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Metformin or Acarbose Treatment Significantly Reduced Albuminuria in Patients with Newly Diagnosed Type 2 Diabetes Mellitus and Low-Grade Albuminuria

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Data Interpretation D
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Background: A urine albumin to creatinine ratio (UACR) >30 mg/g is considered to represent albuminuria, but in type 2 diabetes mellitus, even low-grade albuminuria is associated with increased risk of cardiovascular disease. This study aimed to investigate the effects of metformin and acarbose treatment on urine albumin excretion in Chinese patients with newly diagnosed diabetes and low-grade albuminuria.

Material/Methods: Patients with newly diagnosed diabetes (n=589) were divided into Group I (with a baseline UACR <10 mg/g) (n=331), and Group II (with a baseline UACR of 10–30 mg/g) (n=258). Following 48 weeks of treatment with metformin or acarbose, the UACR, blood pressure, body mass index (BMI), blood glucose, lipid profiles, and homeostasis model assessment of insulin resistance (HOMA-IR) were compared.

Results: Baseline diastolic blood pressure, levels of blood glucose and low-density lipoprotein cholesterol (LDL-C), and HOMA-IR were significantly increased in Group II compared with Group I (all P<0.05). In Group II, both metformin and acarbose treatment significantly reduced the UACR (P<0.001); the effect was significantly greater following acarbose treatment compared with metformin treatment (P<0.05). In Group I, neither metformin nor acarbose treatment significantly changed the UACR, but both Group I and Group II showed a significant and comparable reduction in BMI, blood glucose, blood pressure, and HOMA-IR.

Conclusions: In a group of Chinese patients with newly diagnosed type 2 diabetes mellitus, low-grade albuminuria (baseline UACR of 10–30 mg/g) was associated with metabolic factors before treatment. Treatment with either metformin or acarbose significantly reduced albumin excretion.

MeSH Keywords: **Acarbose • Albuminuria • Diabetes Mellitus, Type 2 • Metformin**

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Background

Microalbuminuria is defined as urine albumin excretion of 30–300 mg per 24 h, or a urinary albumin to creatinine ratio (UACR) of 30–300 mg/g [1]. Microalbuminuria is not only an established prognostic marker for diabetic nephropathy [1], but also a risk factor for cardiovascular morbidity and mortality [2,3]. However, recent studies have shown that low-grade albuminuria, which is lower than the threshold of microalbuminuria (UACR <30 mg/g), is associated with cardiovascular risk factors, including obesity, hypertension, hyperlipidemia, and insulin resistance [4,5]. Low-grade albuminuria is significantly associated with diabetic nephropathy [6], and increased morbidity and mortality from cardiovascular disease in both non-diabetic and diabetic individuals [7–9]. A recent meta-analysis, based on UACR data from 105,872 individuals, showed that a UACR ≥ 10 mg/g was an independent predictor of all-cause and cardiovascular mortality in the general population [10].

Blood glucose control can be effective in the prevention or reversal of microalbuminuria in patients with diabetes [11,12]. A previously published study showed that lifestyle modification combined with metformin treatment reduced urine albumin levels in overweight and obese non-diabetic patients with a urinary albumin excretion rate of 10–29 mg/day [13]. However, no study previously reported studies have assessed whether a UACR <30 mg/g can be reduced by hypoglycemic treatments in patients with type 2 diabetes.

Both metformin and acarbose are classical as oral hypoglycemic drugs. Metformin is the preferred initial drug for type 2 diabetes recommended by current international guidelines [14,15]. Acarbose is an α -glucosidase inhibitor that is commonly used in China, where the proportion of carbohydrates in the diet is high. In a previously published study, we reported that both metformin and acarbose reduced the UACR level in patients with type 2 diabetes mellitus who had a baseline UACR ≥ 30 mg/g [16].

The MARCH (Metformin and AcaRbose in Chinese as the initial Hypoglycaemic treatment) trial was a randomized controlled, multicenter clinical study registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-08000231), with the initial objective to compare the efficacy and safety of acarbose with metformin therapy in newly-diagnosed type 2 diabetes, and was conducted at 11 hospitals in China [17].

