

# Comparison of therapeutic effects of acarbose and metformin under different $\beta$ -cell function status in Chinese patients with type 2 diabetes

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**Abstract.** MARCH study suggested that acarbose had similar therapeutic effect on glycated hemoglobin reduction compared to metformin in newly diagnosed type 2 diabetes patients as initial therapy in China. We aimed to investigate whether the efficacy of acarbose was still similar to metformin under different  $\beta$ -cell function status. According to the homeostasis model assessment (HOMA)- $\beta$  level, 670 patients were divided into better  $\beta$ -cell function group, medium  $\beta$ -cell function group and poor  $\beta$ -cell function group. Patients received acarbose 300 mg/d or metformin 1,500 mg/d for 48 weeks. We found both acarbose and metformin could decrease glycated hemoglobin to similar levels after 48 weeks treatment in all groups. In medium  $\beta$ -cell function group, the decrease of fasting blood glucose after metformin treatment was more significant compared to acarbose ( $p = 0.040$ ); however, the decrease of post-challenge blood glucose after acarbose treatment was more significant compared to metformin ( $p = 0.020$ ). Moreover, in poor  $\beta$ -cell function group, the decrease of body weight and body mass index after acarbose treatment were significant compared to metformin ( $p = 0.004$  and  $p = 0.031$ , respectively). Therefore, acarbose contributed a similar therapeutic effect to plasma glucose control compared to metformin treatment, even under different  $\beta$ -cell function status.

**Key words:** Acarbose, Metformin,  $\beta$ -cell function, Chinese, Type 2 diabetes

**DIABETES MELLITUS (DM)**, a chronic degenerative metabolic disease, is characterized by hyperglycemia and disorders of carbohydrates metabolism, lipids metabolism, and proteins metabolism caused by insulin resistance (IR) and islet  $\beta$ -cell dysfunction [1]. More than 90% of all DM are type 2 diabetes mellitus (T2DM), which is the most common DM [1]. T2DM caused by the complex interaction among gene, environment and other risk factors. T2DM is accelerated by reduced first-phase insulin release, disordered pulsatility of basal insulin secretion, and increased glucagon secretion [2]. Recent

studies have also emphasised the role of early life factors such as maternal undernutrition, maternal obesity, and gestational diabetes linked to increased risk of diabetes in offspring [3]. Complications associated with T2DM are cardiovascular diseases, diabetic neuropathy, nephropathy, and retinopathy [1].

Approximately 7.5% Chinese adults in northwest China interviewed had newly diagnosed T2DM [4]. In Tianjin, China, the percentage for T2DM among school-aged children was small, however, T2DM related risk factors such as overweight and obesity were very common [5, 6]. In a cross-sectional survey in Shanghai adults T2DM was found in 10.1% of subjects with higher incidence among patients with hyperlipidemia. This survey also revealed that there were more males (11.4%) than females (9.2%) [6], more elderly ( $\geq 65$  years 22.5%) than younger ( $< 55$  years,  $< 10\%$ ) individuals, and more urban residents (12.8%) than rural residents (5.2%) among T2DM patients [7].

Joshi *et al.* and Wang *et al.* have reported that metformin/acarbose combination has complimentary mechanisms on reducing glycemic level, HbA1c and

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bodyweight. And this combination could bring out more cardiovascular benefits and minimum adverse events [8, 9]. Another research based on MARCH trial (metformin and acarbose in Chinese as the initial hypoglycaemic treatment) demonstrated that metformin and acarbose treatment individually resulted in a significant decline in urine albumin/creatinine ratio in Chinese newly diagnosed T2DM patients. Furthermore, acarbose exerted prominent effect after 48 weeks [10]. Other studies also showed that comparing metformin, acarbose contributed a similar therapeutic effect to HbA1c and body weight, however, acarbose exerted better effect in improving islet  $\alpha$ -cell in overweight/obese patients [11, 12]. Reductions in HbA1c levels were regardless of body mass index (BMI) status of Chinese T2DM patients [11].

