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Improving insulin resistance with traditional Chinese medicine in type 2 diabetic patients

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Abstract Some clinical studies and animal researches have evaluated the efficacy of Traditional Chinese Medicine (TCM) and compared its effects with placebo or other antidiabetic drugs. TCM involves three particular plants, as an antidiabetic drug. Our present research planned to evaluate the efficacy of TCM on insulin sensitivity and other related metabolic factors in type 2 diabetic patients. There were 43 newly diagnosed type 2 diabetic patients enrolled in this study, who did not use any antidiabetic drugs before. They were randomly assigned into TCM and placebo groups, administrated with TCM and placebo, respectively. Glucose disposal rate, fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin, and other metabolic components were assessed at baseline and end point. Glucose disposal rate increased from 5.12 ± 2.20 to 6.37 ± 3.51 mg kg^{-1} min^{-1} in the TCM group, ANCOVA analysis showed that glucose disposal rate in the TCM group was significantly improved as compared to that in the placebo group ($P < 0.05$). Other metabolic related components such as fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin, systolic blood pressure, diastolic blood pressure, body mass index, retinol binding protein 4 were improved in TCM group, but no statistical differences was detected between the two groups. No severe side effect was found in TCM group. TCM can ameliorate insulin resistance in type 2 diabetes and it is safe and effective in newly diagnosed diabetic patients.

Keywords Traditional Chinese medicine · Type 2 diabetes · Insulin resistance · Glucose disposal rate

Abbreviations

T2D	Type 2 diabetes
TCM	Traditional Chinese medicine
FPG	Fasting plasma glucose
PPG	Postprandial plasma glucose
HbA1c	Glycated hemoglobin
INS0'	Fasting plasma insulin
INS120'	Postprandial plasma insulin
TG	Triglyceride
TC	Total cholesterol
HDL-c	High-density lipoprotein-cholesterol
LDL-c	Low-density lipoprotein-cholesterol
HPLC	High performance liquid chromatography
RBP4	Retinol binding protein 4
HsCRP	C-reactive protein
IL-6	Interleukin-6
GDR	Glucose disposal rate
BMI	Body mass index

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SBP	Systolic blood pressure
DBP	Diastolic blood pressure
AMPK	AMP-activated protein kinase

Introduction

There are about 171 million diabetic patients throughout the world currently, and this number is expected to grow to nearly 366 millions in 2033, among which >90% are T2D [1]. This climbing number reflects not only in the developed countries but in the developing countries as well. T2D has been a crucial health problem globally. Islet β cells dysfunction and insulin resistance are both playing leading roles in the mechanism of T2D, and Insulin resistance correlates tightly with other metabolic related components such as obesity, hypertension, dyslipidemia, and so on, all of which are risk factors of cardiovascular diseases [2, 3].

A traditional Chinese herb compound was applied in this study, and three kinds of plant: *Coptis chinensis*, *Astragalus mambranesceus*, and *Lonicera japonica* were used: they were among those considerate by The Chinese Academy of Medical Sciences as effective and safe herbs in the treatment of diabetes traditionally. In the past several years, many in vitro and in vivo studies confirmed the beneficial effects of traditional Chinese medicine (TCM) on diabetes. The antidiabetic effect of TCM is well established, although its targeted tissues and mechanisms underlying the pharmacological activity are not totally understood. Berberine, as a natural plant alkaloid isolated from the *Coptis chinens*, has been noted for its potential glucose lowering effect, and it is a key component in treating diabetes [4, 5]. TCM can improve glucose tolerance significantly in db/db mice and decrease high serum level of triglyceride (TG) dramatically in high-fat-fed mice [6, 7], and it may increase the insulin sensitiveness index in KK-Ay mice as well [7]. Two important clinical investigations on TCM in the treatment of diabetes were reported in China in the past decade. Vray et al. reported a 2 × 2 factorial multicentre randomized double-blind trial involving 216 diabetic patients divided into four groups. After a 3-month treatment, the 2 h postprandial blood glucose concentration significantly decreased in those patients receiving TCM. And a synergistic effect on blood glucose lowering was observed when patients were given both TCM and glibenclamide [8]. Secondly, in another clinical trial, 442 patients with T2D were randomly treated with TCM and placebo for 2 months without changes in their previous antidiabetic therapy, their fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) concentrations were reduced by 24.5 and 25% respectively. Participants in these clinical studies tolerated TCM well, and no gastrointestinal discomfort was reported.