Therefore, using data from the MARCH trial, this study aimed to investigate the effects of metformin and acarbose treatment on urine albumin excretion in Chinese patients with newly diagnosed diabetes and low-grade albuminuria [16–18]. The study design included a 48-week treatment protocol of metformin or acarbose to determine their effects on lowering urine albumin excretion in type 2 diabetic subjects with a UACR <30 mg/g.

Matyerial and Methods

Data source, participating hospitals, ethical approval, and patient consents

This study used data from the MARCH trial, which was a study was a randomized controlled, multicenter clinical study to compare the efficacy and safety of acarbose with metformin therapy in newly-diagnosed type 2 diabetes, conducted at 11 hospitals in China [17]. The study received approval from the Ethics Committee at each of the following participating hospitals: the Beijing Chaoyang Hospital Affiliated to Capital Medical University, Beijing; the China-Japan Friendship Hospital, Beijing; the Chinese Peoples' Liberation Army General Hospital, Beijing; the West China Hospital, Sichuan University, Chengdu; the Shanxi Province Peoples' Hospital, Taiyuan; the First Hospital of China Medical University, Shenyang; the Xiangya Second Hospital of Central South University, Changsha; the Xijing Hospital, Fourth Military Medical University, Xi'an; the Shanghai Jiaotong University Affiliated Sixth Peoples' Hospital, Shanghai; the Third Affiliated Hospital of Sun Yatsen University, Guangzhou; and the Gansu Provincial Hospital, Lanzhou. The study protocol was implemented in accordance with the Declaration of Helsinki. All participants signed written informed consent to participate in the study.

Patient inclusion and exclusion criteria and treatment groups

All patients were diagnosed with type 2 diabetes within the previous 12 months. A diagnosis of type 2 diabetes was made according to the 1999 WHO criteria. All patients had a urine albumin to creatinine ratio (UACR) of <30 mg/g. Individuals recruited to the study had not received hypoglycemic agents or had only been treated for less than one month or had discontinued treatment for at least three months before enrolment. Full details of the inclusion criteria, exclusion criteria, and randomization have been previously published [17,18]. A preparatory period of four weeks was used for lifestyle instructions and diet counseling, according to current Chinese diabetes clinical management guidelines. The patients were then randomly assigned to receive either acarbose (300 mg/day) or sustained-released metformin (1500 mg/day). The study period was 48 weeks.

Exclusion criteria included subjects without UACR data, with urinary infection (urine leukocytes >5 per high-power field in a standard urinalysis), or with a baseline UACR ≥ 30 mg/g.

Group I and group II

Study participants were divided into two groups, based on their baseline UACR. Group I included individuals with UACR levels

