Original Article
Efficacy and safety of *Sancailianmei Particle* compared with acarbose in patients with type 2 diabetes mellitus inadequately controlled with metformin

Zhimei Tang[1*], Huizhen Chen[1*], Wei Fang[1*], Yulei Luo[1*], Huanping Wang[1], Chenchen Wei[2], Qinwen Xie[1], Yang Gao[1], Huakui Gan[3], Zhihuang Zuo[4], Qi Chen[5], Cuimei Shi[6], Xinli Zhang[7], Jian Guo[8], Xiaoling Xiong[9], Wei Yan[10], Jiao Yang[2], Xiaoran Zhang[2], Lisha Sun[2], Qiu Chen[2]

[1]School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu 610072, China; [2]Department of Endocrinology, Teaching Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, China; [3]Department of Endocrinology, The First People's Hospital of Neijiang, Neijiang 641000, China; [4]Department of Endocrinology, The Central Hospital of Guangyuan, Guangyuan 628000, China; [5]Zizhong Hospital of Traditional Chinese Medicine, Zizhong 641200, China; [6]Hospital of Traditional Chinese Medicine of Xichang, Xichang 615000, China; [7]Liangshan Hospital of Integtrated Traditional and Western Medicine, Xichang 615000, China; [8]Department of Endocrinology, The Second People's Hospital of Leshan, Leshan 614000, China; [9]Department of Endocrinology, Sichuan Integrative Medicine Hospital, Chengdu 610041, China; [10]Department of Endocrinology, The Third People's Hospital of Chengdu, Chengdu 610031, China. *Co-first authors.

Abstract: Objective: To compare the efficacy and safety of *Sancailianmei Particle (SLP)* and Acarbose in type 2 diabetes mellitus (T2DM) patients inadequately controlled with metformin. Methods: A randomized, parallel-group, multi-center clinical trial was conducted. 100 cases of T2DM patients inadequately controlled with metformin were included and randomly divided into Sancai group and Acarbose group. 50 cases of Sancai group were treated with *SLP* combined with Metformin. Another 50 cases of Acarbose group were treated with Acarbose combined with Metformin. The efficacy was evaluated by comparing fasting blood-glucose, 2-hour postprandial blood glucose, glycosylated hemoglobin, blood lipid, weight, body mass index, insulin resistance and its related indicators. The safety was assessed by observing routine blood test, liver and kidney function test, electrocardiogram and incidence of adverse reaction. Results: HbA1C, fasting and postprandial glucose of both groups were effectively reduced (P<0.01), with no significant difference (P>0.05) between the two groups. Total cholesterol (TC) and low density lipoprotein (LDL-C) in Sancai group was significantly decreased (P<0.05), while they were not significantly decreased in Acarbose group (P>0.05). Blood glucose level was effectively reduced in both groups (P<0.05). The 1hINS and 2hINS were significantly increased, but 3hINS was significantly decreased in Sancai group (P<0.05). There was significant improvement of β cell function index in Sancai group (P<0.05). The incidence of gastrointestinal adverse reactions and diarrhea in Sancai group was lower than Acarbose group. Conclusion: *SLP* has advantages of decreasing blood lipid and improving the function of islet β cells with satisfying safety and tolerance.

Keywords: Type 2 diabetes, acarbose, *Sancailianmei Particle*, randomized controlled trials

Introduction

With an increasing global incidence of type 2 diabetes mellitus (T2DM) [1], it represents a challenge for clinicians to achieve effective long-term blood glucose control. Although numbers of hypoglycemic drugs could effectively control blood glucose in the early stage, treatment failure due to the gradual function loss of islet B cell is still a big problem. Therefore, optional hypoglycemic drugs should be combined to strengthen the treatment efficacy [2].

Metformin is a first-line drug for T2DM recommended by guideline, which is wildly used in the early stage of T2DM. It is also recommended to combine Metformin with Acarbose for patients with poor glycemic control with Metformin alone [3]. However, it is limited in clinical practice due to the increasing incidence of intolerance adverse drug reaction such as diarrhea and dyspepsia.

In recent years, many researches have confirmed that traditional Chinese medicine (TCM)
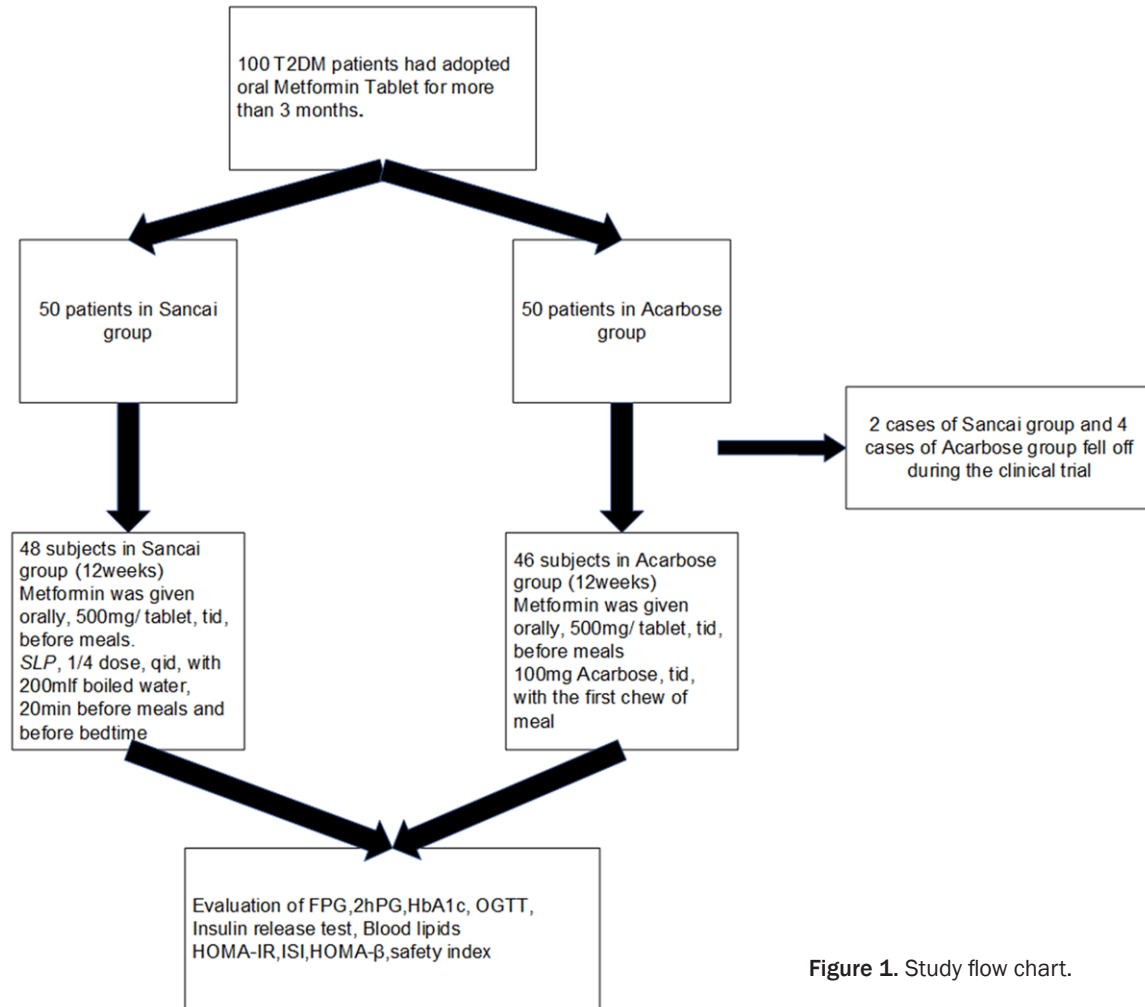
Figure 1. Study flow chart.