The present data does not differentially access the efficacy of the acarbose and metformin in different  $\beta$ -cell function group in T2DM Chinese population. Thus, this study was carried out to illuminate the therapeutic efficacy of acarbose and metformin as the initial therapy with individual drug in T2DM Chinese population based on fasting blood glucose (FBG), post challenge blood glucose (PBG), fasting insulin (FINS), glycated hemoglobin (HbA1C), homeostatic model assessment for insulin resistance (HOMA-IR), body weight, BMI, anthropometric parameters, cardiovascular and lipid metabolic parameters with different  $\beta$ -cell function.

## Materials and Methods

### *Study design, selection of patients, grouping and treatment intervention*

MARCH was a multicenter, prospective and randomized controlled trial. The Chinese Clinical Trial Registry number was ChiCTR-TRC-08000231. The aim was to compare acarbose with metformin as the initial therapy in patients with newly diagnosed T2DM. The rationale and design of the study including inclusion criteria, exclusion criteria and randomization were published previously.

In this study, 784 patients were diagnosed with T2DM based on 1999 WHO diabetes criteria and recruited in the past 12 months [13]. In this analysis, we excluded 114 patients including 31 patients without homeostasis model assessment of  $\beta$  cell function (HOMA- $\beta$ ) data in baseline and 83 patients who received insulin secretagogues. The inclusion criteria included a HbA1c level of 7–10% and a FBG level of 7.0–11.1 mmol/L. According to HOMA- $\beta$  value, the whole data were divided in tertiles. The HOMA- $\beta$  value was showed as median and upper and lower quartiles in each group: better  $\beta$ -cell function group [HOMA- $\beta$  88.18 (74.38–114.62)], medium  $\beta$ -cell function group [HOMA- $\beta$  47.61 (41.22–55.62)] and poor

$\beta$ -cell function group [HOMA- $\beta$  21.91 (16.47–27.71)]. The run-in phase lasted for 4 weeks. Subsequently these patients were randomly assigned to receive metformin hydrochloride 500 mg TID or acarbose 100 mg TID, administered with meals for 48 weeks. All patients provided written informed consent. The protocol was approved by an ethics committee from each clinical site and was implemented in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The clinical trial registry number was ChiCTR-TRC-08000231.

### *Study outcome*

All patients were assessed for glucose metabolism parameters namely FBG, PBG, FINS, HbA1c, HOMA-IR and HOMA- $\beta$ ; anthropometric measurements namely waist circumference, hip circumference, bodyweight and BMI; lipid metabolic parameters in terms of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), Non-HDL-C, optimal LDL-C rate, and optimal HDL-C rate; cardiovascular parameters as systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline and after treatment at 48 weeks. TC (mmol/L) minus HDL-C (mmol/L) figured out Non-HDL-C level (mmol/L). HOMA-IR and HOMA- $\beta$  were calculated by the following equation: HOMA-IR = [FBG (mmol/L)\*FINS (mIU/L)/22.5]; HOMA- $\beta$  = 20\*FINS (mIU/L)/[FBG (mmol/L) – 3.5] [14].

### *Statistical methods*

All data were analyzed using SPSS 22.0 (SPSS, Inc, Chicago, IL). Kolmogorov-Smirnov test and Shapiro-Wilk test were used to normality test. The variable which followed a normal distribution was given as mean  $\pm$  standard deviation. Paired-samples *t*-test was used to compare the changes from baseline values in the same group. Independent sample *t*-test was used to analyze the comparison between groups at baseline and after treatment. Differences between groups were evaluated by the analysis of variance (ANOVA) test and the Tukey test for *post-hoc* comparisons. The variables which did not follow normal distributions, including FINS, HOMA-IR, HOMA- $\beta$  and TG, were expressed as median and upper and lower quartiles. We used Kruskal-Wallis ANOVA to compare differences among groups and a Dunn-Bonferroni test for *post-hoc* comparisons. The comparison of proportions was done with chi-square test. Statistical significance was displayed as a value of  $p < 0.05$ .

