low-grade albuminuria, is a high-risk factor for diabetic nephropathy and atherosclerotic cardiovascular diseases (ASCVDs).⁷⁻¹⁰ According to the Hypertension Genetic Epidemiology Network (HyperGEN) Study, low-grade uACR is associated with adverse cardiac mechanics and a higher E/e' ratio.⁸

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In healthy people with normal blood pressure and normal blood glucose levels, low-grade albuminuria independently predicts the incidence rate of ASCVD and all-cause mortality.⁹ The Heart Outcomes Prevention Evaluation (HOPE) study found that uACR levels were continuously associated with cardiovascular events. At the 4.4 mg/g uACR level, every 3.0 mg/g increase in uACR increased major cardiovascular events by 5.9%.¹⁰ Mild albuminuria is also an important risk factor for ischemic stroke.¹¹ In addition, mild albuminuria is believed to be associated with an increase in the prevalence of other metabolic disorders, such as osteoporosis.¹² In view of the increasing evidence that low-grade urinary albumin excretion that is lower than the current cut point for microalbuminuria is closely related to ASCVD as well as other metabolic diseases, therapy that aims to reduce urinary albumin even at levels below 30 mg/g deserves attention.

The Metformin and AcaRbose in Chinese as the initial Hypoglycemic treatment (MARCH) trial gave acarbose or metformin monotherapy to newly diagnosed T2DM patients. Acarbose was assessed as an initial treatment compared to metformin. The study reported that both acarbose and metformin had similar efficacy in reducing HbA1c levels, improving insulin sensitivity and alleviating abdominal obesity. The aim of this post hoc analysis was to assess the efficacy of acarbose compared to metformin in reducing urinary albumin excretion in patients with newly diagnosed T2DM and low-grade albuminuria or microalbuminuria.

Methods

Subjects

This study was registered in the Chinese Clinical Trial Registry (ChiCTR) and was a multicenter, open, randomized controlled trial. The key inclusion criteria were as follows: all patients had been diagnosed with T2DM according to the 1999 WHO criteria within the past 12 months; they either did not receive any antidiabetic treatment or received treatment for less than one month that was discontinued three months before enrollment; age was between 18 and 75 years; HbA1c level was between 7% and 10%; and fasting plasma glucose (FPG) level was lower than 11.1 mmol/L. The detailed exclusion criteria were described in a previous report.¹³ In total, 788 patients were recruited from 11 clinical sites in China and randomized. All participants were randomly assigned (1:1) to

the two treatment groups (block size 8). Both patients and researchers knew about the treatment allocation.

Clinical Procedures

Detailed clinical procedures were described in our previously published articles.¹³ The study profile has been published elsewhere.¹³ In brief, after a 4-week run-in phase with lifestyle modification, patients were assigned to receive metformin up to 1500 mg once daily (Beijing Double Crane Pharma, Beijing, China) or acarbose up to 100 mg three times a day (Bayer Healthcare, Beijing, China). At 24 weeks, insulin secretagogues were added to patients with fasting blood glucose higher than 7 mmol/L or postprandial blood glucose higher than 10 mmol/L. The study lasted for 48 weeks.

Outcomes

The uACR percent change from baseline to week 48 was calculated. Urine albumin and creatinine were measured by a single urine sample. Other endpoints were the absolute mean change in HbA1c, systolic blood pressure (SBP), body weight evaluated glomerular filtration rate (eGFR), triglycerides and AUCGLP-1 in the standard meal test.

Statistical Analysis

SPSS 25.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The variables with a normal distribution are expressed as the means and standard deviation (SD). The parameters of the two treatment groups were compared by two-tailed independent sample t-tests. The variables with skewed distributions are expressed as the medians and interquartile distances (IQRs). The proportions of patients with absolute reductions in uACR from baseline to week 48 ($\geq 30\%$, $\geq 50\%$ and $\geq 70\%$) were calculated.