Although these TCM trials showed the beneficial effect alone or with other antidiabetic drugs, insulin sensitivity has not been carefully investigated yet. Therefore, the present study aimed to measure insulin sensitivity and other related metabolic factors in patients with T2D before and after treatment with TCM by a randomized, double-blind, placebo controlled trial.

Research design and methods

Study design

This randomized, double-blind, placebo-controlled study consisted of a 2-week run-in and a 3-month treatment period. Participants were recruited between September 2006 and November 2007 from the Shanghai Jiao-Tong University School of Medicine Affiliated Rui-Jin Hospital and the Second Military Medical University Affiliated Chang-Hai Hospital in Shanghai. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethic Committee for Human Research in Rui-Jin Hospital, and written informed consent was obtained from each patient. During the run-in period, all subjects received an initial screening including a medical history collection, physical examination, renal and hepatic function, serum lipid concentrations, blood counts, a standard meal glucose tolerance test, and the hyperinsulinemic euglycemic clamp study, which was conducted in a separate day. After the completion of these studies, patients were allocated randomly into TCM and placebo groups. Randomization was performed centrally and was concealed and stratified in blocks of four. During the 3-month treatment period, patients went to the clinical research centre once a month for follow-up visit, and after 3 months, all metabolic measurements were repeated to evaluate the efficacy and safety of TCM. All participants received diet and exercise advices by diabetologist at the beginning of the test. They were supposed to do some physical activity 150 min/week and take the low-glycemic index diet. In the follow-up period, all patients were phoned once a week to know their daily glucose level and, in another hand, to supervise their lifestyle modification.

Subjects

Forty-three subjects (age range: 18–70 years) with newly diagnosed T2D were enrolled according to the 1999 World Health Organization criteria [9] (FPG $\geq$ 7 mmol/l and/or OGTT 2 h $\geq$ 11.1 mmol/l). These patients were overweight (with a body mass index (BMI) of 23–35 kg/m^2)

and with poor glucose level after a 1-month diet control (i.e., two FPG concentrations between 7.0 and 10.0 mmol/l within a month). They underwent a standard meal glucose tolerance test and a hyperinsulinemic euglycemic clamp to determine the peripheral insulin sensitivity on a single day. Those who had used any antidiabetic drugs were excluded. Patients were generally without the health problem of cardiac, hepatic, renal, other chronic diseases, or acute diabetic complications, including diabetic ketoacidosis or hyperosmolar hyperglycemic non-ketotic coma, as determined by history, examination, and routine blood chemistry. Women of childbearing age included were not pregnant or planning for pregnancy.

Treatment

Patients were randomized into two groups. They received TCM (3 mg of a mixture of plants in powder form with 50 mg of *Coptis chinensis,* 30 mg of *Astragalus mambranesceus*, and 120 mg of *Lonicera japonic*) or placebo prepared in indistinguishable tablets, respectively. Each patient received seven tablets prepared, respectively, for TCM or placebo group three times daily before meals (morning, noon, and evening) for 3 months. If gastrointestinal discomfort occurred and lasted more than 2 weeks, the tablets (TCM or placebo) were reduced by half until the discomfort was relieved. The TCM and placebo tablets were provided by Long Shun Rong Pharmaceutical Inc (Tianjin, China). Any other antidiabetic medication was not allowed and participants continued their basic treatment for other disease during the test.