has significant advances in the reducing blood glucose, improving blood lipid regulation, decreasing insulin resistance (IR), preventing hypoglycemia and chronic complications of diabetes [4-8].

(SLP) contains *Ginseng, Dark plum, Radix rehmanniae, Coptis chinensis,* and *Cinnamon* etc. Modern pharmacological research has shown that *Coptis chinensis* and *Cinnamon* could significantly improve hyperglycemia. The compound preparation of *Jiao tai Pill* could improve hyperglycemia, hyperlipidemia and the accumulation of hepatic lipid for rats as well as human which might be related to the inhibition of the relevant lipid synthesis gene expression [9]. Modern research has also showed that Chinese medicine compound could effectively reduce the HbA1c (%) and weight in type 2 diabetes compared with Metformin [10]. Meanwhile, *Ginseng* contains a variety of anti-

oxidants, such as *Ginseng saponin, Ginseng polyethylene* compounds and *Panaxadiol saponins*, showing an effect of anti-peroxidation of lipid [11]. *Radix rehmanniae decoction* could effectively reduce fasting blood glucose in diabetic rats, and increase the content of hepatic glycogen [12]. A vitro test in mice has found that *Ginsenoside Re* could activate AMPK to improve IR and lipid disorders for T2MD patients [13]. Berberine is the main alkaloid of *Rhizoma coptidis*, which protects pancreatic beta cells by inhibiting insulin gene promoter through the activation of AMP dependent protein kinase (AMPK) [14]. A variety of studies have shown that berberine could reduce glucose, HbA1c and increase insulin sensitivity. Coptis chinensis improves the damage of islet beta cell mediated by oxidative stress via increasing super oxide dismutase and glutathione activity [15]. Coptis chinensis could also stimulate the release of GLP-1 to ascend insu-

Table 1. Demographic and baseline characteristics of the patients in two groups

Characteristic	Sancai group	Acarbose group	T	P value
Sex	-	-	-	-
Male	27	26	-	-
Female	21	20	-	-
Age (years)	53.63±10.62	56.13±9.56	-1.20	0.233
Body weight (Kg)	66.87±9.11	66.68±10.21	0.14	0.924
BMI (Kg/m^2)	24.46±2.52	24.59±2.41	-0.19	0.800
HbA1c (%)	8.20±0.58	8.28±0.70	-0.54	0.592
FPG (mmol/L)	8.49±1.80	8.69±1.50	0.59	0.557
2hPG (mmol/L)	14.79±3.22	15.38±3.44	0.85	0.389
HOMA-IR[A]	2.70 (2.76)	3.28 (1.8)	-0.37	0.715
HOMA-β[A]	25.61 (37.4)	32.02 (31.74)	0.17	0.868
ISI[A]	0.016 (0.019)	0.013 (0.008)	0.24	0.813
TC (mmol/L)	5.38±1.12	5.13±1.33	1.01	0.314
TG (mmol/L)	1.93±1.29	2.60±2.19	-1.82	0.730
HDL-C (mmol/L)	1.37±0.38	1.31±0.39	0.67	0.506
LDL-C (mmol/L)	3.10±0.97	2.98±0.96	0.60	0.551

Notes: A: The data are transformed to logarithms.

lin level [16]. The animal experiments have confirmed that *Cinnamon* could reduce postprandial blood glucose [17] by inhibiting the activity of α-glucosidase. The cinnamon extract helps to reduce the blood glucose and triglyceride [18]. Therefore, theoretically drug combination of *Sancailianmei Particle* has a certain hypoglycemic effect.

One previous multicenter RCT has indicated that *SLP* had favorably curative effect and security on newly diagnosed T2DM patients with satisfactory short-term (12 weeks) control rate of HbA1c and blood glucose, which was similar to Metformin, and there were no adverse events (AE) during the treatment [19]. Moreover, our unpublished data showed that *SLP* had inconspicuous effect on fasting blood glucose (FBG), but significant effect on postprandial glucose, which is similar to Acarbose. Therefore, in the study, we further evaluated and compared the clinical efficacy of *SLP* and Acarbose of treating T2DM patients with poor glycemic control by Metformin alone. Compared with other direct contrast researches, our study mainly focused on ladder-like therapies for T2DM patients after the failure of Metformin treatment alone. We expect to explore a new idea for diabetes ladder-like therapy and a good option for treating T2DM patients inadequately controlled with metformin.

Materials and methods

Participants ethical approval

The study is a randomized controlled trial (RCT). The number of the Clinical Trial registration is ChiCTR-INR-16008440. The study was approved by the Ethics Committee of the Teaching Hospital of Chengdu University of Traditional Chinese Medicine. The informed consent procedure had been obtained from all patients.

The study was sponsored by the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, collaborated with Center Hospital of Guangyuan City, the First People's Hosptial of Neijiang City, the Zizhong Hospital of Traditional Chinese Medicine, the Second People's Hospital of Leshan City, the Xichang Hospital of Traditional Chinese Medicine, the Integrated Traditional Chinese Medicine and Western Medicine of Liangshan State, the Sichuan Integrative Medicine Hospital and the third people's Hospital of Chengdu.

