Gender-differential effects on blood glucose levels between acarbose and metformin in Chinese patients with newly diagnosed type 2 diabetes: a sub-analysis of the MARCH trial

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Abstract. Using the data from the trial of Metformin and AcaRbose in Chinese as the initial Hypoglycemic treatment (MARCH), this study was performed to compare the differential effects of acarbose and metformin on glucose metabolism after stratification by gender. Six hundred and forty patients who had finished the whole 48-week follow-up were included. The reduction of haemoglobin A1c (HbA₁c) was comparable between acarbose- and metformin-treated patients among either females or males, and it was also similar between males and females treated with either acarbose or metformin for 24 and 48 weeks. The dropping of fasting plasma glucose (FPG) in acarbose-treated females was significantly less than that in metformin-treated females at both 24 and 48 weeks. Furthermore, the decrease of 2-hour postprandial glucose (2hPPG) in acarbose-treated males was significantly greater than that in metformin-treated males at both 24 and 48 weeks. Multiple linear regression analysis showed that drug selection was an independent factor affecting the decrease of FPG in female patients while it independently influenced 2hPPG in males at week 24 and 48. The reductions of FPG and 2hPPG at week 24 and 48 were also significantly different between metformin-treated females and metformin-treated males although gender was not an independent regulating factor. Our study indicates that there might be gender-differential effects on FPG and 2hPPG reduction when the comparisons are made between acarbose and metformin treatments.

Key words: Gender difference, Diabetes, Glucose, Body weight

TYPE 2 DIABETES MELLITUS (T2DM) is a common chronic and incurable metabolic disease [1]. It has been a major public health issue worldwide including China [2, 3]. Newly diagnosed T2DM patients are usually treated with oral antidiabetic drugs (OADs). Metformin has been recommended as the first-line oral antidiabetic drug for T2DM based on the present clinical practice guidelines for diabetes established by authorities, such as the American Diabetes Association and so on [4, 5]. Currently, acarbose, as an α-glucosidase inhibitor, is widely used in China, where dietary carbohydrates are the major source of total calorie supply in the general population [6-8].

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The Metformin and AcaRbose in Chinese as the initial Hypoglycemic treatment (MARCH) trial is the first head-to-head clinical investigation performed to compare the glucose-lowering effects of metformin and acarbose as an initial therapy for T2DM patients after failure of therapeutic lifestyle modification [6]. The MARCH trial has shown that the efficacy of acarbose is comparable to that of metformin in decreasing the level of haemoglobin A1c (HbA1c), while acarbose treatment could cause greater reduction in 2-hour postprandial glucose (2hPPG), but less decrease in fasting plasma glucose (FPG) in the total T2DM patients [6]. There are many differences in the lifestyle, body composition, hormonal secretion and hepatic drug-metabolizing enzymes between males and females [9], which indicate the potential effects of gender on the glucose-lowering efficacy of drugs. The impact of female gender on the hypoglycemic effectiveness of tiraglutide has been noted in both an animal model experiment [10] and a population-based study [11]. Recent studies showed that males could benefit more from acarbose treatment as compared with females do. A 0.1% dietary acarbose treatment extended mouse lifespan longer in males than in females [12]. The numbers of significantly altered metabolites in the liver were much more in male mice than in females after treated with 0.1% acarbose [13]. However, no studies have previously compared the glucose-lowering efficacy of acarbose and metformin as stratified by gender, which is focused in the present study to better guide the selection of those hypoglycemic agents in the clinical practice.

Materials and Methods

The design and protocol of the MARCH trial, a randomized controlled, open-label, multicenter trial, have been previously described [6]. All subjects included in the current study had completed the whole 48-week follow-up in the MARCH trial. They were newly diagnosed with T2DM, aged between 30 and 70 years, and had HbA1c levels between 7% and 10%. Among the 640 patients ultimately enrolled in the study, 193 patients were in metformin-treated male group (MGmale), 121 in metformin-treated female group (MGfemale), 199 in acarbose-treated male group (AGmale) and 127 in acarbose-treated female group (AGfemale).

The MARCH trial was approved by the ethics committees of the First Affiliated Hospital of China Medical University and other clinical centers. The registry number was ChiCTR-TRC-08000231. Written informed consent was obtained from all patients.