Clinical and biochemical measurements

After an overnight fast of 10–12 h, patients went to the clinical research center between 0700 and 0800 h in the morning. Patient's age, sex, smoking habits, and alcohol consumption were recorded and a questionnaire with personal and family history of diabetes was completed. The height and weight (light clothes and without shoes), waist and hip circumference, and seated blood pressure were determined by a senior physician. Biochemical measurements of serum lipids, HbA1c, and insulin were performed in the laboratory (Shanghai Institute of Endocrinology and Metabolism, Shanghai, China). Following immediately, plasma glucose concentration was measured using an enzymatic method (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). Serum insulin was measured using a double antibody radioimmunoassay (DSL, Webster, Texas, USA). Serum total cholesterol (TC) and TG were measured by enzymatic methods (Beckman coulter Inc, Fullerton, CA, USA). High-density lipoprotein-cholesterol (HDL-c) and low-density Lipoprotein-cholesterol (LDL-c) were determined by immunoinhibition methods (HDL-c, LDL-c Direct, Wake Pure Chemical Industries Ltd. GmbH, Neuss, Germany). HbA1c was measured by high performance liquid chromatography (HPLC) using the BioRad Variant Hemoglobin HbA1c assay (Hercules, CA, USA). Serum retinol binding protein 4 (RBP4) level was measured in duplicate by an in-house developed sandwich ELISA, utilizing affinity-chromB atography purified polyclonal and monoclonal antibodies (horseradish peroxides conjugated anti-rabbit IgG, Bio-Rad Laboratories, Hercules, CA) generated against recombinant human RBP4 protein. C-reactive protein (HsCRP) was measured using ELISA kits (Biocheck Inc, Foster, CA, USA). Interleukin-6 (IL-6) was measured using ELISA kits (R&D Systems, Minneapolis, USA).

Hyperinsulinemic euglycemic clamp

All patients arrived at the clinical research center in Rui-Jin Hospital at 0700 h after an approximately 13 h overnight fasting and then received the hyperinsulinemic euglycemic clamp test. Patients' last meal before the test was taken between 1800 and 1900 h, and were advised not to take any more food or drink. For blood sampling, a polyethylene cannula was inserted into an antecubital vein of the patients. A second catheter was inserted retrogradely into a wrist vein on the dorsum of the patients' hand for infusion of all test substances. The hand engaged for the blood sampling was kept in a heated box at 65°C. After a 30–45 min stabilization period, a 10-min priming insulin infusion was administered, followed by a constant infusion of 60 min/m^2 surface area per min over 140 min. A variable infusion of 20% glucose was adjusted based on the negative feedback principle to maintain the plasma glucose concentration at 5–5.5 mmol/l. During the clamp test, blood glucose concentrations were repeatedly measured with a glucose analyzer (Biosen 5130, Neckar Healthcare. Co. Ltd. Magdeburg, Germany) at 5 min intervals. Blood samples for insulin measurement were collected at 10 min intervals. The glucose disposal rate (GDR) (mg kg^{-1} min^{-1}), defined as the amount of glucose required to maintain stable blood glucose concentrations during the last 30 min of the equilibration period, was used to evaluate insulin sensitivity [10–13].

Evaluation and outcomes

Patients visited the clinical research center at 0, 1, 2, and 3 month for follow-up study. Patients' age, weight, height, waist and hip circumference, blood pressure, personal and family history of diabetes, and past medical history were collected at 0-month visit. FPG concentration was checked at each visit and PPG, HbA1c, TC, TG, HDL-c, and LDL-c were evaluated at 0-month and 3-month visit and GDR was

collected from the hyperinsulinemic euglycemic clamp as well.

Statistical analysis

As planned in advance, this study had a sample size of 20 participations in each of the two group in order to demonstrate a difference with a power of 95% (with a drop-out rate up to 10% was planned to provide a 90% power to detect a $\geq$20% (with 95% CIs, $\alpha = 0.05$ $\beta = 0.1$) reduction in GDR in the TCM group compared with the placebo group at the end of the study). To make the results more effective, we used end-point analysis to compare the end point treatment values with baseline values, which included those patients who stopped their treatment because of side effect or inefficacy and were lost to follow-up. Statistical analysis was performed using the SPSS 13.0 system, and data were presented as mean $\pm$ SD. For each statistical test, the level of significance (type 1 error) was set at 0.05. Paired-sample *t*-test was performed to compare the difference within groups from baseline. Independent-sample *t*-test and the ANCOVA analysis with a model that included the baseline value of the dependent variable as a covariate were also used for comparison between groups.