Participants

The diagnosis of T2DM was made according to the 1999 WHO diagnostic criteria. The age of the patients was between 18 and 70, BMI was between 18.5 kg/m^2 and 30 kg/m^2 and HbA1c was between 7.0% and 9.5%. The Patients whose blood glucose level was poorly controlled after taking Metformin (1500 mg/d) alone over 12 weeks were included. All patients volunteered to participate in this study, and signed informed consent. The exclusion criteria included T1DM or other special types of diabetes; gestation; diabetes mellitus complicated with severe complications including the insufficiency of heart, liver or kidney; any history of tumor and other severe diseases; acute or chronic pancreatitis; the combined use of other drugs which affect glucose metabolism.

Interventions

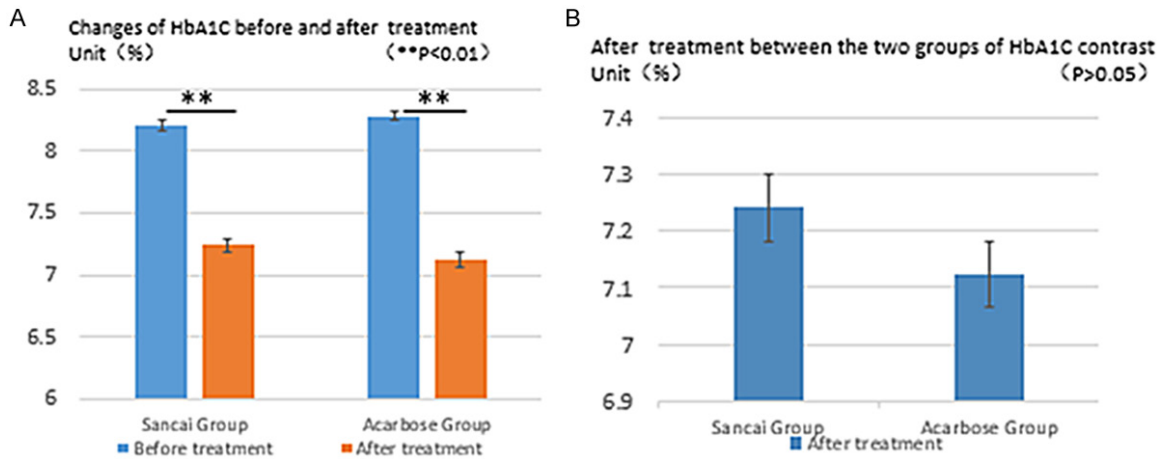The *SLP* was purchased from Sichuan new green pharmaceutical development holding

Figure 2. HbA1C measurement of the two groups. A. Compare of the HbA1C before and after treatment in two groups. B. Compare of the HbA1C of the two groups after treatment.

Table 2. Comparison of clinical features and glucose parameters between two groups before and after treatment ($\overline{x} \pm s$)

Group	n	BMI (kg/m²)	FPG (mmol/L)	2hPG (mmol/L)	HbA1c (%)
Sancai group					
Before treatment	48	24.46±2.52	8.49±1.80	14.79±3.22	8.20±0.58
After treatment	48	23.68±1.92	7.05±0.82[b]	8.89±0.92[b]	7.24±0.55[b]
P		0.790	0.000	0.000	0.000
Acarbose group					
Before treatment	46	24.59±2.41	8.69±1.50	15.38±3.44	8.28±0.70
After treatment	46	24.19±2.37	7.30±0.90[b]	9.59±1.29[b]	7.12±0.68[b]
P		0.431	0.000	0.000	0.000

Notes: b: compared with before treatment in same group, P<0.01.

company. Metformin was purchased from Sino American Shanghai Squibb Pharmaceuticals Limited production of Metformin and Acarbose was purchased from Bayer healthcare Co. Ltd. Acarbose.

All subjects were recruited and randomly assigned into Sancai group and Acarbose group. Metformin was given orally, 500 mg/ tablet, tid, before meals. In addition, the subjects in Sancai group took *SLP*, 1/4 dose, qid, with 200 mlf boiled water, 20 min before meals and before bedtime. The subjects in Acarbose group took 100 mg Acarbose, tid, with the first chew of meal. All subjects were not allowed to take any other anti-diabetic drugs during 12-week intervention. Moreover, proper diet intervention and exercise guide were adopted for all subjects during the trial.