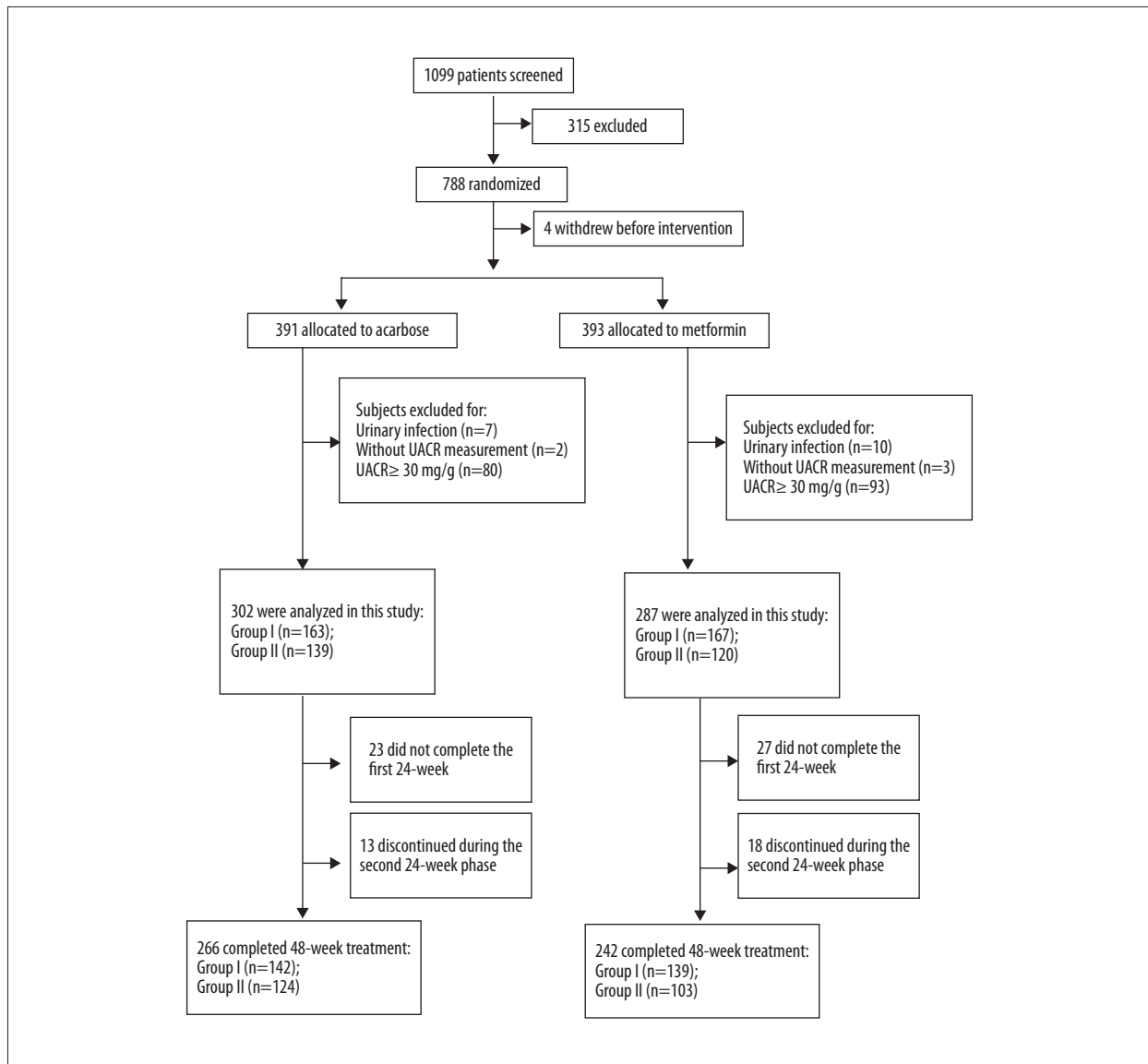


Figure 1. Flowchart of subject selection in the study. Subjects were grouped according to baseline levels in the urine albumin to creatinine ratio (UAR): group I (UACR of <10 mg/g); group II (UACR of 10–30 mg/day). UACR – urine albumin to creatinine ratio (mg/g).

<10 mg/g; Group II (low-grade albuminuria Group) included individuals with UACR levels of 10–30 mg/g (Figure 1). The cut-off of 10 mg/g used in the present study was based on the results from a recent meta-analysis and the Third Copenhagen City Heart Study, which showed that a UACR ≥ 10 mg/g [10], or an albuminuria equivalent to a UACR of 9.2–30 mg/g was associated with the increased risk of cardiovascular morbidity and mortality [19].

Measurement of biochemical variables

Plasma glucose, creatinine, and lipids were measured in the laboratories of each study site. Serum insulin was measured

by radio-immunoassay. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC). Urine albumin was measured using an immunoturbidimetric assay, and creatinine was measured using an enzymatic assay, on morning urine samples.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting insulin ($\mu\text{U/mL}$) \times fasting plasma glucose (mmol/L)/22.5.

The homeostatic model assessment of β cell function (HOMA-B) was calculated as follows:

$20 \times$ fasting insulin in $\mu\text{U/mL}$ / (fasting plasma glucose in $\text{mmol/L} - 3.5$) [20,21].