Results

Baseline characteristics

Forty-three recruited subjects were randomized into TCM group and placebo group (Fig. 1), most of whom were middle aged Chinese living in Shanghai region or its vicinity. Among the 43 patients, 2 dropped out after 2 visits, both were in the TCM group. The baseline characteristics of the 43 patients including 2 lost cases were analyzed as shown in Table 1. The TCM- and placebo-treated groups were well matched for age, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, PPG, HbA1c, fasting plasma insulin (INS0'), postprandial plasma insulin (INS120'), TG, TC, HDL-c, and LDL-c.

Metabolic measurements

Comparisons of clinical and metabolic data between the two groups were summarized in Table 1. After a 3-month treatment, BMI of both groups decreased ($P < 0.05$) compared with the baseline values but waist circumference remained unchanged in the two groups. The decreases in SBP and DBP between visit 0 and visit 3 were from 129 to 122 mmHg ($P < 0.05$) and 83 to 77 mmHg ($P < 0.01$), respectively, for patients given the TCM, whereas no significant changes occurred in the placebo group. However, there were no detectable differences between the two groups according to the ANCOVA analysis.

After the treatment period, the TCM group had decreased in FPG [from 7.4 $\pm$ 1.2 to 6.5 $\pm$ 1.3 mmol/l (decreased by 10.19%, $P < 0.05$)], PPG [from 11.3 $\pm$ 2.4 to 10.0 $\pm$ 2.4 mmol/l (decreased by 8.29%, $P < 0.05$)], and HbA1c [from 7.8 $\pm$ 1.3 to 7.1 $\pm$ 0.9% (decreased by 10.28%, $P < 0.05$)]. PPG and HbA1C in the placebo group did not change much as compared to baseline. However, ANCOVA analysis showed that FPG, PPG, and HbA1c values at the 3rd month were not significantly different between the two groups. Insulin measurements (INS0' and INS120') and serum lipid measurement (TG and TC) showed no significant difference between baseline and end-point in both groups.

All 43 patients received the hyperinsulinemic euglycemic clamp tests at baseline, and 41 patients were available for repeated clamp tests after the 3-month treatment (21 from the

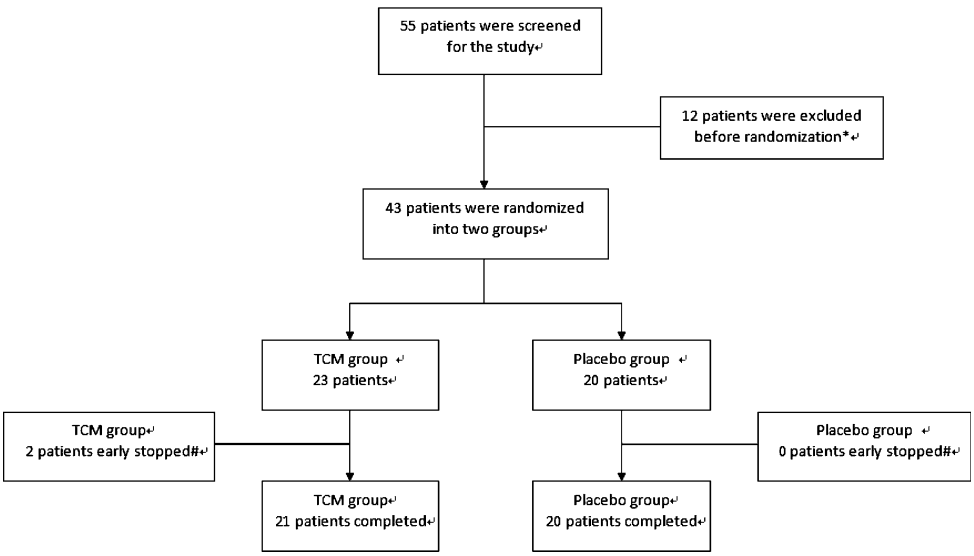

Fig. 1 Patients who were screened and randomized in the study. *12 patients were excluded because of fasting glucose concentrations >10 mmol/l or <7 mmol/l. #Reasons for early stop in Jinqi group: 2 had personal conflicts