Efficacy index

Primary efficacy index: Fasting plasma glucose (FPG) and 2-hour postprandial glucose (2hPG) were measured with glucose oxidase method. Venous plasma was tested at 0 and 12 weeks, and fingertip blood were detected at preliminary screening and at 1, 2, 4, 6, 8 and 10 weeks. HbA1c, OGTT, Insulin release test, Blood lipids were detected before the baseline and in the 0 and 12 week after randomization. HbA1c was detected by High performance liquid chromatography at 0 and 12 weeks. OGTT: standard 100 g steamed bun was adopted. Plasma glucose and insulin levels were detected at 0, 1, 2 and 3 hours after eat. During the standard meal test, other foods or beverages containing calories or xanthine (such as caffeine) should not be taken. Insulin release test
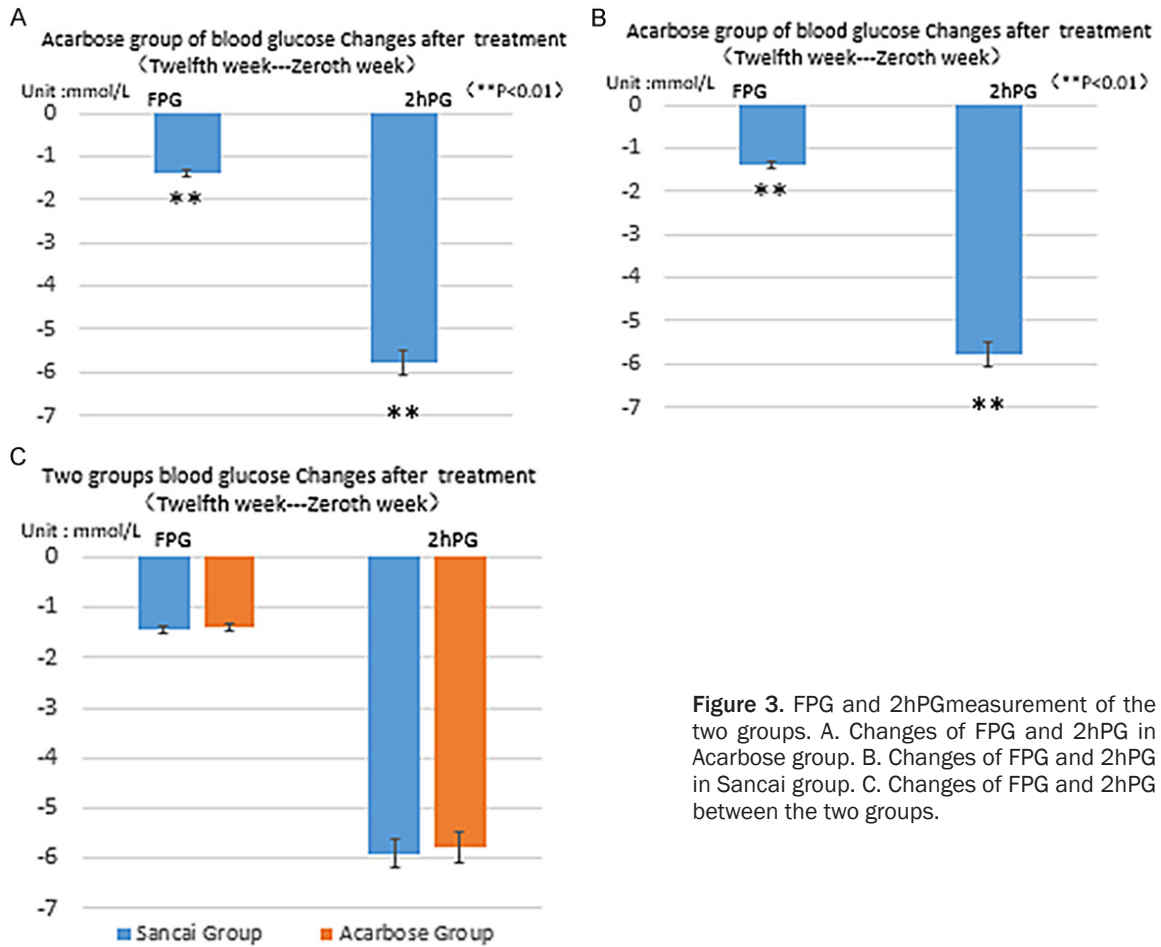
Figure 3. FPG and 2hPGmeasurement of the two groups. A. Changes of FPG and 2hPG in Acarbose group. B. Changes of FPG and 2hPG in Sancai group. C. Changes of FPG and 2hPG between the two groups.
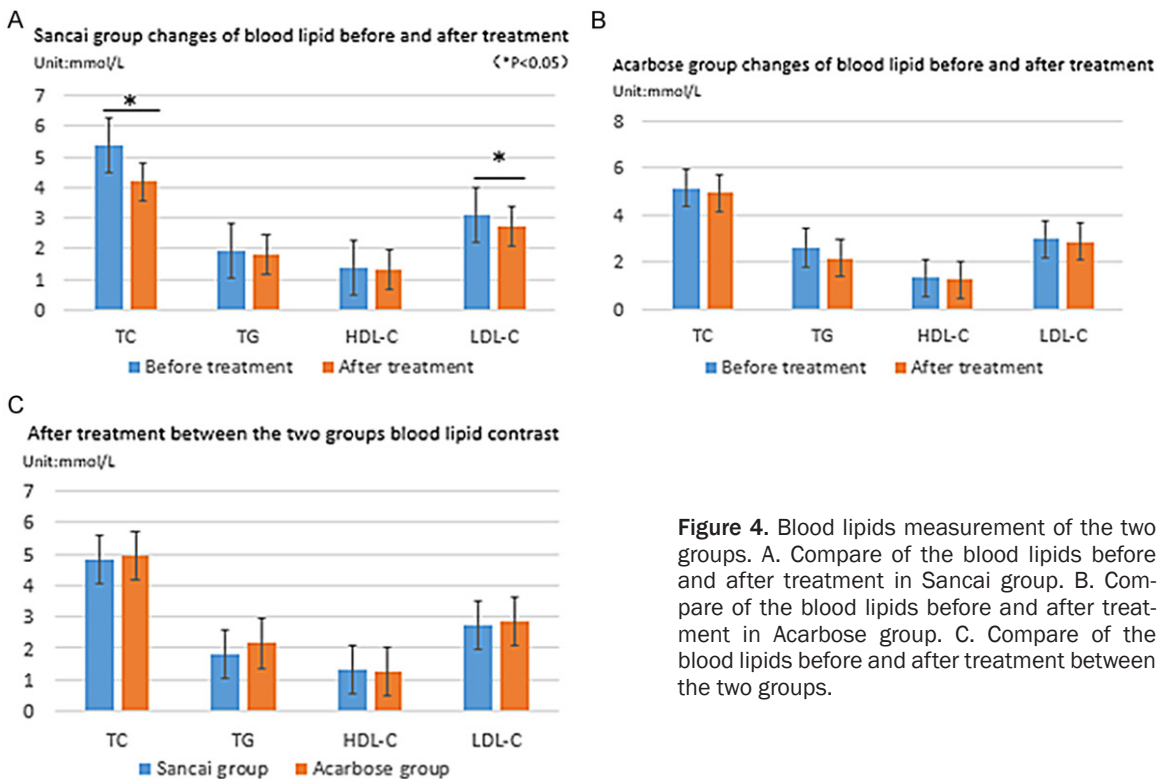

Figure 4. Blood lipids measurement of the two groups. A. Compare of the blood lipids before and after treatment in Sancai group. B. Compare of the blood lipids before and after treatment in Acarbose group. C. Compare of the blood lipids before and after treatment between the two groups.