The estimated glomerular filtration rate (eGFR) ($\text{mL/min}/1.73 \text{ m}^2$) was calculated as follows: $175 \times (\text{serum creatinine [mg/dL]})^{-1.234} \times (\text{age})^{-0.179}$ in men, and as $138.25 \times (\text{serum creatinine [mg/dL]})^{-1.234} \times (\text{age})^{-0.179}$ in women [21].

In addition to type 2 diabetes, four other metabolic syndrome components, based on the National Cholesterol Education Program criteria were assessed, including hyperlipidemia, increased blood glucose, increased BMI, and increased blood pressure [22]. Metabolic syndrome was diagnosed if the patient had type 2 diabetes together with more than two of the other metabolic syndrome components.

Statistical analysis

Data with a normal distribution were expressed as the mean \pm standard deviation (SD), and data with a non-normal distribution were presented as the medians, upper and lower quartiles. Categorical variables were described numerically and as percentages. Baseline characteristics of the subjects in Group I and Group II were compared by two-tailed t-test or the Kruskal-Wallis test. Baseline and post-therapy values within each treatment group were compared by paired t-test or nonparametric Wilcoxon rank test. Categorical variables were compared using the chi-squared (χ^2) test. For analysis of percentage change from baseline for the UACR, homeostasis model assessment of insulin resistance (HOMA-IR), and triglyceride levels, these data were initially \log^{10} transformed because of the skewed distribution. The values were then back-transformed to geometric means of the ratio for treatment effects (expressed as percentage changes in the geometric mean from baseline). All statistical analysis was performed using SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). A P-value <0.05 was considered to be statistically significant.

Results

The current study included the analysis of data from 589 newly diagnosed patients with type 2 diabetes who had a urine albumin to creatinine ratio (UACR) $<30 \text{ mg/g}$. Baseline characteristics were compared between Group I (with a UACR level $<30 \text{ mg/g}$) ($n=331$) and Group II (with a UACR level of $10\text{--}30 \text{ mg/g}$) ($n=258$) (Table 1).

Significantly higher diastolic blood pressure, fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), low-density lipoprotein cholesterol (LDL-C), and homeostasis model assessment of insulin resistance (HOMA-IR) were found in patients in Group II compared with patients in Group I (all $P<0.05$).

The proportion of patients with metabolic syndrome in Group II was also significantly higher than that in Group I ($P=0.017$). There were no significant differences in gender, age, body mass index (BMI), waist circumference, duration of diabetes, systolic blood pressure, glycosylated hemoglobin (HbA1c) levels, homeostasis model assessment of beta cell function (HOMA-B), levels of high-density lipoprotein cholesterol (HDL-C), triglyceride, estimated glomerular filtration rate (eGFR) and the percentage of patients using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), statins or fibrates between the two groups.

In all subjects included in this study, both metformin and acarbose treatment decreased the UACR level in the presence of low-grade albuminuria, defined as a UACR of $10\text{--}30 \text{ mg/g}$ (all $P<0.05$) (Table 2).

The changes of the UACR and metabolic parameters following treatment with metformin and acarbose in patients in Group I and Group II were analyzed. In Group II, both metformin and acarbose treatment significantly decreased the UACR levels (all $P<0.001$), which was significantly higher in subjects taking acarbose compared with those taking metformin ($P<0.05$) (Figure 2). Although BMI, diastolic blood pressure, HbA1c, and HOMA-IR were significantly reduced by both acarbose and metformin treatment in both Group I and Group II (all $P<0.001$) (Figure 3), there was no significant change in the UACR after metformin or acarbose therapy in Group I. In both Group I and Group II, the triglyceride level was significantly reduced by acarbose (all $P<0.01$), but not significantly by metformin (Figure 3).