Table 1 Comparison of clinical characteristics between two groups

	TCM			Placebo			*P value
	Before	After	ΔP value	Before	After	ΔP value	
No. (male/female)	21 (11/10)			20 (11/9)			0.854
Age (year)	54 ± 7			53 ± 10			0.628
BMI (kg/m^2)	27.0 ± 3.5	26.5 ± 3.5	0.036	27.4 ± 3.3	26.9 ± 3.1	0.026	0.954
Waist-hip	0.92 ± 0.07	0.90 ± 0.04	0.156	0.94 ± 0.08	0.92 ± 0.06	0. 140	0.917
SBP (mmHg)	129 ± 16	122 ± 11	0.011	129 ± 10	126 ± 13	0.355	0.246
DBP (mmHg)	83 ± 9	77 ± 9	0.004	83 ± 8	81 ± 7	0.340	0.073
FPG (mmol/l)	7.4 ± 1.2	6.5 ± 1.3	0.006	7.2 ± 1.2	6.6 ± 1.0	0.001	0.434
PPG (mmol/l)	11.3 ± 2.4	10.0 ± 2.4	0.018	11.4 ± 3.4	9.8 ± 2.1	0.052	0.750
HbA1C (%)	7.8 ± 1.3	7.1 ± 0.9	0.012	7.2 ± 0.8	6.9 ± 0.7	0.306	0.958
TG (mmol/l)	2.07 ± 1.39	1.93 ± 1.50	0.463	1.92 ± 0.67	1.90 ± 0.81	0.940	0.657
TC (mmol/l)	5.10 ± 1.06	5.12 ± 1.05	0.869	5.35 ± 1.04	5.37 ± 0.88	0.912	0.683
HDL (mmol/l)	1.08 ± 0.27	1.23 ± 0.26	0.035	1.12 ± 0.24	1.10 ± 0.26	0.757	0.072
LDL (mmol/l)	2.83 ± 0.73	2.93 ± 0.78	0.398	3.23 ± 0.93	3.14 ± 0.69	0.638	0.93
INS0' (mIU/l)	10.2 ± 6.6	9.7 ± 7.0	0.750	10.8 ± 7.7	9.3 ± 7.1	0.445	0.745
INS120' (mIU/l)	42.3 ± 44.5	28.4 ± 17.6	0.198	45.5 ± 73.9	32.4 ± 20.9	0.404	0.546
GDR (mg kg^{-1} min^{-1})	5.12 ± 2.43	6.37 ± 3.51	0.004	5.42 ± 2.14	5.82 ± 2.22	0.205	0.043
CRP (mg/l)	2.53 ± 2.23	3.25 ± 5.50	0.554	1.32 ± 1.16	3.20 ± 5.55	0.136	0.602
IL-6 (pg/ml)	2.14 ± 1.41	2.04 ± 2.50	0.848	1.91 ± 1.30	2.14 ± 1.66	0.624	0.739
RBP4 (mg/l)	25.77 ± 17.52	12.26 ± 7.47	0.006	24.55 ± 14.82	16.04 ± 7.46	0.070	0.149
Adiponectin (μg/ml)	9.26 ± 4.25	10.89 ± 3.55	0.260	11.55 ± 4.88	12.28 ± 4.98	0.422	0.596
ALT (IU/l)	31.76 ± 15.09	23.90 ± 7.13	0.016	34.30 ± 17.55	31.30 ± 24.64	0.495	0.228

Δ *P*-value refers to comparison between before vs. after treatment within each group using paired sample *t*-test

* *P*-value refers to comparison between TCM and placebo groups after treatment using the ANCOVA analysis