After a 4-week run-in phase of therapeutic lifestyle modification, the patients were randomly assigned to receive monotherapy with either acarbose up to 100 mg three times per day (50 mg per tablet, Bayer Healthcare, Beijing, China), or sustained-release metformin hydrochloride up to 1,500 mg once per day (500 mg per tablet, Beijing Double Crane Pharma, Beijing, China), from the 1st to the 24th week of treatment. The patients under one of the following conditions had received sulfonylurea (SU) as add-on treatment from the 25th to the 48th week: 1) HbA1c level higher than 7% at the 24th week after the intervention; 2) FPG level higher than 7 mmol/L at the time point above; and 3) self-monitored 2hPPG level higher than 10 mmol/L for three consecutive days.

Finally, 2 participants in AGmale (gliclazide controlled-release tablets 5 mg per day and glimepiride tablets 1 mg per day, respectively), 1 in AGfemale (gliclazide tablets 80 mg per day), 2 in MGmale (glimepiride tablets 2 mg per day and gliclazide tablets 30 mg per day, respectively) and 1 in MGfemale (gliclazide tablets 30 mg per day) had received sulfonylurea as add-on treatment for the last 24-week treatment.

The visits were scheduled every 2 to 4 weeks since the 4th week after drug treatment. All participants had completed questionnaires regarding their dietary macronutrients on the day before each visit. Calorie intake from carbohydrates, proteins and fats (CPF) at baseline and at 24 and 48 weeks was calculated independently by clinical dieticians. Body weight, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured during all visits. Fasting fingertip blood glucose (the average of two measurements) was collected every four weeks. At baseline, 24 and 48 weeks of treatments, patients underwent clinical assessments and laboratory tests, including FPG, HbA1c, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDL-C), glucagon-like peptide-1 (GLP-1), insulin and glucagon. Plasma glucose, insulin, glucagon, and GLP-1 levels were also measured after the intake of a standard test meal, which is the ingestion of 70 g of instant noodle (500 kcal, 70 g carbohydrate) [6]. To assess the production of insulin and its sensitivity, parameters such as the homoeostatic model assessment (HOMA) index and body mass index (BMI) were collected as follows: fasting insulin (FINS); HOMA-β = 20 × FINS/(FPG-3.5); HOMA-insulin resistance (HOMA-IR) = FINS × FPG/22.5; early insulin secretion index (EISI) = ΔI30/ΔG30; and whole body insulin sensitivity index (WBISI) = 10 000/(FPG[mg/dL] × FINS) × (mean glucose [mg/dL] × mean insulin). Areas under the curve (AUC) were also calculated, e.g. AUC-GLP-1 = (GLP-10 min + GLP-130 min) × 30/2 + (GLP-110 min + GLP-1120 min) × 90/2 + (GLP-1120 min + GLP-1150 min) × 60/2.

Changes in the clinical and biological parameters described above during the interventions were not only
compared between the acarbose- and metformin-treated groups after stratification by gender, but also between female and male patients in either of the two drug-treated groups. All analyses were performed using PASW statistics software (v. 17.0; SPSS Inc, IBM Company, Chicago, Illinois, USA). We performed efficacy analyses using per-protocol populations. Data are shown as mean ± standard deviation (SD) or median (interquartile range, IQR) according to the type of data as appropriate. Differences between those groups were analyzed by the independent sample t-test and Wilcoxon rank-sum test, where appropriate. One-sample t-test or one-sample Wilcoxon test was applied to compare the mean or median of Δvalues with zero according to the type of Δvalues. Analysis of covariance (ANCOVA) was used to adjust for the imbalance in covariate baseline values when Δvalues were compared. To control the confounding factors, multiple linear regression analysis was used to determine whether drug selection (i.e. acarbose or metformin) and gender (male or female) independently affected the reductions of FPG and 2hPPG. Logistic regression analysis was performed to assess the impact of gastrointestinal symptoms (GS) on weight loss. P-values <0.05 were considered statistically significant.