Discussion

The normal value for urine albumin excretion is less than 30 mg per 24 h , and the normal value of the urine albumin to creatinine ratio (UACR) is less than 30 mg/g . Persistent urine albumin excretion of $30\text{--}300 \text{ mg}/24\text{h}$ or a UACR between $30\text{--}300 \text{ mg/g}$ represents microalbuminuria or moderately increased albuminuria or [23]. Microalbuminuria is a prognostic marker for diabetic nephropathy and predicts an increased risk for cardiovascular disease, and requires intervention [2,3]. However, the findings from recent studies have shown that the albumin excretion rate is a continuum, and the lower the albumin excretion, the lower the cardiovascular risk [4,5]. The findings of this present study showed that the patients with UACR levels from $10\text{--}30 \text{ mg/g}$ had a significantly increased diastolic blood pressure, fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), LDL cholesterol (LDL-C), and homeostasis model assessment of insulin resistance (HOMA-IR) compared with patients with UACR levels $<10 \text{ mg/g}$. These findings were consistent with those of previously published studies [4,5].

Table 1. Baseline characteristics of the subjects with urine albumin to creatinine ratio (UACR) <10 mg/g (group I) and with aUACR 10–30 mg/g (group II).

Characteristics	Group I (UACR <10 mg/g)	Group II (UACR 10–30 mg/g)	P-value
N	330	259	
Age, years	50.16±9.19	50.71±9.07	0.63
Male (%)	209 (63.3%)	151 (58.3%)	0.07
Duration of diabetes, months	1.47 (1.08–2.95)	1.67 (1.08–3.47)	0.20
Body mass index, kg/m ²	25.52±2.54	26.60±2.64	0.52
Waist Circumference, cm	89.16±8.31	89.14±8.53	0.95
Systolic BP, mmHg	123.39±12.43	125.38±11.85	0.39
Diastolic BP, mmHg	78.79±7.63	80.66±7.81	0.028
HbA1c,%	7.50±1.21	7.67±1.24	0.06
FPG, mmol/L	8.12±1.45	8.45±1.58	0.008
PPG, mmol/L	12.24±2.97	12.90±3.05	0.009
HOMA-IR	3.50 (2.24–5.56)	4.30 (2.82–6.59)	0.001
HOMA-B	46.07(26.78–71.42)	50.54(31.20–78.69)	0.137
LDL-C, mmol/L	2.96±0.88	3.15±0.87	0.013
HDL-C, mmol/L	1.24±0.32	1.23±0.29	0.511
Triglyceride, mmol/L	1.77 (1.25–2.48)	1.92 (1.24–2.73)	0.184
Hypertension history, n (%)	85 (25.4%)	69 (26.4%)	0.844
ACEi/ARB therapy, n (%)	40 (12.0%)	22 (8.2%)	0.056
Hyperlipidemia history, n (%)	47 (14.2%)	46 (17.8%)	0.246
Statin therapy, n (%)	20 (6%)	18 (6.9%)	0.645
Fibrate therapy, n (%)	9 (2.7%)	12 (4.6%)	0.227
MetS, n (%)	229 (68.6%)	204 (78.2%)	0.017
eGFR, mL/min/1.73 m ²	113.37±34.44	109.66±32.04	0.185
UACR, mg/g	4.27 (1.14–6.88)	15.30(12.39–20.16)	<0.001

Data are presented as the mean ±SD, median (interquartile range) or n (%). UACR – urine albumin to creatinine ratio (mg/g); BP – blood pressure; HbA1c – hemoglobin A1c; FPG – fasting plasma glucose; PPG – 2 hour postprandial plasma glucose; HOMA-IR – homeostasis model assessment of insulin resistance; HOMA-B – homeostasis model assessment of b cell function; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; ACEi/ARB – angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MetS – metabolic syndrome; eGFR – estimated glomerular filtration rates.