To analyze the percentage reduction of uACR from baseline to week 48, first, the uACR values (including baseline and week 48) were logarithmically transformed: \ln baseline uACR and \ln week 48 uACR. Then, ANCOVA was used to analyze the percentage change of uACR from baseline to week 48 (\ln [week 48 uACR/baseline uACR]). Finally, the percentage change of the main outcome uACR from baseline was expressed by the least squares geometric mean estimate and the corresponding two-sided 95% confidence interval (CI).

Model 1 included the treatment group and antihypertensive drug type (using angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers or not) as fixed

effects and ln uACR as a covariate. In model 2, log changes from baseline to week 48 in HbA1c, eGFR, body weight, SBP and triglycerides were added to model 1 as covariates. In model 3, log changes from baseline to week 48 in AUCGLP-1 were added to model 2 as a covariate.

To explore whether differences in the reduction in uACR between acarbose and metformin were consistent across subgroups, subgroup analyses included uACR category (uACR < 30 mg/g or uACR ≥ 30 mg/g, eGFR category (eGFR < 90 mL/min or eGFR ≥ 90 mL/min), HbA1c category (HbA1c < 7.0% or HbA1c ≥ 7.0%) and sex category (female or male). The proportion of improvement from microalbuminuria to normal albuminuria was also analyzed.

Results

Baseline Characteristics

From November 8, 2008, to June 27, 2011, a total of 784 patients received the two treatments (788 patients were randomly assigned to treatment groups, and four withdrew before the intervention). A total of 711 participants completed 48 weeks of therapy with acarbose or metformin. Only five patients in the acarbose group and three patients in the metformin group received insulin secretagogues as

add-on therapy after 24 weeks of monotherapy. This post hoc analysis included 604 patients who completed 48 weeks of treatment and had a baseline uACR higher than 4.4 mg/g. There were 299 participants in the acarbose group and 305 participants in the metformin group. Baseline metabolic characteristics were comparable between the two groups (Table 1).

Changes in uACR Following Acarbose or Metformin Therapy

Both acarbose and metformin treatment resulted in an adjusted mean percent decrease in the uACR from baseline to week 48 (acarbose: -73.8% with 95% CI -78.8 to -67.6; metformin: -61.7% with 95% CI -69.1 to -52.6, difference: -31.5% with 95% CI -48.4 to -7.5). In model 2, log changes in HbA1c, SBP, eGFR, and body weight were included to adjust the influence of metabolic changes on the reduction in uACR. The results showed that the effect of acarbose on reducing the uACR compared to metformin was not weakened after adjustment for changes in HbA1c, eGFR, body weight, SBP and triglycerides (acarbose: -73.2% with 95% CI -78.3 to -66.9, metformin: -62.7% with 95% CI -69.9 to -53.7, difference: -28.2% with 95% CI -47.0 to -2.8). Since acarbose treatment increased the secretion of GLP-1, and GLP-1 reduces urinary albumin

Table 1 Baseline Demographics and Clinical Characteristics

	Acarbose	Metformin
N	299	305
Age (years)	50.9 (9.1)	50.1 (9.5)
Sex (Male/Female)	169/130	183/122
Waist circumference (cm)	89.3 (8.6)	89.5 (8.0)
Body weight (kg)	69.2 (10.8)	70.5 (10.6)
BMI (kg/m ²)	25.4 (2.7)	25.6 (2.6)
SBP (mmHg)	124.0 (12.8)	123.5 (13.0)
DBP (mmHg)	79.4 (8.8)	79.1 (8.2)
HbA1c (%)	7.5 (1.3)	7.5 (1.2)
FPG (mmol/L)	8.3 (1.6)	8.5 (1.5)
2hPPG (mmol/L)	12.6 (2.8)	12.4 (2.8)
TC (mmol/L)	5.3 (1.1)	5.3 (1.2)
TG (mmol/L)	2.5 (2.2)	2.4 (2.4)
HDL-C (mmol/L)	1.2 (0.3)	1.2 (0.3)
LDL-C (mmol/L)	3.1 (0.9)	3.0 (1.0)
AUCGLP-1 (mIU/mL×min)	2.5 (1.6 to 3.8)	2.5 (1.6 to 3.2)
uACR (mg/g)	16.3 (9.7 to 31.2)	14.8 (9.5 to 33.9)
eGFR (mL/min)	99.9 (35.4)	100.3 (29.8)