**Table 1** Baseline characteristics of Chinese patients with newly diagnosed T2DM under various  $\beta$ -cell function groups

Variables	better $\beta$ -cell function group HOMA- $\beta$ 88.18 (74.38–114.62) ( $n = 223$ )	medium $\beta$ -cell function group HOMA- $\beta$ 47.61 (41.22–55.62) ( $n = 223$ )	poor $\beta$ -cell function group HOMA- $\beta$ 21.91 (16.47–27.71) ( $n = 224$ )	$p$ value
Age, y	50.97 $\pm$ 9.37	49.68 $\pm$ 8.93	50.93 $\pm$ 9.53	.298
Gender, Males/Females, $n$	117/106	120/103	102/122	.177
Waist circumference, cm	91.66 $\pm$ 8.70	89.85 $\pm$ 7.53	87.29 $\pm$ 8.22	.000
Hip circumference, cm	100.70 $\pm$ 7.65	99.44 $\pm$ 6.73	97.11 $\pm$ 7.64	.000
Body weight, kg	71.99 $\pm$ 11.30	71.05 $\pm$ 10.00	67.83 $\pm$ 10.20	.000
BMI, kg/m <sup>2</sup>	26.43 $\pm$ 2.64	25.81 $\pm$ 2.46	24.87 $\pm$ 2.31	.000
Systolic BP, mmHg	125.04 $\pm$ 13.02	125.44 $\pm$ 12.67	124.87 $\pm$ 11.48	.880
Diastolic BP, mmHg	80.32 $\pm$ 7.89	80.87 $\pm$ 7.74	79.51 $\pm$ 7.36	.169
Metabolic parameters				
TC, mmol/L	5.35 $\pm$ 1.10	5.25 $\pm$ 1.12	5.19 $\pm$ 1.13	.309
LDL-C, mmol/L	3.09 $\pm$ 0.89	3.05 $\pm$ 0.95	2.98 $\pm$ 0.85	.430
HDL-C, mmol/L	1.25 $\pm$ 0.31	1.21 $\pm$ 0.27	1.24 $\pm$ 0.31	.262
TG, mmol/L	1.91 (1.32–2.74)	2.02 (1.36–2.92)	1.72 (1.20–2.51)	.016
Non-HDL-C, mmol/L	4.10 $\pm$ 1.10	4.03 $\pm$ 1.11	3.95 $\pm$ 1.10	.365
FBG, mmol/L	7.66 $\pm$ 1.24	8.19 $\pm$ 1.24	8.90 $\pm$ 1.60	.000
PBG, mmol/L	11.42 $\pm$ 2.75	12.33 $\pm$ 2.42	13.62 $\pm$ 3.11	.000
FINS, uIU/mL	18.75 (14.97–24.25)	11.32 (9.17–11.42)	5.83 (4.44–8.05)	.000
optimal LDL-C rate, %	26.4	32.6	32.1	.285
optimal non-HDL-C rate, %	22.7	28.1	33.9	.030
HbA1c, %	8.09 $\pm$ 0.92	8.22 $\pm$ 0.90	8.36 $\pm$ 0.95	.009
HOMA-IR	6.31 (4.81–8.49)	4.00 (3.04–5.72)	2.20 (1.59–3.35)	.000
HOMA- $\beta$	88.18 (74.38–114.62)	47.61 (41.22–55.62)	21.91 (16.47–27.71)	.000

Data are means  $\pm$  SD unless indicated otherwise. TG, INS, HOMA-IR and HOMA- $\beta$  are shown as median and the upper and lower quartiles. HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cell function. BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; PBG, 2 h post-challenge blood glucose; FINS, fasting insulin; Optimal LDL-C rate, the proportion of patients with optimal levels of LDL-C; optimal non-HDL-C rate, the proportion of patients with optimal levels of non-HDL-C. The optimal levels of LDL-C and non-HDL-C were defined as: LDL-C <100 mg/dL (2.6 mmol/L) and non-HDL-C <130 mg/dL (3.4 mmol/L); HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance.