A recent study has shown that increased carotid artery intimal and medial thickness was found in the patients with an increased UACR (10.7–30 mg/g) compared with those with a lower UACR level [24]. Also, low-grade albuminuria (UACR 10.62–30 mg/g) has been shown to be associated with a higher prevalence of carotid artery atherosclerotic plaques in patients with diabetes [25]. Also, recent studies have shown

that the risk of morbidity and mortality from cardiovascular disease is significantly increased in subjects with low-grade albuminuria, indicating that low-grade albuminuria also requires treatment [7,10,26]. A study has shown that lifestyle modification plus metformin treatment reduced urine albumin levels in overweight and obese subjects with a baseline urine albumin of 10–29 mg/day [13]. A further study showed that treatment

Table 2. Urine albumin to creatinine ratio (UACR) and the presence of low-grade albuminuria (defined as UACR of 10–30 mg/g) before and after treatment with acarbose or metformin in patients with newly diagnosed type 2 diabetes (with UACR <30 mg/g).

Characteristics	Acarbose group			Metformin group		
	Baseline (n=302)	24 weeks (n=279)	48 weeks (n=266)	Baseline (n=287)	24 weeks (n=260)	48 weeks (n=242)
Urine UACR, mg/g	8.97 (3.84–15.54)	4.0 (0.89–11.14)***	3.56 (0.73–9.27)***	8.54 (3.68–13.49)	4.67 (0.97–12.72)*	5.64 (1.63–11.98)*
Low-grade albuminuria, n (%)	143 (45.83%)	83 (27.21%)***	71 (23.91%)***	124 (41.89%)	65 (26.86%)**	62 (27.56%)**

Data are presented as median (interquartile range) or n (%). UACR – urine albumin to creatinine ratio (mg/g); * P<0.05, ** P<0.01, *** P<0.001 compared with baseline within groups.

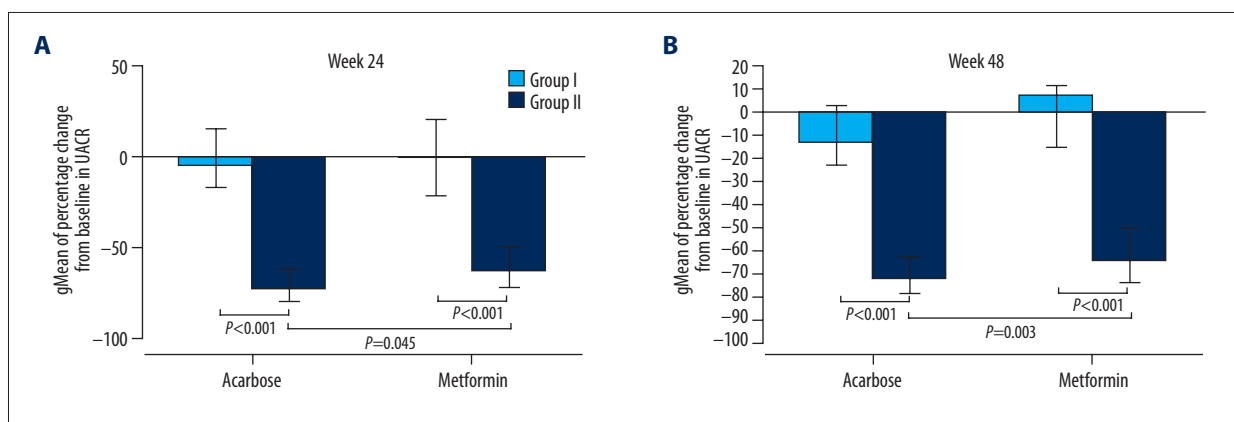


Figure 2. Effects of acarbose or metformin treatment on urine albumin to creatinine ratio (UACR) in group I (baseline UACR of <10 mg/g) and group II (baseline UACR of 10–30 mg/day). Data are presented as the mean, with 95% confidence interval (CI), of percentage change from baseline in the urine albumin to creatinine ratio (UACR) at week 24 (A) and at week 48 (B). UACR, urine albumin to creatinine ratio (mg/g).

with valsartan, an angiotensin receptor blocker, could reduce low-grade albuminuria in normotensive renal transplant patients [27]. The findings of the present study showed that both metformin and acarbose could decrease urine albumin excretion in newly diagnosed patients with diabetes with a UACR level of 10–30 mg/g. These findings added to current knowledge that in newly diagnosed type 2 diabetes, low-grade albuminuria can be reduced by metformin or acarbose therapy. These results are clinically important because low-grade albuminuria is likely to be a sensitive marker for cardiovascular disease early in life, and could represent a target for early disease prevention [28].