Notes: Data are shown as the means (SD) or median (interquartile range); all p-values were >0.05.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; 2hPPG, 2 h postprandial plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; AUCGLP-1, area under curve of glucagon-like peptide 1; uACR, urinary albumin/creatinine ratio; eGFR, estimated glomerular filtration rate.

excretion, log changes in GLP-1 levels were added to model 1 and model 3. The adjusted mean percent decrease in uACR and the difference compared to metformin did not change (acarbose: -73.2% with 95% CI -78.4 to -66.7 , metformin: -62.4% with 95% CI -69.7 to -53.2 , difference: -28.9% with 95% CI -47.7 to -3.3) (Table 2).

Effects of Acarbose Compared to Metformin on uACR in Participant Subgroups

Subgroup analysis showed that the effect of acarbose versus metformin was consistent across subgroups. Acarbose changed the adjusted mean percentage uACR compared to metformin by -6.7% (95% CI -49.7 to 42.4) in patients with microalbuminuria vs by -37.6% (95% CI -55.9 to -11.5) in patients with low-grade microalbuminuria. In participants whose eGFR was higher than 90 mL/min before treatment, acarbose changed the adjusted mean percentage uACR in comparison with metformin by -23.3% (95% CI -47.9 to 29.8) versus by -40.2% (95% CI -63.0 to -3.2) in patients whose eGFR was lower than 90 mL/min. If stratified by blood glucose level, acarbose changed the adjusted mean percent uACR compared to metformin by -41.6% (95% CI -61.0 to -12.5) in patients with an HbA1c higher than 7% versus by -8.4% (95% CI -41.8 to 44.1) in patients with HbA1c lower than 7%. Differences also existed across gender subgroups: the adjusted mean percent change in uACR treated with acarbose was -25.6% (95% CI -55.6 to 25.0) in

female patients versus -35.0% (95% CI -55.0 to -6.1) in male patients (Figure 1 and Supplemental Table S1).

Proportions of Patients with Different Reductions in uACR Following Acarbose or Metformin Therapy

The proportions of patients with a reduction in uACR from at least 30% to 70% in the acarbose group at week 48 were higher than those in the metformin group. The ratio of participants whose uACR decreased by no less than 30% compared with baseline was 70.5% in the acarbose group and 56.5% in the metformin group. Similarly, the proportions of patients with at least a 50% uACR reduction were 61.0% and 48.0%, and the proportions of patients with at least a 50% uACR reduction were 48.6% and 34.1% respectively (Figure 2).

UACR decreased below 4.4 mg/g in 32.0% of patients with low-grade microalbuminuria in the acarbose group and 24.2% of patients in the metformin group. In patients with microalbuminuria, the portion of uACR decreasing below 30mg/g was 58.1% and 57.7% (Supplemental Figure S1).

Discussion

Our study showed that chronic acarbose or metformin monotherapy both improved glycemic and weight control and reduced urinary albumin excretion.

Table 2 ANCOVA Analysis of Percent Change in Urinary uACR from Baseline to Week 48 for Patients with Baseline uACR ≥ 4.4 mg/g

Summary Statistics	uACR (mg/g)					
	Adjusting for baseline uACR Treatment group, antihypertensive treatment, Ln baseline uACR		Adjusting for baseline uACR treatment, antihypertensive treatment, Ln baseline uACR, Log changes in HbA1c, body weight, SBP, eGFR, and triglycerides		Adjusting for baseline uACR treatment, antihypertensive treatment, Ln baseline uACR, Log changes in HbA1c, body weight, SBP, eGFR, triglycerides and AUCGLP1 in standard meal test	
	Acarbose	Metformin	Acarbose	Metformin	Acarbose	Metformin
N	299	305	299	305	299	305
Baseline, median (IQR)	12.5 (4.9, 25.8)	11.6 (5.3, 28.8)	12.5 (4.9, 25.8)	11.6 (5.3, 28.8)	12.5 (4.9, 25.8)	11.6 (5.3, 28.8)
Adjusted % change from baseline to week 48						
LS mean (95% CI)	-73.8 ($-78.8, -67.6$)	-61.7 ($-69.1, -52.6$)	-73.2 ($-78.3, -66.9$)	-62.7 ($-69.9\%, -53.7$)	-73.2 ($-78.4, -66.7$)	-62.4 ($-69.7, -53.2$)
Difference (95% CI)	-31.5 ($-48.4, -7.5$)		-28.2 ($-47.0, -2.8$)		-28.9 ($-47.7, -3.3$)	