Results

Baseline characteristics of T2DM patients after stratification by gender

Approximately 84% of the participants in the acarbose-treated group and 80% in the metformin-treated group had finished the whole 48-week follow-ups in MARCH trial, and had all been included in this study. Firstly, HOMA-β and HOMA-IR were significantly lower in AGmale as compared with those in MGmale while serum levels of HbA1c and FPG were markedly lower in AGfemale than those in MGfemale at the baseline (Table 1, Fig. 1a). There were no significant differences in the other parameters between acarbose- and metformin-treated groups in either females or males (Table 1). Furthermore, compared with those in MGfemale, body weight and waist circumference were significantly higher, while age and serum HDL-C were significantly lower in MGmale. Body weight, waist circumference, DBP, FPG and WBISI were significantly higher, while age, serum HDL-C, HOMA-β and HOMA-IR were significantly lower in AGmale than those in AGfemale.

Changes in the parameters directly related to glucose metabolism after stratification by gender

HbA1c, FPG and 2hPPG were all significantly reduced in both males and females after 24- and 48-week either acarbose or metformin treatment (Fig. 2a, b, c). The level of HbA1c in acarbose-treated patients was comparable to that in metformin-treated ones at the two follow-up visits in either males or females (Fig. 1a). The reduction of HbA1c level after both 24 week- and 48 week-treatment with acarbose was comparable to that with metformin in both genders (Fig. 2a). There was no significant difference in the proportion of either female or male patients with HbA1c levels below 7% between the acarbose- and the metformin-treated group at week 24 and 48 (data not shown). The fasting fingertip blood glucose measured in either females or males showed less reduction in acarbose-treated patients than that in metformin-treated ones at several follow-up visits during the first 28 weeks of treatment (Fig. 1b). Furthermore, the reduction of FPG level in AGfemale was significantly less than that in MGfemale at week 24 and 48; However, it was similar between AGmale and MGmale at the two follow-up visits (Fig. 2b). The decrease in 2hPPG level was significantly greater in AGmale than in MGmale at both week 24 and 48, whereas it was comparable between AGfemale and MGfemale (Fig. 2c).

The decrease of HbA1c, FPG and 2hPPG were also compared between female and male patients treated with the same drugs. The reduction of HbA1c level in male patients was comparable to that in females after 24 week- and 48 week-treatment with either acarbose or metformin (Fig. 2a). The reductions of FPG and 2hPPG in MGmale were significantly less than that in MGfemale at week 24 and 48, whereas they were similar between AGmale and AGfemale (Fig. 2b, c).

There was only a significant increase of HOMA-β (basic insulin secretion index) in MGfemale after 24-week treatment (Table 2), and no markedly change was found in AGfemale, AGmale or MGmale after either 24-week or 48-week treatment. ΔHOMA-β was similar between AGmale and MGmale while it was significant less in AGfemale than that in MGfemale at week 24 and 48 (Table 2). The mean AUC for serum insulin after a standard meal was more significantly further decreased in the acarbose-treated patients than that in the metformin-treated patients, except for males at week 48 (a similar trend but p = 0.117, Table 2). No significantly differential alterations in EISI, HOMA-IR, WBISI, or the postprandial AUCs for plasma glucagon and GLP-1 were found at week 24 and 48 between AGmale and MGmale as well as AGfemale and MGfemale. There were no significant differences in the changes of indices for insulin sensitivity and β-cell function between AGmale and AGfemale as well as MGmale and MGfemale after 24 week- and 48 week-treatment (Table 2).

Changes in serum lipid and body weight after stratification by gender

Lipotoxicity and obesity are the most common factors
which affect the functions of pancreatic β cells and insulin resistance. Serum TG level was decreased after acarbose treatment in both genders at week 24 and 48, but after metformin treatment, serum TG level was decreased only in females at week 48 (Fig. 3a). Both acarbose and metformin treatments led to significant reductions of serum TC in female and male patients at week 24 and 48 (Fig. 3b). Serum LDL-C level was only significantly reduced in acarbose-treated females but not males at week 24 and 48 (Fig. 3c). Serum LDL-C level was significantly lowered in metformin-treated females at week 24 and males at week 24 and 48 (Fig. 3c). There was no significant change in HDL-C level in either acarbose- or metformin-treated patients (data not shown). Serum TG reduction was more after acarbose treatment than metformin in both genders at week 24 and 48 (Fig. 3a). LDL-C level was decreased less in MG male after both 24 and 48 weeks of treatment (Fig. 3c). The decrease of serum lipid was also compared between different genders with the same drug treatment. TC level was decreased less in AG female than that in AG male metformin-treated female group.