The findings of this study showed that significantly reduced BMI, diastolic blood pressure, blood glucose levels, HMOA-IR, and triglyceride levels after both treatments, with metformin and acarbose, in Group I (with a basal UACR <10mg/g) showed negligible change in the UACR and in Group II (with a basal UACR level of 10–30 mg/g) showed significant change in the UACR. Therefore, the difference in the UACR between Group I and Group II following treatment could not be explained by the

differences in the changes in metabolic parameters between these two groups. Since albuminuria is also considered to be a marker for endothelial dysfunction and vascular inflammation [29], the difference in endothelial function and vascular inflammation might explain the differences in the changes in the UACR. However, in the present study, endothelial function and vascular inflammation were not evaluated.

The findings of this study showed that treatment with acarbose, compared with metformin, had a more significant effect on the UACR in the low-grade albuminuria group. In this study, triglyceride levels were significantly reduced by treatment with acarbose, but not by metformin, after 48 weeks of treatment. Increased plasma triglyceride levels have been previously shown to be associated with albuminuria in type 2 diabetes [30,31]. It has also been previously reported that the anti-hypertriglyceridemic agent, fenofibrate, could reduce urine albumin excretion in both the Fenofibrate Intervention and Event Lowering in Diabetes study (FIELD) and the Diabetes Atherosclerosis Intervention Study (DAIS) [32,33]. The increased efficacy of acarbose on the reduction of hypertriglyceridemia