Abbreviations: ANCOVA, analysis of covariance; uACR, urinary albumin/creatinine ratio; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; AUCGLP-1, area under curve of glucagon-like peptide 1.

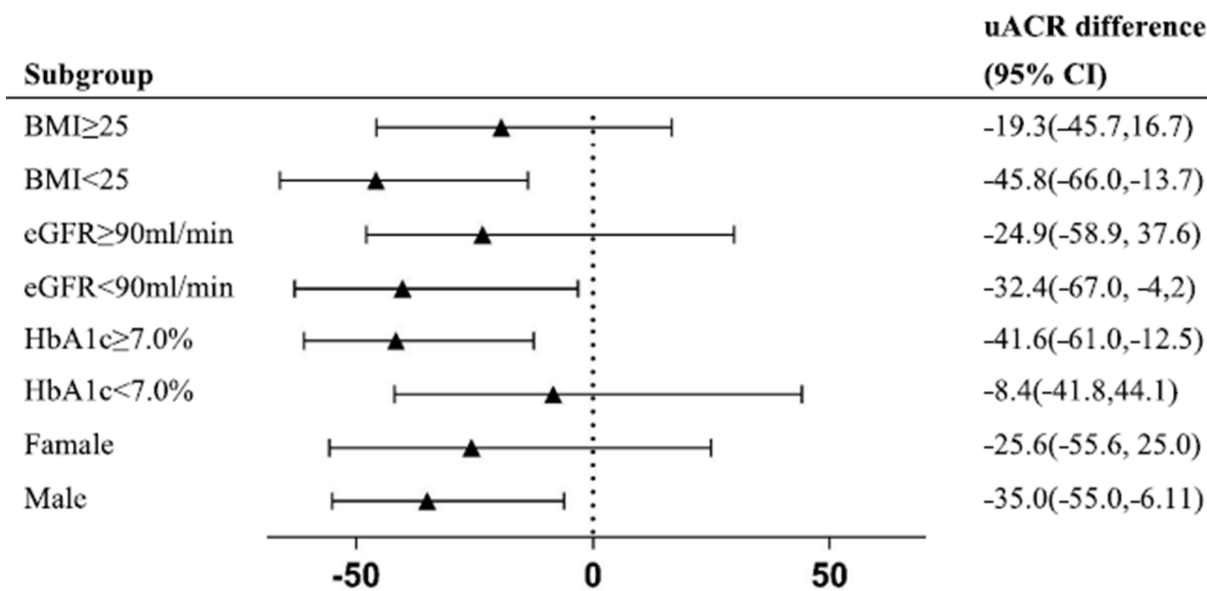


Figure 1 Subgroup analysis of the relative effect of acarbose versus metformin on the uACR from baseline to week 48. ANCOVA model adjusted for ln (baseline uACR), treatment group, antihypertensive treatment, subgroup, and subgroup by treatment group interaction.

Abbreviations: BMI, body mass index (kg/m^2); eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; CI, confidence interval.