## Results

### Baseline characteristics in newly diagnosed T2DM patients

The data from 670 patients (334 commenced acarbose and 336 commenced metformin) were involved in the analysis. Table 1 shows baseline characteristics in better  $\beta$ -cell function group, medium  $\beta$ -cell function group and poor  $\beta$ -cell function group. There were no significant differences for age, gender ratio, SBP, DBP, Non-HDL-C, TC, LDL-C, HDL-C and the proportion of patients with LDL-C <2.6 mmol/L among all groups (all  $p$  values >0.05). We found significant differences for waist circumference, hip circumference, BMI, body weight, FBG,

PBG, FINS, TG, proportion of patients with non-HDL-C <3.4 mmol/L, HbA1c, HOMA-IR and HOMA- $\beta$  among the three groups (all  $p$  values <0.05).

### Variables of glucose metabolism after acarbose or metformin treatment after 48 weeks treatment

After 48 weeks, the reductions of HbA1c were similar between the acarbose and metformin treatment group of all the three  $\beta$ -cell function groups ( $p$  values were 0.348, 0.966 and 0.592 in better, medium and poor  $\beta$ -cell function group respectively). In medium  $\beta$ -cell function group, the decrease of FBG after metformin treatment was more significant compared to acarbose treatment group at 48 weeks [−1.87 (−2.13 to −1.61) vs. −1.37

**Table 2** Glucose metabolism variables after acarbose/metformin treatment in newly diagnosed T2DM patients under various  $\beta$ -cell function groups

Glucose metabolism variables	better $\beta$ -cell function group HOMA- $\beta$ 88.18 (74.38–114.62) ( <i>n</i> = 223)		medium $\beta$ -cell function group HOMA- $\beta$ 47.61 (41.22–55.62) ( <i>n</i> = 223)		poor $\beta$ -cell function group HOMA- $\beta$ 21.91 (16.47–27.71) ( <i>n</i> = 224)	
	Acarbose ( <i>n</i> = 107)	Metformin ( <i>n</i> = 116)	Acarbose ( <i>n</i> = 109)	Metformin ( <i>n</i> = 114)	Acarbose ( <i>n</i> = 118)	Metformin ( <i>n</i> = 106)
FBG, mmol/L	–1.29 (–1.60––0.99)	–1.57 (–1.86––1.27)	–1.37 (–1.57––1.18)	–1.87 (–2.13––1.61)*	–1.61 (–1.98––1.24)	–1.96 (–2.42––1.49)
PBG, mmol/L	–2.23 (–2.91––1.58)	–1.94 (–2.55––1.32)	–3.19 (–3.68––2.70)	–2.14 (–2.54––1.75)*	–3.32 (–4.03––2.61)	–2.79 (–3.60––1.98)
FINS, uIU/mL	–9.24 (–14.68––3.88)	–8.52 (–14.96––2.55)	–3.29 (–6.34––0.30)	–4.72 (–8.32––0.87)	–0.71 (–2.33––2.96)	2.58 (–0.48––5.64)
HbA1C, %	–1.79 (–2.02––1.56)	–1.99 (–2.22––1.76)	–1.95 (–2.21––1.70)	–1.98 (–2.18––1.79)	–1.89 (–2.12––1.66)	–1.70 (–1.95––1.45)
HOMA-IR	–3.68 (–5.55––1.72)	–3.45 (–5.49––1.42)	–1.43 (–2.87––0.42)	–2.07 (–3.79––0.79)	–0.79 (–1.54––0.37)	0.34 (–0.86––1.54)
HOMA- $\beta$	–26.50 (–57.10––13.39)	–18.37 (–48.80––23.85)	–4.37 (–17.45––23.60)	–2.65 (–20.77––25.89)	7.05 (–3.13––28.14)	33.06 (15.49––50.63)

Data are shown as difference (95% CI) vs. baseline. HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cell function; FBG, fasting blood glucose; PBG, 2 h post-challenge blood glucose; FINS, fasting insulin; HbA1C, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance. \* significantly different at  $p < 0.05$  between acarbose and metformin arms of the same group.