### Table 1 Baseline demographic data in all the participants

|              | MG_{female} | AG_{female} | MG_{male} | AG_{male} |
|--------------|-------------|-------------|-----------|-----------|
| N            | 121         | 127         | 193       | 199       |
| Age (years)  | 53.00 (45.00–56.50) | 52.00 (45.00–57.00) | 46.50 (42.00–55.00)$^{ab}$ | 47.00 (42.00–55.00)$^{ab}$ |
| Duration of diabetes (years) | 0.18 (0.09–0.36) | 0.13 (0.09–0.24) | 0.14 (0.10–0.25) | 0.13 (0.09–0.25) |
| Body Weight (kg) | 63.13 ± 7.99 | 63.30 ± 8.72 | 75.41 ± 9.4$^{ab}$ | 74.80 ± 8.81$^{ab}$ |
| BMI (kg/m²)   | 25.35 (23.40–27.45) | 25.50 (23.50–27.70) | 25.95 (24.60–28.30) | 26.00 (24.60–27.70) |
| Waist circumference (cm) | 85.25 (80.25–90.60) | 85.50 (80.00–90.00) | 93.00 (88.00–97.00)$^{ab}$ | 92.50 (88.00–98.00)$^{ab}$ |
| SBP (mmHg)    | 125.00 (120.00–130.00) | 121.00 (110.00–130.00) | 120.00 (115.00–130.00) | 120.00 (118.0–130.00) |
| DBP (mmHg)    | 80.00 (71.50–84.00) | 75.00 (70.00–80.00) | 80.00 (75.00–85.00) | 80.00 (75.00–85.00)$^{ab}$ |
| TG (mmol/L)   | 1.94 (1.39–2.66) | 1.74 (1.18–2.22) | 2.13 (1.44–2.95) | 1.92 (1.32–2.91) |
| TC (mmol/L)   | 5.11 (4.40–5.93) | 5.26 (4.76–5.98) | 5.17 (4.47–5.93) | 5.08 (4.57–5.71) |
| LDL-C (mmol/L) | 2.85 (2.29–3.56) | 3.15 (2.67–3.58) | 3.14 (2.43–3.70) | 2.99 (2.53–3.49) |
| HDL-C (mmol/L) | 1.24 (1.10–1.43) | 1.30 (1.12–1.53) | 1.17 (0.99–1.35)$^{ab}$ | 1.11 (0.96–1.31)$^{ab}$ |
| HbA1c (%)     | 7.60 (6.70–8.25) | 7.20 (6.70–8.00)$^*$ | 7.50 (6.90–8.50) | 7.40 (6.70–8.20) |
| FPG (mmol/L)  | 8.49 ± 1.31 | 7.93 ± 1.20$^{**}$ | 8.42 ± 1.52 | 8.44 ± 1.49$^{**}$ |
| 2hPPG (mmol/L)$^4$ | 12.94 ± 2.97 | 12.32 ± 2.82 | 12.30 ± 3.07 | 12.67 ± 2.82 |
| HOMA-β        | 50.20 (28.68–73.12) | 50.72 (33.80–79.32) | 53.54 (29.70–74.36) | 42.38 (28.16–65.39)$^{*, ab}$ |
| HOMA-IR       | 4.54 (3.10–6.44) | 4.36 (2.63–6.00) | 4.25 (2.56–6.46) | 3.69 (2.39–5.98)$^*$ $^v$ |
| EISI$^b$      | 2.91 (1.08–3.98) | 2.47 (1.28–4.37) | 2.11 (1.10–4.44) | 2.27 (0.85–4.54) |
| WBISI$^b$     | 3.66 (2.47–5.03) | 3.47 (2.56–5.04) | 3.82 (2.68–5.75) | 4.09 (2.82–5.94)$^{abw}$ |
| AUC for serum insulin (uIU/mL × min)$^5$ | 4,739.48 (3,293.33–6,267.60) | 4,883.40 (3,781.50–6,718.50) | 4,230.68 (3,026.10–6,060.30) | 4,092.45 (3,016.35–5,676.15)$^{abw}$ |
| AUC for glucagon (pg/mL × min)$^5$ | 12,052.58 (9,445.88–15,472.95) | 12,105.00 (9,362.25–15,164.75) | 12,640.88 (9,917.25–16,215.45) | 11,873.85 (10,003.50–15,790.50) |
| AUC for plasma GLP-1 (pmol/mL × min)$^5$ | 2,917.05 (1,646.78–4,921.73) | 2,784.00 (1,736.25–4,372.35) | 2,940.00 (1,874.10–5,032.95) | 2,808.68 (1,829.70–4,454.55) |