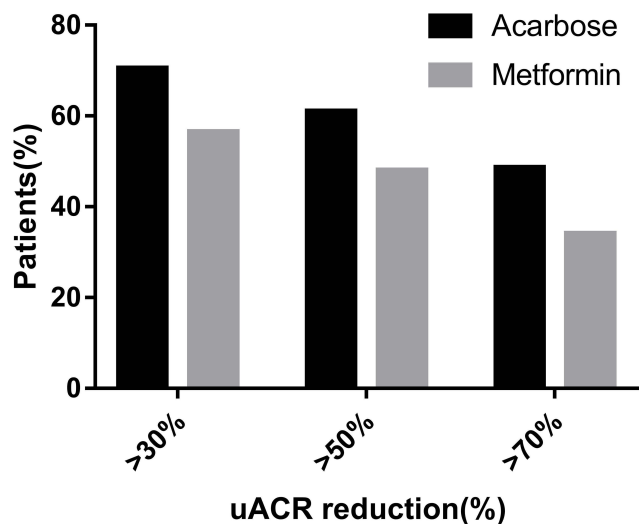


Figure 2 Proportion of patients with $\geq 30\%$, $\geq 50\%$ and $\geq 70\%$ reductions in uACR from baseline to week 48. Acarbose, N = 299; Metformin, N = 305. Percent change = (week 48 uACR – baseline uACR)/baseline uACR \times 100.

Abbreviations: uACR, urinary albumin/creatinine ratio; N, number of patients with observed baseline uACR ≥ 4.4 mg/g and week 48 uACR values.

Pan et al first reported the albuminuria-lowering effect of acarbose or metformin in patients with newly diagnosed T2DM and low-grade albuminuria.¹⁴ As shown by the results, in patients with an uACR of 10–30 mg/g, both acarbose and metformin treatment reduced the uACR. However, although they found a greater effect of acarbose than metformin on reducing urinary albumin, whether or not this was mediated by metabolic improvement was not

investigated further. In this post hoc study, we identified that acarbose reduced the uACR independent of reductions in blood glucose, body weight, blood pressure and triglycerides.

Few reports have confirmed the effect of α -glucosidase inhibitors on lowering urinary albumin excretion. It has been reported that additional acarbose therapy for 6 months slightly reduced the uACR in T2DM patients who were receiving sulfonylureas and metformin treatment, with glycated HbA1c levels between 7% and 10%.¹⁵ Another alpha-glucosidase inhibitor, miglitol, was also reported to decrease urinary albumin excretion in T2DM patients.¹⁶ The MARCH trial is the first multicenter, head-to-head clinical trial to show that acarbose has comparable hypoglycemia efficacy and better effects on reducing albuminuria. In contrast to previous studies, the subjects in our study had not been treated before and were characterized by a short diabetes duration of less than 3 months. More than three-quarters of these patients had low-grade albuminuria or microalbuminuria. In this trial, acarbose and metformin reduced the uACR as the initial treatment for T2DM patients after 48 weeks of monotherapy. The current analysis showed that patients taking acarbose had a larger percent mean reduction in uACR at week 48.

Several risk factors are associated with elevated urinary albumin excretion, including older age, male sex,

hyperglycemia, obesity, hypertension, elevated serum triglyceride levels and smoking.¹⁷ Glucose-lowering treatment always reduces albuminuria because glucose control is improved, weight loss is achieved, blood pressure is reduced and the lipid profile is changed. However, some antidiabetic drugs have albuminuria-lowering effects independent of glycemic control, reduction in blood pressure, and weight loss. The results of the present analysis showed that, although acarbose treatment achieved more weight loss and a reduction in triglycerides than metformin, the uACR-lowering effect of acarbose compared to metformin treatment was not attenuated after additional adjustment for changes in body weight and triglyceride levels. Additionally, secretion of GLP-1 was significantly increased after acarbose and metformin treatment. Since the albuminuria-lowering effect of GLP-1 and GLP-1 receptor agonists has been reported by several cardiovascular outcome trials, we investigated whether secretion of GLP-1 mediated the albuminuria-lowering effect of acarbose compared to metformin. However, no association was found between an increase in AUCGLP-1 during a standard meal test and changes in uACR. Likewise, the difference in the adjusted percent mean reduction in the uACR of acarbose compared to metformin was not changed after additional adjustment for increased AUCGLP-1. Therefore, acarbose may reduce urinary albumin excretion independent of changes in blood glucose levels, eGFR, body weight, blood pressure and serum triglyceride levels. It has been reported that other mechanisms are involved in the development and progression of albuminuria, including inflammation, oxidative stress and insulin resistance, which are potentially interrelated during diabetes.^{18–20} For example, excessive production of reactive oxygen species in renal endothelial cells or vascular smooth muscle cells activates proinflammatory cytokines, chemokines and profibrogenic factors in diabetic nephropathy.^{21,22} On the other hand, activation of the tumor necrosis factor (TNF)- α system may have an independent effect on ln ACR and eGFR in T2DM patients.²³