Table 3. Comparison of lipid levels between two groups before and after treatment ($\bar{x} \pm s$)

Group	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Sancai group					
Before treatment	48	5.38±1.12	1.93±0.38	1.37±0.38	3.10±0.97
After treatment	48	4.81±0.92[a]	1.81±1.06	1.32±0.41	2.72±0.82[a]
P		0.025	0.640	0.530	0.039
Acarbose group					
Before treatment	46	5.13±1.33	2.60±2.19	1.31±0.39	2.98±0.96
After treatment	46	4.94±0.91	2.16±1.17	1.26±0.31	2.86±0.68
P		0.433	0.240	0.560	0.518

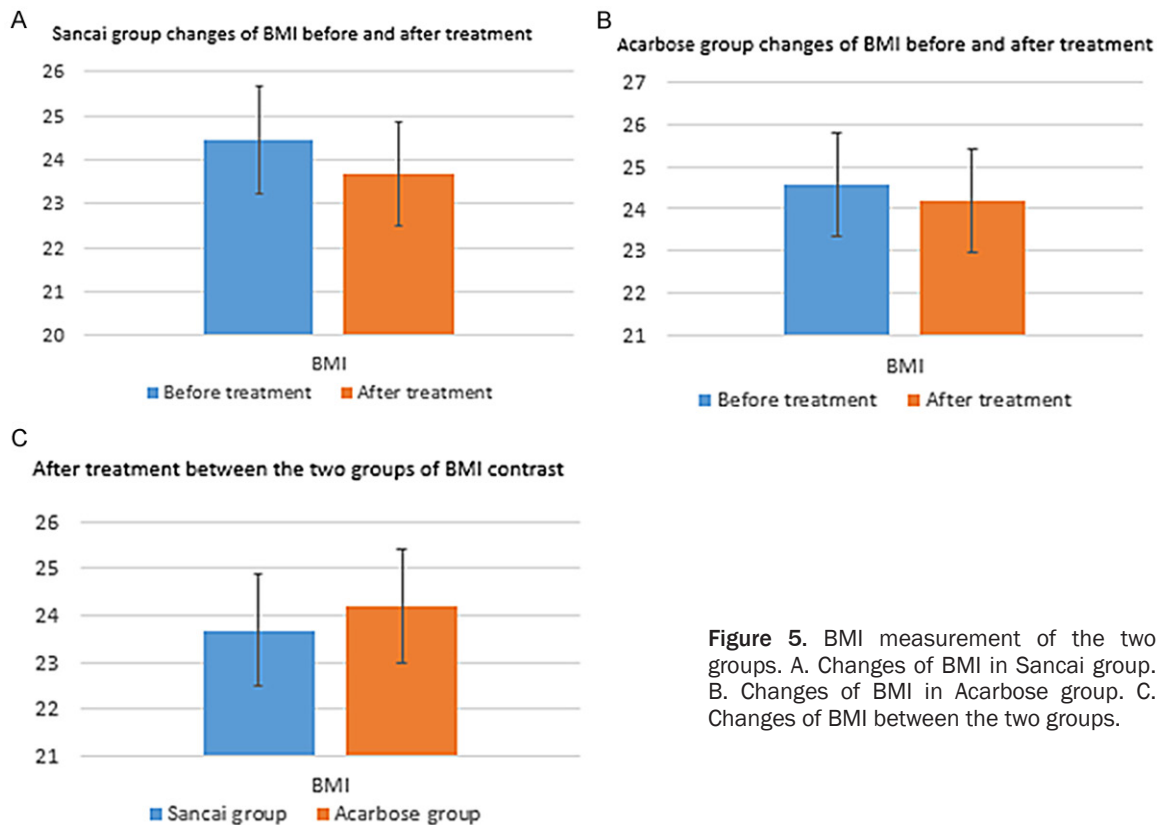Notes: a: compared with before treatment in same group, P<0.05.

Figure 5. BMI measurement of the two groups. A. Changes of BMI in Sancai group. B. Changes of BMI in Acarbose group. C. Changes of BMI between the two groups.

were measured with the chemiluminescence method. Blood lipids including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were analyzed by automatic biochemical analyzer.

Secondary efficacy index: Secondary efficacy indexes were calculated according to insulin release test result. HOMA insulin resistance index (HOMA-IR) = (FPG × FINS)/22.5. Insulin sensitivity index (ISI): ISI = 1/(FPG × FINS). HOMA pancreatic β cell function index (HOMA-β): HOMA-β = (20 × FINS)/(FPG-3.5).

Safety index: Safety index included general physical examination items (body temperature, respiration, heart rate, blood pressure, etc.), blood routine test, urine routine test, and liver function test (ALT and AST), renal function test (Cr and BUN) and adverse reactions.

Statistical analysis

The SPSS 21.0 statistical analysis software was used for statistical analysis. Quantitative data fitting a normal distribution was expressed as mean ± standard deviation ($\bar{x} \pm s$). Count data described in number (percentage).
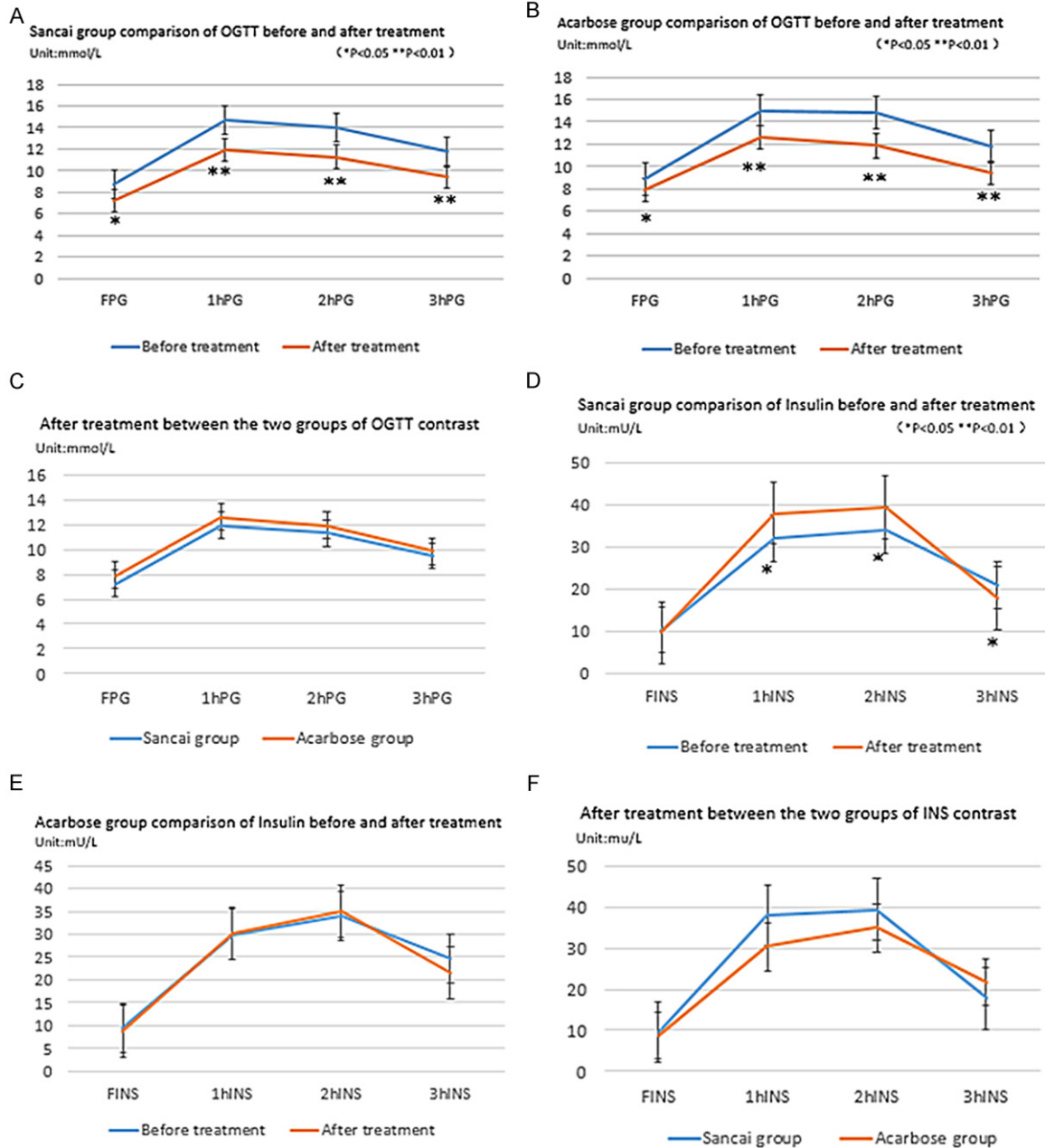
Figure 6. OGTT and insulin release test of the two groups. A. Changes of OGTT in Sancai group. B. Changes of OGTT in Acarbose group. C. Changes of OGTT between the two groups. D. Changes of insulin in A Sancai group. E. Changes of insulin in Acarbose group. F. Changes of insulin between the two groups.