MG_{female}, metformin-treated female group; AG_{female}, acarbose-treated female group; MG_{male}, metformin-treated male group; AG_{male}, acarbose-treated male group. Data are shown as the mean ± SD or median (IQR) according to the type of the data as appropriate. BMI, body mass index; SBP, systemic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; 2hPPG, 2-hour postprandial plasma glucose; HOMA, homeostatic model assessment; EISI, early insulin secretion index; WBISI, whole body insulin sensitivity index; AUC, area under the curve; GLP-1, plasma glucagon-like peptide-1. $^*$ After a standard meal test. ** $p < 0.05$. ** $p < 0.01$ vs. metformin-treated group in the same gender. *** $p < 0.05$, ** $p < 0.01$ vs. female group treated with the same drug.
Both acarbose and metformin administrations caused significant weight loss in female and male patients at week 24 and 48 (Fig. 2d). Body weight decrease in AGmale was significantly more than that in MGmale at week 24. Body weight decrease in AGfemale was significantly more than that in MGfemale at week 24 and 48 (Fig. 2d). Besides, both metformin and acarbose decreased less body weight in males than in females at week 24 and 48 (Fig. 2d). GS were assessed by gender, which might affect weight loss. Twenty-four (12.06%) participants in AGmale, 16 (12.60%) in AGfemale, 7 (3.63%) in MGmale and 15 (12.40%) in MGfemale experienced mild to moderate GS during treatment. Logistic regression analysis showed that GS was not an independent risk factor for weight loss in all groups (data not shown).

Calorie intake analysis after stratification by gender

Food-intake habits have important impacts on blood glucose, serum lipid and body weight. In this study, no significant difference in total daily calorie intake was observed between AGmale and MGmale, as well as AGfemale and MGfemale at baseline, week 24 and 48. Furthermore, there was no significant difference between the acarbose- and metformin-treated patients in both genders in the contributions of CPF to calorie intake at week 24 and 48 (Supplementary Table 1).

However, total daily calorie intake of males was significantly more than that of females in both acarbose- and metformin-treated patients (Supplementary Table 1). The increase in daily calorie intake of MGmale was due to significantly more intake of CPF at baseline and 24 weeks, and more intake of carbohydrates and proteins at 48 weeks as compared with those of MGfemale. The significantly increased CPF intake at baseline, carbohydrates and proteins at week 24 and proteins at week 48 contributed to the more daily calorie intake of AGmale when compared with those of AGfemale (Supplementary Table 1). Especially, among the total participants, daily calorie intake and the contribution of three macronutrients at baseline, 24 and 48 weeks were all markedly higher in males than those in females (Supplementary Table 2).

Multiple linear regression analysis of the factors affecting the decreases in FPG and 2hPPG

Since there were some potential confounding factors, such as baseline parameters, gastrointestinal symptoms, energy intake and add-on treatment with SU in the comparison of the glucose-lowering efficacy between acarbose and metformin in addition to gender, multiple linear regression analysis was used to determine whether gender was indeed involved in the influence of drug selection (metformin or acarbose) on the decreases of FPG and 2hPPG.

Multiple linear regression analysis indicated drug selection of metformin or acarbose was an independent factor affecting the decrease degree of FPG in the females but not males, while drug selection indeed influenced the dropping of 2hPPG in the males other than females at week 24 and 48 after adjusted by such covariates as baseline parameters, gastrointestinal symptoms, energy intake and add-on treatment with SU (Table 3).

Although the reductions of FPG and 2hPPG in MGmale group were markedly less than those in MGfemale at week 24 and 48, whereas they were similar between AGmale and AGfemale (Fig. 2b, c), multiple linear regression analysis did not found gender as an independent factor affecting the decrease of FPG and 2hPPG during metformin treatment (Supplementary Table 3). Besides, gender
was not an independent factor affecting the reduction of FPG and 2hPPG during acarbose treatment (Supplementary Table 3).