(–1.57 to –1.18),  $p = 0.040$ ]. Moreover, the decrease of PBG after acarbose treatment for 48 weeks was more significant compared to metformin group [–3.19 (–3.68 to –2.70) vs. –2.14 (–2.54 to –1.75),  $p = 0.020$ ]. After 48 weeks, the improvements of IR were similar between the acarbose and metformin treatment group of all the three  $\beta$ -cell function groups ( $p$  values were 0.524, 0.223 and 0.369 in better, medium and poor  $\beta$ -cell function group respectively) (Table 2).

#### **Anthropometric variables after acarbose or metformin treatment after 48 weeks treatment**

After 48 weeks drug treatment, both acarbose group and metformin group showed a significant and similar reduction of anthropometric variables namely waist circumference, hip circumference, body weight and BMI in all the three  $\beta$ -cell function group (all  $p < 0.05$ ). However, the body weight and BMI were decreased significantly in patients treated with acarbose when compared with metformin after 48 weeks in poor  $\beta$ -cell function group [–2.80 (–3.53 to –2.07) vs. –1.78 (–2.39 to –1.17),  $p = 0.004$ , and –1.02 (–1.30 to –0.75) vs. –0.65 (–0.87 to –0.42),  $p = 0.031$ , respectively] (Table 3).

#### **Effect of acarbose and metformin treatment on lipid profile and blood pressure after 48 weeks treatment**

Comparing with metformin, acarbose decreased TG level significantly both in medium  $\beta$ -cell function and poor  $\beta$ -cell function groups [–0.52 (–1.22 to 0.04) vs.

0.11 (–0.67 to 0.43),  $p = 0.000$ ; –0.35 (–0.78 to 0.11) vs. –0.07 (–0.58–0.37),  $p = 0.000$ , respectively]. Furthermore, in patients with better  $\beta$ -cell function, the proportion of patients with LDL-C  $< 2.6$  mmol/L was higher in metformin treatment group than acarbose (41.1% vs. 26.7%,  $p = 0.035$ ) (Table 4).

In the three groups, acarbose reduced DBP by 2.1–3.2 mmHg ( $p$  values were 0.004, 0.012 and 0.026 in better, medium and poor  $\beta$ -cell function group respectively), whereas the reduction of DBP in metformin treatment group was about 2.2–4.0 mmHg in all groups ( $p$  values were 0.013, 0.000 and 0.013 in better, medium and poor  $\beta$ -cell function group respectively). Acarbose reduced SBP by 2.6 mmHg in poor  $\beta$ -cell function group ( $p = 0.030$ ), while metformin decreased SBP by 3.6 mmHg in medium  $\beta$ -cell function group ( $p = 0.011$ ). The decreases of SBP and DBP were similar among all groups (Table 4).

## **Discussion**

Acarbose, which plays a role in the small intestine, could bind with  $\alpha$ -glucosidases in the brush border, then reversibly inhibit a number of  $\alpha$ -glucosidase and consequently delay the absorption of carbohydrate from the gut [15]. Therefore, acarbose is an appropriate therapeutic strategy in Chinese due to the traditional carbohydrate-rich diet [16]. Many researches have confirmed the powerful therapeutic efficacy of acarbose, including the MARCH study [11, 17]. Previous reports about MARCH

**Table 3** Anthropometric variables after acarbose/metformin treatment in newly diagnosed T2DM patients under various  $\beta$ -cell function groups