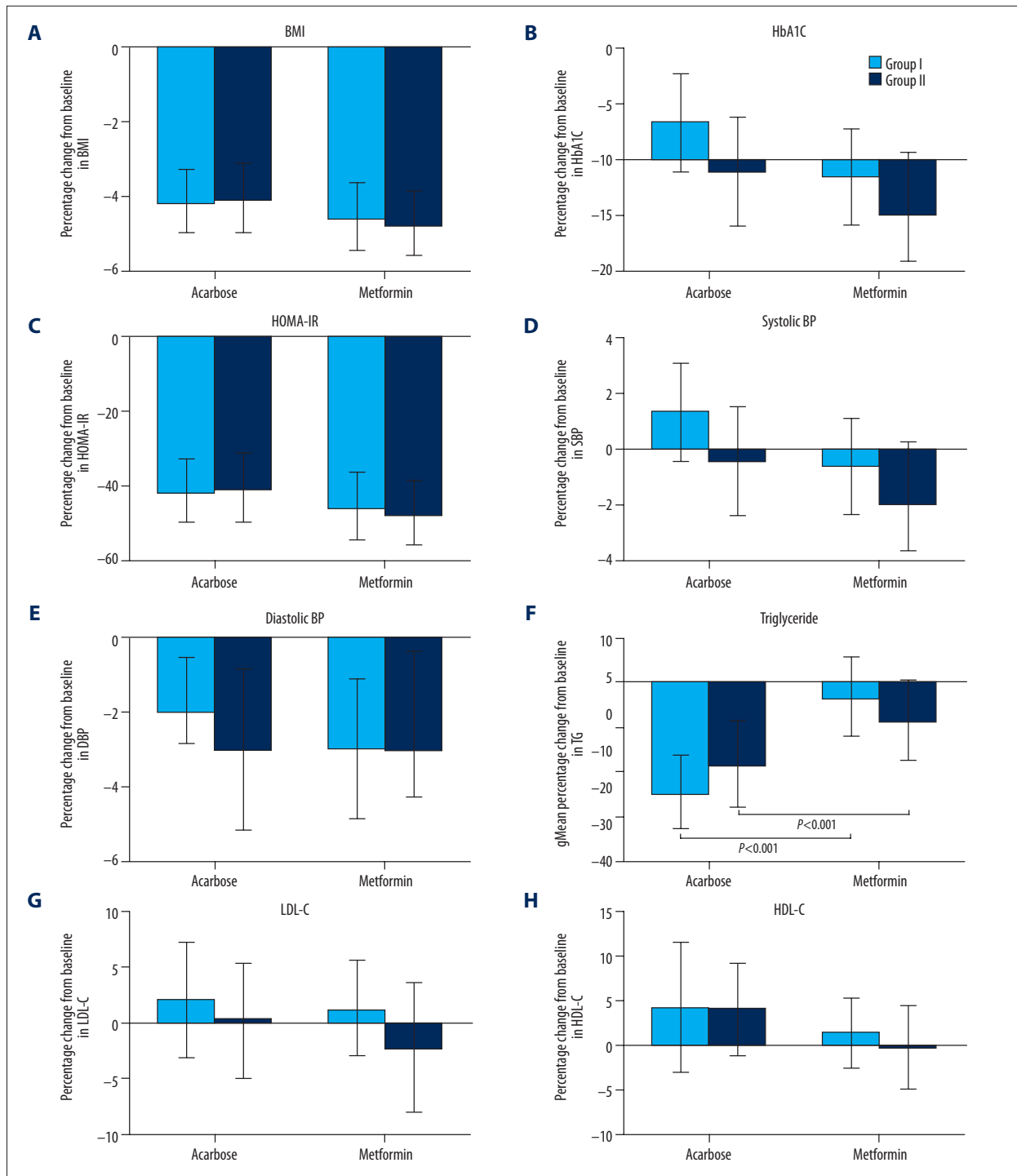


Figure 3. The effects of acarbose or metformin treatment in group I (with baseline UACR of <10 mg/g) and group II (with baseline UACR of 10–30 mg/day). **(A)** The effects on the body mass index (BMI). **(B)** The effects on glycated hemoglobin (HbA1c) levels. **(C)** The effects on the homeostasis model assessment of insulin resistance (HOMA-IR). **(D)** The effects on systolic blood pressure (BP). **(E)** The effects on diastolic blood pressure (BP). **(F)** The effects on triglyceride levels. **(G)** The effects on low-density lipoprotein cholesterol (LDL-C). **(H)** The effects on high-density lipoprotein cholesterol (HDL-C). Data are presented as mean or geometric mean (with 95% CI) of percentage change from baseline. gMean – geometric mean; BMI – body mass index; HbA1c – hemoglobin A1c or glycated hemoglobin; HOMA-IR – homeostasis model assessment of insulin resistance; BP, – blood pressure; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol.

probably contributed to the improved reduction in UACR by acarbose therapy in this study. However, it is important to note that all participants in this study were Chinese. The Chinese diet includes a high proportion of carbohydrates, including rice and noodles as a staple food. In the Chinese population, more than 66% of dietary energy is derived from carbohydrates [18,34]. Acarbose, which can inhibit carbohydrate absorption, may have a more protective effect on a population with a high carbohydrate dietary intake, such as the Chinese.

This study had several limitations. First, for ethical reasons, the study did not include a placebo group. Also, this study sample size was small, and there was a short follow-up period. All of the study participants were Chinese. Further large-scale studies that include other ethnic groups are needed to confirm that these findings can be applied to other populations.

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Conclusions

The findings of this study showed that in Chinese patients with newly diagnosed type 2 diabetes and low-grade albuminuria, with a urine albumin to creatinine ratio (UACR) of 10–30mg/g, these patients already had adverse metabolic factors. In patients with low-grade albuminuria, both acarbose and metformin treatment reduced UACR, with the effect of acarbose on UACR being greater than that of metformin. Neither acarbose nor metformin treatment resulted in a significant change in the UACR in patients with baseline UACR level <10 mg/g. These results indicate that in Chinese patients with newly diagnosed type 2 diabetes, low-grade albuminuria can be effectively reduced by both metformin and acarbose therapy.

Conflict of interests

None.

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