**Discussion**

Several studies have compared the therapeutic efficacy of acarbose and metformin in patients with T2DM [6, 14, 15], which showed their similar potencies in improving metabolic disorders in patients. In this study, we mainly analyzed the difference in the glucose-lowering efficacy between metformin and acarbose in newly-diagnosed patients with T2DM as stratified by gender using the data of the MARCH trial. As far as we know, this is the first study to compare the efficacy of the two drugs as stratified by gender. In this study, a similar reduction of HbA$_{1c}$ level was observed not only between the acarbose- and metformin-treated patients after stratified by gender, but also between the males and females treated with either acarbose or metformin. Drug selection (acarbose or metformin) was independently associated with the decrease of FPG in different drugs-treated females and metformin was a better choice for FPG reduction in females than acarbose. Drug selection (acarbose or metformin) was independently associated with 2hPPG reduction in different drugs-treated males and acarbose might be better in decreasing 2hPPG in males than metformin. The decrease of FPG and 2hPPG levels were significantly less in metformin-treated males than those in metformin-treated females, but gender was not an independent risk factor. It suggests that the efficacy of the two drugs in FPG and 2hPPG reduction might not always be similar in either females or males.

In order to investigate the potential mechanisms involved, the alterations of those parameters related to insulin secretion and resistance were further analyzed in male and female patients after 24- and 48-week treatments. After 24- and 48-week treatment, AG$_{female}$ showed a decreased trend in HOMA-β while MG$_{female}$ exhibited an increase tendency. However, we did not observe any significantly differences in ΔEISI, ΔHOMA-IR, ΔWBISI, ΔAUC for glucagon, ΔAUC for plasma GLP-1, total calorie intake or even macronutrients intake between the acarbose- and metformin-treated patients in both genders. The mean AUC for serum insulin after a standard meal was significantly decreased in acarbose-treated patients than that in metformin-treated ones and a better insulin-sparing effect of acarbose was shown in both males and females. Nevertheless, it only indicates that acarbose treatment does not result in the development of hyperinsulinemia when 2hPPG is lowered, but could not explain the gender-differential effects of acarbose and metformin on blood glucose levels in Chinese patients with newly diagnosed type 2 diabetes.
Table 2 Changes in indices for insulin sensitivity and β-cell function from baseline to week 24 and to week 48 after stratification by gender

| Index                      | MGfemale Median (IQR) | AGfemale Median (IQR) | MGmale Median (IQR) | AGmale Median (IQR) |
|----------------------------|-----------------------|-----------------------|---------------------|---------------------|
| ΔHOMA-β                    |                       |                       |                     |                     |
| At 24 weeks                | 15.72 (6.99 to 24.45) | –14.35 (–34.86 to 6.16)** & a | 4.84 (–21.77 to 28.27) | 6.20 (–14.28 to 26.92) |
| At 48 weeks                | 3.60 (–17.16 to 29.65)** & a | –6.41 (–25.44 to 23.32)** & a | 4.26 (–18.58 to 31.19)** & a | 0.47 (–15.45 to 24.29)** & a |
| ΔHOMA-IR                   |                       |                       |                     |                     |
| At 24 weeks                | –2.30 (–2.87 to –1.72) | –2.55 (–3.41 to –1.69) | –1.59 (–3.22 to –0.19) | –1.01 (–2.93 to 0.24) |
| At 48 weeks                | –2.21 (–4.10 to –0.88) | –1.67 (–4.19 to –0.33) | –1.53 (–3.50 to 0.00) | –1.42 (–3.63 to –0.11) |
| ΔEISI¹                     |                       |                       |                     |                     |
| At 24 weeks                | 1.20 (–0.98 to 4.16)  | 1.27 (–1.08 to 4.16)  | 1.03 (–2.02 to 3.67) | 1.03 (–2.25 to 3.94) |
| At 48 weeks                | 1.14 (–0.94 to 3.16)  | 0.80 (–2.32 to 4.41)** & a | 0.65 (–2.49 to 2.56)** & a | 0.31 (–2.95 to 3.47)** & a |
| ΔWBISI²                    |                       |                       |                     |                     |
| At 24 weeks                | 2.96 (0.83 to 6.47)   | 3.48 (0.46 to 6.49)   | 2.03 (0.40 to 4.78)  | 2.49 (–0.02 to 5.58) |
| At 48 weeks                | 2.61 (1.06 to 5.59)   | 3.43 (0.90 to 6.22)   | 1.88 (–0.10 to 4.77) | 2.81 (0.64 to 5.71)  |
| ΔAUC for serum insulin (uIU/mL × min)³ | –569.47 (–968.64 to –170.31) | –1,568.52 (–2,114.54 to –1,022.51)** | –247.20 (–1,644.30 to 833.25) | –821.03 (–2,138.10 to 378.15)** |
| At 24 weeks                | –584.85 (–1,665.15 to 755.03) | –1,350.30 (–3,249.15 to –116.10)** | –447.15 (–2,351.25 to 1,231.50) | –978.60 (–2,449.95 to 308.70) |
| At 48 weeks                | –1,742.25 (–6,237.30 to 1,353.68) | –2,523.75 (–5,852.25 to 1,882.95) | –2,380.88 (–5,447.10 to 1,412.85) | –1,619.93 (–5,223.75 to 2,300.40) |
| ΔAUC for glucagon (pg/mL × min)³ | –74.45 (–1,277.58, 1,149.55) | –1,386.23 (–2,567.08 to –153.51) | –9.90 (–4,036.05 to 3,267.15)** | –3,522.60 (–3,645.60)² |
| At 24 weeks                | –1,742.25 (–6,237.30 to 1,353.68) | –2,523.75 (–5,852.25 to 1,882.95) | –2,380.88 (–5,447.10 to 1,412.85) | –1,619.93 (–5,223.75 to 2,300.40) |
| At 48 weeks                | –1,742.25 (–6,237.30 to 1,353.68) | –2,523.75 (–5,852.25 to 1,882.95) | –2,380.88 (–5,447.10 to 1,412.85) | –1,619.93 (–5,223.75 to 2,300.40) |
| ΔAUC for plasma GLP-1 (pmol/mL × min)³ | 1,028.84 (482.75 to 1,555.57) | 872.48 (405.96 to 1,311.06) | 1,028.18 (–622.65 to 2,355.15) | 825.15 (–506.85 to 2,681.70) |
| At 24 weeks                | 1,229.55 (546.38 to 2,862.83) | 1,545.45 (–831.00 to 2,758.05) | 1,391.40 (–735.60 to 3,001.80) | 858.60 (–583.80 to 2,564.70) |