Variables	better $\beta$ -cell function group HOMA- $\beta$ 88.18 (74.38–114.62) ( <i>n</i> = 223)		medium $\beta$ -cell function group HOMA- $\beta$ 47.61 (41.22–55.62) ( <i>n</i> = 223)		poor $\beta$ -cell function group HOMA- $\beta$ 21.91 (16.47–27.71) ( <i>n</i> = 224)	
	Acarbose ( <i>n</i> = 107)	Metformin ( <i>n</i> = 116)	Acarbose ( <i>n</i> = 109)	Metformin ( <i>n</i> = 114)	Acarbose ( <i>n</i> = 118)	Metformin ( <i>n</i> = 106)
Waist circumference, cm	–3.37 (–4.30––2.45)	–2.38 (–3.24––1.53)	–2.96 (–3.90––2.01)	–3.00 (–4.04––1.96)	–2.29 (–3.27––1.31)	–2.11 (–3.19––1.04)
Hip circumference, cm	–3.06 (–4.05––2.07)	–2.31 (–3.34––1.28)	–2.61 (–3.51––1.71)	–2.19 (–2.94––1.43)	–2.49 (–3.56––1.43)	–1.20 (–2.33––0.06)
Body weight, kg	–2.95 (–3.82––2.07)	–2.20 (–2.82––1.58)	–2.44 (–3.24––1.64)	–1.94 (–2.53––1.34)	–2.80 (–3.53––2.07)	–1.78 (–2.39––1.17)**
BMI, kg/m <sup>2</sup>	–1.26 (–1.60––0.92)	–1.05 (–1.31––0.79)	–1.09 (–1.39––0.78)	–0.91 (–1.20––0.62)	–1.02 (–1.30––0.75)	–0.65 (–0.87––0.42)*

Data are shown as difference (95% CI) vs. baseline. HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cell function; BMI, body mass index. \* significantly different at  $p < 0.05$  between acarbose and metformin arms of the same group; \*\* significantly different at  $p < 0.01$  between acarbose and metformin arms of the same group.

**Table 4** Changes in lipid profile and blood pressure after acarbose/metformin treatment in newly diagnosed T2DM patients under various  $\beta$ -cell function groups

Variables	better $\beta$ -cell function group HOMA- $\beta$ 88.18 (74.38–114.62) ( <i>n</i> = 223)		medium $\beta$ -cell function group HOMA- $\beta$ 47.61 (41.22–55.62) ( <i>n</i> = 223)		poor $\beta$ -cell function group HOMA- $\beta$ 21.91 (16.47–27.71) ( <i>n</i> = 224)	
	Acarbose ( <i>n</i> = 107)	Metformin ( <i>n</i> = 116)	Acarbose ( <i>n</i> = 109)	Metformin ( <i>n</i> = 114)	Acarbose ( <i>n</i> = 118)	Metformin ( <i>n</i> = 106)
Systolic BP, mmHg	–2.63 (–5.39––0.13)	–1.85 (–4.17––0.47)	–1.33 (–4.32––1.66)	–3.57 (–6.44––0.69)	–2.64 (–5.08––0.20)	–0.61 (–3.03––1.82)
Diastolic BP, mmHg	–3.18 (–5.11––1.25)	–2.18 (–4.01––0.35)	–2.30 (–4.08––0.52)	–4.03 (–5.98––2.08)	–2.12 (–3.96––0.29)	–2.31 (–4.17––0.46)
Metabolic parameters						
TC, mmol/L	–0.41 (–0.63––0.18)	–0.46 (–0.65––0.27)	–0.41 (–0.61––0.21)	–0.30 (–0.53––0.06)	–0.31 (–0.52––0.11)	–0.22 (–0.45––0.02)
LDL-C, mmol/L	–0.05 (–0.25––0.16)	–0.13 (–0.32––0.06)	–0.10 (–0.28––0.10)	–0.13 (–0.31––0.06)	–0.03 (–0.19––0.12)	–0.12 (–0.29––0.06)
HDL-C, mmol/L	0.00 (–0.06–0.06)	–0.10 (–0.17––0.03)	0.05 (–0.01–0.11)	–0.01 (–0.06–0.04)	0.02 (–0.03–0.08)	0.02 (–0.06–0.10)
TG, mmol/L	–0.24 (–0.95––0.15)	–0.16 (–0.96––0.48)	–0.52 (–1.22––0.04)	0.11 (–0.67–0.43) **	–0.35 (–0.78–0.11)	–0.07 (–0.58–0.37)**
Non-HDL-C, mmol/L	–0.40 (–0.64––0.17)	–0.37 (–0.54––0.19)	–0.46 (–0.65––0.28)	–0.28 (–0.52––0.04)	–0.34 (–0.54––0.14)	–0.23 (–0.47–0.00)
optimal LDL-C rate, %	26.7	41.1*	33.0	34.0	32.7	37.2
Optimal non-HDL-C rate, %	43.3	39.0	45.4	45.4	39.8	43.0