Homeostasis model assessment (HOMA) index was described as median (interquartile spacing) in conformity normal distribution, and it was analyzed after logarithm transition. The differences between before and after treatment are evaluated by paired samples T-test. Comparison between two groups was analyzed with independent sample T-test. The comparison of incidence of adverse events between the two groups using X^2 test or Fisher's exact probabili-

ty method, $P<0.05$ was considered as a statistically significant difference.

Results

General information

100 T2DM patients had adopted oral Metformin Tablet for more than 3 months. Random numbers were generated by SAS software. All

Table 4. Comparisonof homeostasis model assessment index between two groups before and after treatment [M (QR)]

Group	n	HOMA-IRA	HOMA-βA	ISIA
Sancai group				
Before treatment	48	2.70 (2.769)	25.61 (37.4)	0.016 (0.019)
After treatment	48	2.10 (1.22)	42.13 (23.75)[a]	0.021 (0.013)
P		0.073	0.032	0.073
Acarbose group				
Before treatment	46	3.28 (1.8)	32.02 (31.74)	0.013 (0.008)
After treatment	46	2.69 (1.96)	37.39 (36.78)	0.016 (0.011)
P		0.198	0.112	0.269

Notes: a: compared with before treatment in same group, P<0.05. A: The data are transformed to logarithms.

patients were assigned into Sancai group and Acarbose group in a 1:1 ratio. 2 cases of Sancai group and 4 cases of Acarbose group fell off during the clinical trial. Finally, there are 48 subjects in Sancai group and 46 subjects in Acarbose group completed the experiment after 12 weeks of treatment (**Figure 1**). There were no significant differences of the indicators between the two groups before the intervention (**Table 1**).

HbA1C measurements

HbA1C was observed in both groups before and after 12 weeks of intervention. Our results showed that HbA1c was decreased in both groups (**Figure 2A**). HbA1c was decreased from 8.20±0.58% to 7.24±0.55% in Sancai group, while from 8.28±0.70% to 7.12±0.68% in Acarbose group (P<0.01, **Table 2**). The difference was no significance(P>0.05, **Figure 2B**). These results indicated that *SLP* and Acarbose could decrease HbA1c and no statistically significant difference was observed (**Table 2**).

FPG and 2hPG measurements

FPG and 2hPG were measured before and after the intervention. After treatment, fasting and postprandial blood glucose of two groups were significantly reduced (**Figure 3A** and **3B**) (P<0.01). The FPG was decreased by 1.49 mmol/L and the 2hPG was decreased by 5.90 mmol/L in Sancai group (P<0.01, **Table 2**). The FPG was decreased by 1.39 mmol/L and the 2hPG was decreased by 5.79 mmol/L in Acarbose group (P<0.01, **Table 2**). The changes of FPG and 2hPG between the both groups

were not significant before and after intervention (**Figure 3C**, P>0.05).

Blood lipids measurements

Levels of TC, TG, HDL and LDL were measured before and after the intervention. In Sancai group, the levels of TC and LDL-C prominently were significantly decreased after intervention (**Figure 4A**, P<0.05). However, in the Acarbose group, there were no significant difference of TC and LDL-C (**Figure 4B**). The blood lipids between the both groups were not significantly different after intervention. (**Figure 4C**, P>0.05) (**Table 3**).

BMI comparsion

BMI was measured before and after the intervention. BMI of Sancai group had a decrease trend but not significantly difference (**Figure 5A**, P>0.05). BMI in Acarbose group was not decreased (**Figure 5B**, P>0.05). BMI between the two groups were not significantly different after intervention (**Figure 5C**, P>0.05).

OGTT and insulin release test

The blood glucose significantly decreased at all time points in both groups (**Figure 6A** and **6B**) (P<0.05). Insulin level of Sancai group increased at one and two hours after intervention, decreased at three hours after intervention (**Figure 6D**). While the Insulin level of Acarbose group was not significantly changed after the intervention (**Figure 6E**). There were no significant differences of glucose and insulin levels between the two groups after intervention (**Figure 6C** and **6F**) (P>0.05).