MGfemale, metformin-treated female group; AGfemale, acarbose-treated female group; MGmale, metformin-treated male group; AGmale, acarbose-treated male group. HOMA, homoeostatic model assessment; EISI, early insulin secretion index; WBISI, whole body insulin sensitivity index; AUC, area under the curve; GLP-1, plasma glucagon-like peptide-1. ³ After a standard meal. ² The median values of the changes were not significantly different from zero. * p < 0.05, ** p < 0.01 vs. metformin-treated group in the same gender.

Acarbose could decrease postprandial glucose by inhibiting the activity of α-glucosidases on cell membrane brush-border in small intestine, resulting in mono‐saccharides absorption delay. The effect of α-glucosidase inhibitor on postprandial plasma glucose was related to the amount of carbohydrates in diets [16]. A better post‐prandial plasma glucose control of acarbose than metformin was shown in males not in females and that might relate to males’ diets contained more carbohydrates than females’. No significant difference was observed between acarbose-treated males and acarbose-treated females in 2hPPG reduction, although patients in AGmale took more carbohydrates than those in AGfemale. Acarbose-treated males had relatively higher body weight compared with acarbose-treated females, but both gender groups took the same dosage of acarbose. So the dosage of acarbose per kilogram of weight in acarbose-treated males was less than that in acarbose-treated females, which might reduce the effect of acarbose in 2hPPG level decrease in males.

Another possible mechanism involved might be the different intestinal microbiota composition in different genders. It has been demonstrated that acarbose could regulate the intestinal microbiota composition [17-20]. On the other hand, the composition of intestinal microbiota could predict the response to acarbose in patients with T2DM [17]. Recently, one study suggested that a higher Firmicutes/Bacteroidetes ratio and a lower abundance of the Prevotella in faecal samples from premenopausal females was observed than those from males.
or post-menopausal women, excluding the influence of nutritional factors [21]. Compared to those with a gut microbiota dominated by Prevotella, T2DM patients with a high abundance of Bacteroides have greater improvement in hyperglycaemia after acarbose treatment [17]. We speculated that acarbose might have a stronger effect in lowering postprandial glucose in males than that in females. In this article, we found that acarbose reduced 2hPPG to a greater extent in males than that in females, but there was no significant difference. A possible reason is that post-menopausal women were not separated when the comparison was made.