TCM group and 20 from the placebo group). At baseline, GDRs were generally similar in both groups. During the first phase of clamp test, serum insulin concentration increased and peaked at about 170 mIU/l in both groups and then descended gradually, maintaining at a high level of nearly 100 mIU/l at the end of the test. Serum insulin concentration under fasting condition and hyperinsulinemic phase (120–150 min) of the clamp tests were 12.07 ± 6.80 and 91.98 ± 24.03 mIU/l at baseline, 12.39 ± 5.73 and 93.78 ± 27.84 mIU/l at end point in the TCM group, and 9.50 ± 4.84 and 92.44 ± 27.98 mIU/l at baseline, 9.76 ± 5.00 and 89.62 ± 25.84 mIU/l at end point in the placebo group. No significant difference was found between these two groups. During the stable period, the glucose level achieved 5.16 and 5.20 mmol/l in the TCM group, 5.17 and 5.19 mmol/l in the placebo group, showing no statistical difference, either. After treatment, GDR increased significantly in the TCM group (5.12 ± 2.20 vs. 6.37 ± 3.51 mg kg^{-1} min^{-1}, $P = 0.004$), while no change was found in the placebo group (5.42 ± 2.15 vs. 5.82 ± 2.23 mg kg^{-1} min^{-1}, $P = 0.205$). ANCOVA analysis showed that GDR value in the TCM group significantly increased as compared with that in the placebo group ($P < 0.05$) (Table 1, Fig. 2).

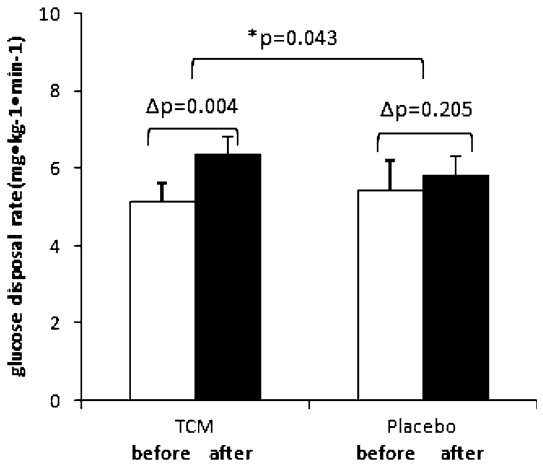

Fig. 2 Comparison of GDR between two groups before and after treatment

Concentration of serum RBP4 decreased statistically from 25.77 ± 17.52 to 12.26 ± 7.47 mg/l ($P = 0.006$) in the TCM group, but no difference was found in the placebo group. Nevertheless, according to the ANCOVA analysis, there was no significant difference in RBP4 between the

two groups. Other adipokines were evaluated such as CRP, IL-6, but no change was detected after the treatment (Table 1).

Safety

No severe side effect occurred during our study as reported by the patients. Two subjects in the TCM group and two in the placebo group suffered from moderate constipation and were improved after 1 or 2 weeks without dose reduction. One patient in TCM group took the tablets after the meals instead of before because of abdominal distension, and the symptom was relieved with this change of timing. The frequency of side effects was not significantly different between the two groups. Renal and hepatic function, blood counts were assessed at baseline and the end of the study for safety purpose. Serum alanine aminotransferase showed noticeable reduction at the third month compared to baseline in the TCM group (32 ± 15 vs. 24 ± 7 IU/L, $P = 0.016$; 34 ± 18 vs. 31 ± 25 IU/L, $P = 0.495$). No episode of hypoglycemia was reported.

Discussions

Since the introduction of the 2×2 factorial design study comparing the effects of TCM versus placebo and sulfonylurea [8], the TCM has been used in China for several years. Many beneficial effects of TCM in diabetes have been reported in animal researches, which predict TCM may alleviate insulin resistance. In some clinical researches, although TCM is proved to reduce fasting glucose concentration and postprandial glucose concentration without increasing insulin level and body weight, the effect of TCM on insulin resistance is not fully clarified.