Data are shown as difference (95% CI) vs. baseline, unless optimal LDL-C rate and optimal non-HDL-C rate. HOMA- $\beta$ , homeostasis model assessment of  $\beta$  cell function; BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; The optimal levels of LDL-C and non-HDL-C were defined as: LDL-C <100 mg/dL (2.6 mmol/L) and non-HDL-C <130 mg/dL (3.4 mmol/L). optimal LDL-C rate, the proportion of patients with optimal levels of LDL-C; optimal non-HDL-C rate, the proportion of patients with optimal levels of non-HDL-C. \* significantly different at  $p < 0.05$  between acarbose and metformin arms of the same group; \*\* significantly different at  $p < 0.01$  between acarbose and metformin arms of the same group.



shows that acarbose and metformin could reduce HbA1c similarly as initial treatment in patients with newly diagnosed T2DM in China [17]. Whereas, it is still unknown whether the therapeutic effect is still similar in patients with different  $\beta$ -cell function. This study presents that acarbose and metformin could reduce HbA1c levels similarly in T2DM patients with different  $\beta$ -cell function status. Many studies have demonstrated that acarbose exerts better effect in PBG and metformin exerts better effect in FBG. In this study, FBG and PBG had significant differences between acarbose and metformin in only medium  $\beta$ -cell function group. In better and poor  $\beta$ -cell function groups, we only found the trends in FBG and PBG between acarbose and metformin, but not the statistical differences. The main reason may patients with better  $\beta$ -cell function could overcome the weakness of drugs by regulating islet function in better  $\beta$ -cell function group. Previous studies show the higher the FBG and PBG levels, the better the improvement after treatment [17]. In poor  $\beta$ -cell function group, patients got higher FBG and PBG levels on baseline. And the improvements in FBG and PBG were significant after acarbose or metformin treatment. This may lead to no statistical differences in two treatment groups.

Insulin resistance and insulin deficiency are two main causes of T2DM. The continuous decline in  $\beta$ -cell function is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis. In our study, the variations in  $\beta$ -cell function may have implication on duration of diabetes, although all patients were newly diagnosed. We found patients in better  $\beta$ -cell function group owned higher levels of FINS and HOMA-IR, higher weight, higher BMI, lower FBG, PBG and HbA1c%.

We also found acarbose and metformin could improve insulin sensitivity similarly in patients with different  $\beta$ -cell function. This efficacy of metformin could be accounted for its positive effects on insulin receptor expression, glucose transporter 4 (GLUT4) expression and tyrosine kinase activity [18, 19]. Metformin may also improve IR by reducing body weight and modulating lipid profile [20]. Postprandial hyperglycemia caused by traditional carbohydrate-rich diet leads to IR by many mechanisms, including enhancing advanced glycation end products and oxidative stress, promoting production of inflammatory factors and disturbing insulin signaling pathway [15, 21]. So acarbose may improve IR by lowering the PBG and insulin levels [22].