It is noteworthy that metformin could regulate the composition of intestinal microbiota [22]. A previous study indicated that the gut, especially the distal intestine, was responsible for the major glucose-lowering
Metformin and acarbose differ by gender

Table 3  Multiple linear regression analysis of the decreases in FPG and 2hPPG at 24 and 48 weeks in same gender group treated with different drugs

|                | Males at 24 weeks | Males at 48 weeks | Females at 24 weeks | Females at 48 weeks |
|----------------|-------------------|-------------------|---------------------|---------------------|
| ΔFPG 0.085     | 0.132             | 0.051             | 0.054               | 0.169               |
| Δ2hPPG −0.121  | 0.278             | 0.008             | −0.137              | 0.309               |

ΔFPG at 24 weeks: Adjusted by baseline variables (age, body weight, waist circumference, lipid profile, HbA1c, FPG, HOMA-β, HOMA-IR and WBISI), contribution of CPF for daily calorie intake and GS at 24 weeks as shown in Table 1 and Supplementary Table 1.

ΔFPG at 48 weeks: Adjusted by baseline variables (age, body weight, waist circumference, lipid profile, HbA1c, FPG, HOMA-β, HOMA-IR and WBISI), contribution of CPF for daily calorie intake, GS and add-on treatment with SU at 48 weeks as shown in Table 1 and Supplementary Table 1.

Δ2hPPG at 24 weeks: Adjusted by baseline variables (age, body weight, waist circumference, lipid profile, HbA1c, 2hPPG, EISI, WBISI, AUC for serum insulin, AUC for glucagon and AUC for plasma GLP-1), contribution of CPF for daily calorie intake and GS at 24 weeks as shown in Table 1 and Supplementary Table 1.

Δ2hPPG at 48 weeks: Adjusted by baseline variables (age, body weight, waist circumference, lipid profile, HbA1c, 2hPPG, EISI, WBISI, AUC for serum insulin, AUC for glucagon and AUC for plasma GLP-1), contribution of CPF for daily calorie intake, GS and add-on treatment with SU at 48 weeks as shown in Table 1 and Supplementary Table 1.

different lowering-FPG mechanisms between metformin and acarbose. Metformin lowers FPG by reducing hepatic gluconeogenesis and recovering islet β-cell function [26], whereas the effect of acarbose on FPG is glucotoxicity alleviation and insulin sensitivity improvement [27]. In fact, we found that both serum TG and body weight reduced to a greater extent in acarbose-treated patients (both male and female) than in metformin-treated ones. Although weight loss and lipotoxicity improvement might increase insulin sensitivity, we did not find greater improvement of fasting insulin resistance in the acarbose-treated group. We speculated that the better 2hPPG-lowering effect induce better glucotoxicity improvement in acarbose-treated males than that in metformin-treated males, so that we could see comparable HOMA-β improvement and FPG control in the acarbose- and metformin-treated male group. Thereby the less FPG decline in female patients treated with acarbose compared with metformin might be related to the comparable 2hPPG control and significantly less HOMA-β recovery. In this study, metformin exerted a stronger effect in improvement of HOMA-β than acarbose throughout the study in females. Moreover, we found metformin reduced FPG to a greater extent than acarbose in females. Multiple linear regression analysis showed that drug selection was an independently factor for the decreased FPG in females. More studies are needed to examine these findings.

We appreciate there were several limitations in this study. Firstly, the tendency of changes in 2hPPG could not be precisely described since postprandial fingertip blood glucose was not collected at each visit. Secondly, menopausal status, physical activity, and socioeconomic status were not investigated. At last, intestinal microbiota composition was not analysed in those newly-diagnosed T2DM patients. Nonetheless, our study was a reliable investigation based on the well-designed MARCH trial with long-period follow-ups, and systemically assessed the between acarbose and metformin in T2DM patients after stratification by gender. Of course, although the multivariate analyses were conducted, we could not completely exclude the impacts of the differences in baseline characteristics on the above comparisons between the two genders or acarbose- and metaformin-treated groups.

Our results suggest that newly diagnosed type 2 diabetes Chinese patients could considerate the characteristics such as gender differences and the predominance of fasting or postprandial hyperglycemia when selecting...
acarbose or metformin as the initial therapy. More studies are needed to validate the results.

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