Based on previous studies, we performed a randomized, double-blind, and placebo controlled trial to investigate the efficacy of TCM on insulin sensitivity in newly diagnosed T2D. After 3 months treatment with TCM, GDR increased from 5.12 to 6.37 mg kg^{-1} min^{-1}, showing a significant change compared to both initial level and that of placebo group. This result showed that insulin resistance was improved in the early period of T2D with TCM. TCM also had a moderate glucose-lowering effect by reducing fasting and postprandial plasma glucose by 0.9 and 1.3 mmol/l, respectively, at the third month, as well as HbA1c by 0.7% from 7.8%. The above values, however, did not differ significantly between the two groups by ANCOVA analysis. The decline in glucose concentration achieved by TCM was in accord with the results from pervious clinical trials. However, the serum fasting and postprandial insulin concentrations, cholesterol, TGs, and LDL-c did not change significantly from baseline to the end point in both groups; and the TCM group did not lead to increased secretion of endogenous insulin. Because of the lipid levels of enrolled patients (We did not choose hyperlipidemia patients.), the cholesterol and TGs lowering effects of TCM were not performed obviously. After a 3-month period, body weight, BMI, SBP, and DBP of patients in the TCM group decreased significantly ($P < 0.05$). The differences between the two groups, though, were not significant enough. We supposed the improvement on insulin resistance happened earlier than the other metabolic components when treated with TCM. Since all participants received lifestyle modification, which was proven effective for glucose control especially in the early stage of diabetes, this might be one of the reason for the undetectable difference between the two groups. Furthermore, the number of enrolled patients and the length of administration period could weaken the effect of TCM, either. As an important component of TCM, Berberine has been proved as a glucose- and cholesterol-lowering drug; it can upregulate LDL receptor expression independent of sterol regulatory element binding protein, but dependent on ERK activation in human hepatoma cells [14]. Berberine also improves insulin resistance in db/db mice and high-fat-fed rats, activates AMP-activated protein kinase (AMPK) in 3T3-L1 adipocytes and L6 myotubes and facilitates GLUT4 translocation in L6 myotubes in a PI-3K independent manner [15]. In the latest research, Turner et al. [16] found a novel derivative of berberine, which could improve its efficacy in vivo, and Complex I of the respiratory chain represents a major target for compounds that improve whole-body insulin sensitivity through increased AMPK activity. Yin et al. [17] and Zhou et al. [18] reported that berberine promoted glucose uptake in HepG2 and 3T3-L1 cells independent of insulin action. In addition, berberine can effectively inhibit sucrose and maltase activities to the same extent as acarbose does in Caco-2 intestinal cells and possibly inhibit α-glucosidase activities to reduce glucose absorption [19]. Recently, a multicentre, double-blind, placebo-controlled clinical trial was accomplished to evaluate the efficacy of berberine in the treatment of T2D with dislipdemia in our clinical research center [13]. One hundred and sixteen type 2 diabetic patients with dislipdemia were randomized into two groups with one receiving berberine (1 g/daily) and the other placebo. Participants in the berberine group showed significant glucose lowering and lipid lowering effects after 3 months treatment compared to the placebo group, and GDR assessed by euglycemic hyperinsulimia clamp increased in the berberine group, but without statistical difference compared to the placebo group. Berberine displays most importantly in the efficacy of the treatment. The mechanism of TCM in insulin resistance improvement has not been fully understood and further in vitro and in vivo studies should be taken in the near future. However, since the subjects in the

present study were newly diagnosed diabetes, TCM may not be a suitable single therapy for all diabetic patients. It can be used in mild T2D without complications and as an adjuvant to standard therapy.

Some inflammatory factor and adiponectins were also measured in this study. Except RBP4, other factors showed no difference between baseline and end point. In TCM group, RBP4 concentration decreased from 25.77 to 12.26 mg/l ($P < 0.01$), while no significant change happened in the placebo group. RBP4, as a newly found inflammatory factor, is confirmed as a close connection with insulin resistance and thought to have earlier change than other factors [20]. It indicated that a reduction of inflammation was realized with the improvement of insulin sensitivity in the TCM-treated patients.

Traditional Chinese medicine was confirmed as a safe administration in our study. We did not find any severe side effect or significant differences about the side effects between the two groups. Six patients in the TCM group and seven in the placebo group reported moderate side effect such as abdominal distention and constipation. All the adverse effects were relieved within 1 week without dosage reduction.

In conclusion, this multicentre controlled trial shows that TCM can improve insulin resistance in T2D. It also improves glucose metabolism including FPG, PPG as well as HbA1C and blood pressure to a certain extent. But TCM does not show increasing effect on endogenous insulin secretion and lowering effect on lipid level. Last but not the least, no episode of hypoglycaemia or severe side effect happened when T2D patients were treated with TCM.

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