HOMA-IR, HOMA-β and ISI measurements

HOMA-IR was decreased and HOMA-ISI was increased in both groups, but there were no significant difference (P>0.05, **Table 4**) (**Figures 7A-C** and **8**). The HOMA-β was significantly improved in Sancai group after the intervention (**Figure 7D**, P<0.05) while that was not significant change in Acarbose group (**Figure 7E**, P>0.05). No significant difference was observed between the two groups (**Figure 7F**, P>0.05).
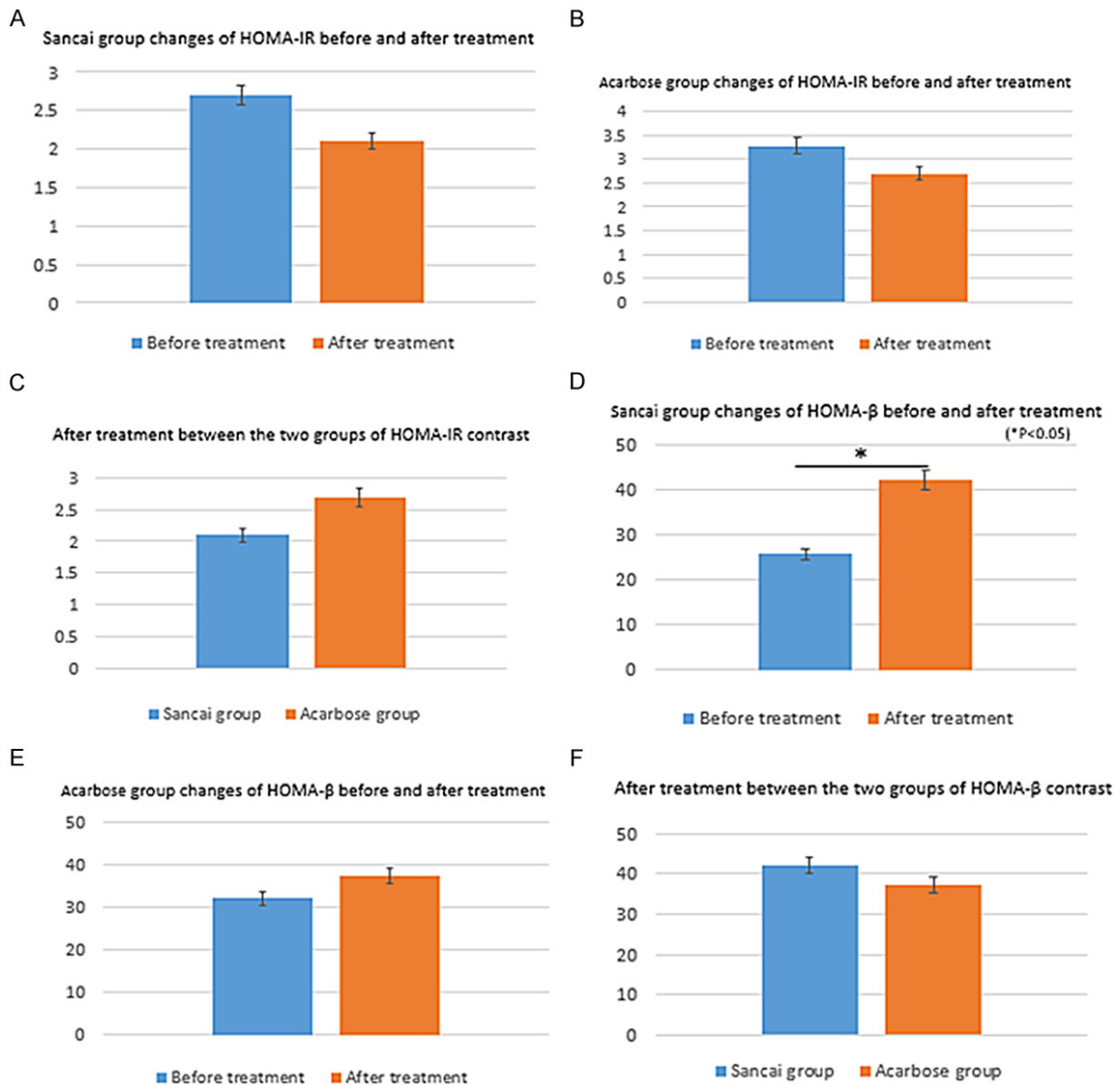
Figure 7. HOMA-IR, HOMA-β measurement the two groups. A. Changes of HOMA-IR in Sancai group. B. Changes of HOMA-IR in Acarbose group. C. Changes of HOMA-IR between the two groups. D. Changes of HOMA-β in Sancai group. E. Changes of HOMA-β in Acarbose group. F. Changes of HOMA-β between the two groups.

Safety evaluation

During the treatment, there were no serious adverse reactions, severe hypoglycemia or abnormality in liver or kidney functions. In Sancai group, there were 5 subjects suffered with transient nausea, vomiting, anorexia or other upper gastrointestinal adverse reactions (10.4%, **Table 5**). 3 subjects got temporary constipation (6.0%, **Table 5**). In Acarbose group, there were 12 subjects suffered with upper gastrointestinal adverse reactions (26.0%, **Table 5**), 3 subjects got transient astriction (6.5%, **Table 5**), and one subject got hypoglyce-

mia (2.0%, **Table 5**). The incidence rate of upper gastrointestinal adverse reactions and diarrhea of Acarbose group is significantly higher than that of Sancai group (P<0.05, **Table 5**).

Discussion

In our study, the HbA1c was decreased from 8.20% to 7.24% in Sancai group, while from 8.28% to 7.12% in Acarbose group. The fasting and postprandial blood glucose was decreased in both groups. From the above results, there were similar effects on lowering glucose and HbA1c (%) of *SLP* and Acarbose.