Obesity or overweight leads to many negative effects in the patients with T2DM. Thus, the effect on body weight is a significant aspect for evaluating an antidiabetic agent. In this study both acarbose and metformin showed the significant effect on decreasing body weight

in the three groups. Acarbose resulted in a stronger weight loss in poor  $\beta$ -cell function group compared to metformin. The underlying mechanism of weight reduction by acarbose therapy may include the release of ghrelin and gastric inhibitor peptide (GIP) and the increase of glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK) [23]. Furthermore, acarbose may reduce weight by increasing the content of gut *Bifidobacterium longum*, decreasing some inflammatory cytokines [24], altering the concentration of short-chain fatty acids (SCFAs) [25] and regulating hunger and satiety at the brain level [9, 26]. Metformin causes body weight loss by stimulating phosphorylation of adenosine monophosphate activated protein kinase (AMPK) [27]. AMPK plays important roles in mitochondrial biogenesis, glucose transport, insulin secretion, and lipogenesis [28]. Metformin may also reduce weight loss through IR-improving, the induction anorectic effect and the reduction of carbohydrates absorption [28]. The effect of metformin on lowering weight depends on the weight level before treatment. The reduction of weight after metformin treatment is more significant in patients with higher weight on baseline. However the reduction of weight is less in the thin patients. In this study the weight level is more lower in poor  $\beta$ -cell function group than in other two groups. This may account for the lesser body weight and BMI reductions after metformin treatment in poor  $\beta$ -cell function group.

Metabolic syndrome, a very common epidemic disease nowadays, is composed of central obesity, hypertension, hyperglycemia and dyslipidemia. Previous reports revealed that acarbose and metformin both had some beneficial effects on metabolic syndrome. Our finding was consistent with others [29-32] and revealed that acarbose and metformin could decrease plasma TC and non-HDL-C slightly in the three groups. The proportion of patients with optimal LDL-C levels with metformin treatment was higher than acarbose in better  $\beta$ -cell function group. Comparing with metformin, acarbose showed more intensive effect on improving TG in medium  $\beta$ -cell function and poor  $\beta$ -cell function groups.

Acarbose can reduce the serum TG levels by reducing blood glucose levels, improving IR, decreasing weight, and decreasing the rate of hepatic uptake of precursor molecules for *de novo* lipogenesis [33]. As previous report, acarbose could decrease oleic acid absorption, the amount of secreted TG-rich lipoprotein and apo B-48 secretion in Caco-2 cells. Thus acarbose may decrease serum lipids by reducing chylomicron synthesis or secretion by intestinal cells [34]. Metformin could improve lipid profile by glucose-lowering, IR-improving, inhibiting the production of cholesterol and TG and stimulating fatty acid oxidation by promoting AMPK [27].

MARCH study demonstrates that acarbose showed more intensive effect on improving TG than metformin. In this subgroup analysis we only found the differences between acarbose and metformin in medium and poor  $\beta$ -cell function group. In better  $\beta$ -cell function group we only found the trend in TG between acarbose and metformin, but not the statistic difference. This may be related to the slightly decrease on blood glucose levels in better  $\beta$ -cell function group.

The characteristic of metformin is improving IR, however acarbose is lowering PBG by inhibiting the  $\alpha$ -glucosidase in gut. Because of the traditional carbohydrate-rich diet in Chinese, we observed the similar reduction on HbA1c in different  $\beta$ -cell function groups. So we consider that acarbose also can be used as initial therapy in newly diagnosed T2DM patients in China regardless of  $\beta$ -cell function status.

The strength of this study is comparison of various glucose and lipid metabolism parameters, cardiovascular and anthropometric parameters in different  $\beta$  cell function group T2DM patients after 48 weeks treatment.

Meanwhile, there are two main limitations of this study. *In vivo* acarbose and metformin could affect many other gut hormones which were was not assessed, and there was no placebo-controlled group.

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## Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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