Some evidence suggests that acarbose has benefits beyond hypoglycemic effects, possibly via special mechanisms. Acarbose suppressed interferon inducible protein 10, monocyte chemokine-1, and TNF- α production in THP-1 cells stimulated by lipopolysaccharide, indicating that acarbose exerts anti-inflammatory effects possibly by suppressing intracellular signaling and histone acetylation.²⁴ Another *in vivo* study in mice showed that

acarbose administration alleviates diabetes-related insulinitis and protects β cells against inflammatory cytokine-induced apoptosis.²⁵ Acarbose treatment has a beneficial effect on mitigating inflammation by reducing the levels of related cytokines.²⁶ Furthermore, acarbose treatment can reduce hyperglycemia-related production of reactive oxygen species and protect vascular endothelial function.²⁷ As shown by a clinical trial in Japanese patients with T2DM, increased hydrogen production was associated with decreased IL-1 β mRNA expression in peripheral blood leukocytes in Japanese patients with T2DM after a single dose of acarbose.²⁸ Alternatively, acarbose changes gut microbiota, improves dysbiosis, and increases the abundance of *Bifidobacterium*.²⁹ *Bifidobacterium* has been reported to protect against diabetic nephropathy by increasing fecal and systemic SCFA concentrations.^{30,31} In summary, acarbose likely reduces urinary microalbumin through the above mechanism, thereby preventing diabetic nephropathy.

There are several limitations of the study. First, it was a post hoc analysis that was not designed to compare the albuminuria-lowering effects of acarbose and metformin. Therefore, no effort was made to explore the mechanisms of acarbose in reducing urinary microalbumin, such as analyzing gut microbiota, serum metabolites and inflammatory cytokines. Additionally, albuminuria was measured in a single spot morning urine sample. In future trials, multiple urine samples, including 24-hour urine collection for albumin measurement, are warranted. Finally, the effect of dietary structure on reducing urinary protein should be analyzed to eliminate interference from diet. Introducing an assessment of the impact of lifestyle changes, especially the intake of fiber and protein, on the reduction in the uACR can further strengthen the conclusions.

Conclusion

In this study, we identified acarbose monotherapy as having a better effect than metformin in reducing low-grade albuminuria in newly diagnosed T2DM patients. The kidney-protective effect of acarbose is independent of reductions in blood glucose, blood pressure, body weight and eGFR. These results provide new evidence supporting the benefit of acarbose for diabetes, which prevents diabetic nephropathy beyond glycemic control, as compared to other antidiabetic drugs that lower albuminuria, such as GLP-1 receptor agonists.

Declarations

This trial was registered at the Chinese Clinical Trial Registry Center. The registration name was Study on the Mechanism of Glucobay in Chinese Newly diagnosed Type 2 Diabetic Patients and the clinical trial registration number was ChiCTR-TRC-08000231. This trial was approved by the ethics committee of drug/device clinical trials of China-Japan Friendship Hospital on July 23rd, 2008. The approval number was 2008–23. All patients provided informed consent, in accordance with the Declaration of Helsinki.

Data Sharing Statement

Data are available from Wenying Yang upon reasonable request. Email: ywyang_1010@163.com.

Consent for Publication

All authors approved the paper publication.

Acknowledgments

The authors express appreciation to the participants in MARCH study. We also thank all investigators for their effort in this clinical trial.

Author Contributions

Lulu Song did analyzation of the data and drafted the manuscript, Xin Wang was the major investigator, Wenying Yang was the principal investigator of the trial, Xiaomu Kong provided important advices and instructed statistical analysis, Zhaojun Yang developed design of the trial, Jinping Zhang was sub investigator, Xiaoping Chen and Bo Zhang contributed conduction of the study. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

No funding or product was received for the present post hoc analysis.

Disclosure

The authors declare no conflicts of interest.

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