A

Sancai group changes ISI before and after treatment

B

Acarbose group changes of ISI before and after treatment

C

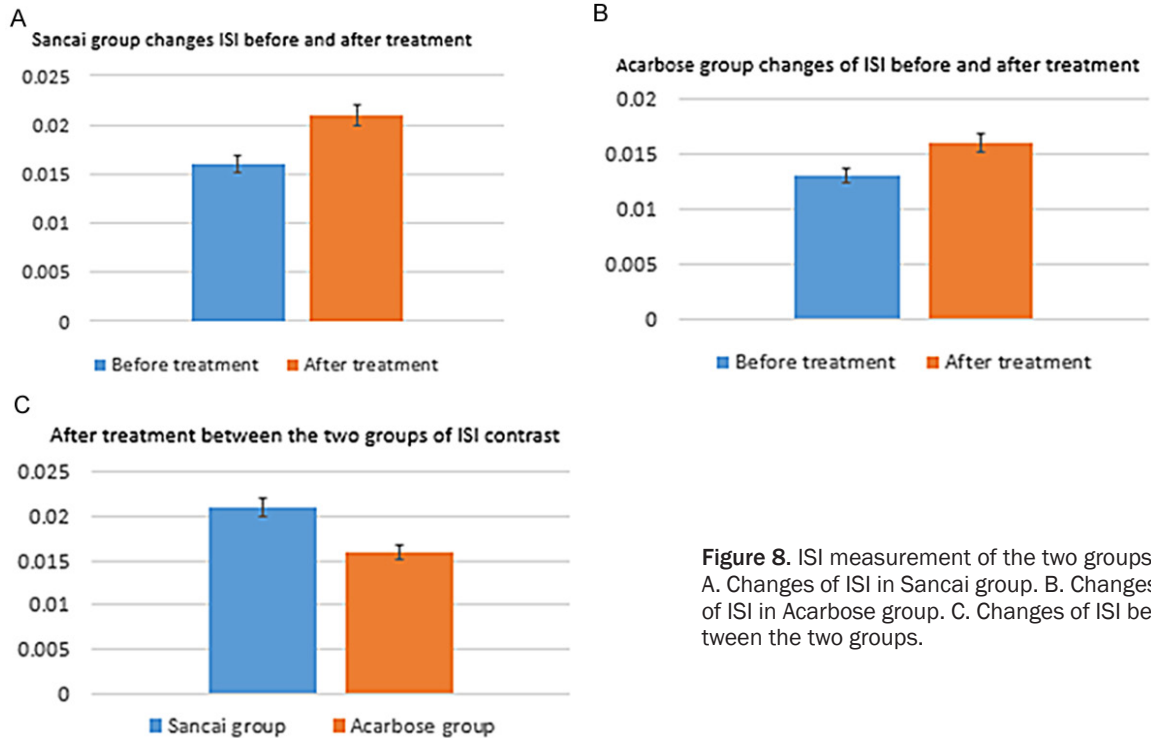**After treatment between the two groups of ISI contrast**

Figure 8. ISI measurement of the two groups. A. Changes of ISI in Sancai group. B. Changes of ISI in Acarbose group. C. Changes of ISI between the two groups.

Table 5. Comparison of adverse effect between two groups after the 12-week treatment [n (%)]

Group	n	Upper gastrointestinal Adverse	Diarrhea	Astrietion	Mild hypoglycemia
Sancai group	48	5 (10.4%)	2 (4%)	3 (6.0%)	0
Acarbose group	46	12 (26.0%)[c]	8 (17.3%)[c]	3 (6.5%)	1 (2%)
P		0.048	0.038	0.957	0.495

Notes: c: compared with Acarbose group after 12 weeks of treatment, P<0.05.

Considering the treating time, the 2hPG lowering effects were significant in two groups. It should be noted that the subjects were taken Metformin, with pancreatic dysfunction and under poor glycemic control before recruited. The results showed that *SLP* had a clear hypoglycemic effect. After 1-week treatment, the fasting and 2hPG were significantly reduced. The short term reduction of blood glucose proved that *SLP* might stimulate insulin secretion. As we known that berberine could stimulate the release of GLP-1 to increase the insulin level [16], and cinnamon could inhibit α-glucosidase activity to reduce postprandial glucose [17].

Comparing the insulin level before and after the treatment, the changes were significant in Sancai group. The insulin level was increased in 1 h and 2 hrs, decreased in 3 hrs. The results suggested the islet β-cell function have been improved and a recovery of their physiological curve. OGTT result indicated the same as that glucose level decreased significantly at 1 h, 2 h, 3 h. The ISI, HOMA-IR and HOMA-β results also showed that *Sancailianmei Particle* effectively improved β-cell function. The results confirmed the efficacy of *SLP* on improving IR, increasing insulin sensitivity and protecting the function of islet β cell. Some specific herbs of the compound might reduce glucose and improve IR through various of channels and targets.

It is believed that 60% to 90% incidence of diabetes is closely related to obesity [20]. For diabetic patients, obesity is such a negative factor for cardiovascular emergencies and even death, that weight control is particularly important [21]. In addition, studies have shown that increasing concentration of free fatty acids or the intracellular fat-the "toxic fat" could cause

or enhance IR and pancreatic β cell dysfunction, and hence start or promote the onset of type 2 diabetes [22]. Therefore, some scholars believe that diabetes should be called "glycolipid disease" [23]. In our study with lifestyle intervention, BMI showed a downward trend but no obvious change in Sancai group, so did the BMI in Acarbose group. There was little difference in BMI index level between the two groups. TC and LDL-C levels in the Sancai group were effectively decreased, but not changed in the Acarbose group.

Several studies have shown that Acarbose could reduce weight of T2MD patients instead of increasing weight. Compared with placebo, no statistic difference was observed [24-26]. Previous meta-analysis has proposed that Acarbose was more effective on losing weight to T2MD patients in eastern diets than western diets. Acarbose worked better than placebo, Metformin and Nateglinide on losing weight for T2MD patients with each type of diets [27]. Considering the previous long-term use of Metformin and the poor glycemic controlling of the subjects, the impact of the basic drug on body weight and blood lipids were not taken into consideration. Based on the discussion above, it is inferred that *SLP* regulates lipid metabolism.

No serious adverse reaction was observed during the treatment. The rate of upper gastrointestinal adverse reactions and diarrhea of Acarbose group in our study is higher than in MARCH study [28], which may be caused by being combined use of Metformin. However, the incidence of adverse reactions in Sancai group was lower than Acarbose group, which is confirmed that *SLP* in combination with Metformin has better safety and tolerability.

There were also some limitations in our study. Due to the limitations of TCM formulations, a double-blind trial can hardly be implennented. The research on the molecular mechanism of *SLP is lacked,* further researches are required.

In conclusion, this study indicated that Metformin combined with *SLP* or Acarbose has the same effects of decreasing blood glucose level and HbA1c for the T2DM patients whose blood glucose level were poorly controlled by Metformin alone. Moreover, *SLP* exerts the effects on decreasing blood lipid, improving the

function of islet B cells. *SLP* could obviously decrease gastrointestinal adverse reactions and increase the patient's tolerance and medication compliance, which provided a new idea for therapy of diabetes and option for the treating T2DM whose blood glucose level was poorly controlled.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Qiu Chen, Department of Endocrinology, Teaching Hospital of Chengdu University of Traditional Chinese Medicine, Twelve Bridge Road No. 37, Jinniu District, Chengdu 610-072, China. Tel: +86-28-87766249; E-mail: wantro@126.com

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