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Original Article

Efficacy of Shenqi compoundparticle on blood glucose and oxidative stress compared with metformin for patients with newly siagnosed type 2 diabetes mellitus: randomized clinical trial

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Abstract: Objective: The aim of the current study was to compare the efficacy of Shenqi Compound Particle (SCP) on blood glucose and oxidative stress with metformin for newly diagnosed type 2 diabetes mellitus (T2DM) patients. Methods: A randomized and parallel-group clinical trial was conducted. A total of 46 cases of patients with newly diagnosed T2DM were randomly distributed to the Shenqi group and metformin group using the SAS software package. A total of 23 cases in the Shenqi group were treated with SCP. A total of 23 cases in the metformin group were treated with metformin. Both groups were observed for 12 weeks. Efficacy was evaluated by comparing fasting blood glucose (FBG), two hour post-prandial blood glucose (2hPBG), glycosylated hemoglobin (Hb1AC), body mass index (BMI), blood lipids (TC, LDL-C), and oxidative stress indicators (SOD, NO, ROS, MDA, T-AOC). Results: FBG, 2hPBG, and Hb1AC in both groups were effectually reduced ($P<0.05$), with no distinct differences ($P>0.05$) indicated. BMIs in both groups were significantly decreased ($P<0.05$), while the metformin group was reduced more obviously ($P<0.05$). TC and LDL-C were significantly decreased ($P<0.05$), with no significant differences between the two groups ($P>0.05$). There was significant improvement in SOD, NO, and T-AOC in the Shenqi group ($P<0.05$). SOD and T-AOC levels of the Shenqi group enhanced more distinctively than those in the metformin group. Levels of NO in both groups showed no significant differences. ROS and MDA levels of both groups decreased ($P<0.05$), but the reduction of ROS was not significant ($P>0.05$). Reduction of MDA in the Shenqi group was more outstanding than that in the metformin group ($P<0.05$). Conclusion: SCP has the advantages of decreasing blood glucose and blood lipids, while improving oxidative stress.

Keywords: Type 2 diabetes, Shenqi compound particle, blood glucose, oxidative stress

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease that causes blood glucose and lipid metabolism abnormalities due to insulin secretion and/or utilization disorders [1]. It is one of the main chronic diseases in the world [2]. According to data released by the 2017 International Diabetes Federation (IDF), the number of patients with diabetes, worldwide (20-79 years old), has reached about 425 million. Prevalence rates have reached as high as 8.8% [3]. The World Health Organization (WHO) predicts that, by 2030, there will be 440 million cases of the disease [4].

Diabetic macroangiopathy is a chronic complication of T2DM. It is also an important cause of disabilities and deaths in diabetic patients [5]. Many hypotheses have suggested that the formation of macrovascular disease is related to oxidative stress [6]. In the environment of high glucose, high fat, and other metabolic disorders, excessive oxidative stress is triggered. Many oxygen free radicals are generated, exceeding the ability of the body's antioxidant system to clear them. The destruction of biological macromolecules, such as proteins, nucleic acids, and lipids by oxygen free radicals can cause abnormal gene expression, cell damage, apoptosis, and accumulation of metabolites,

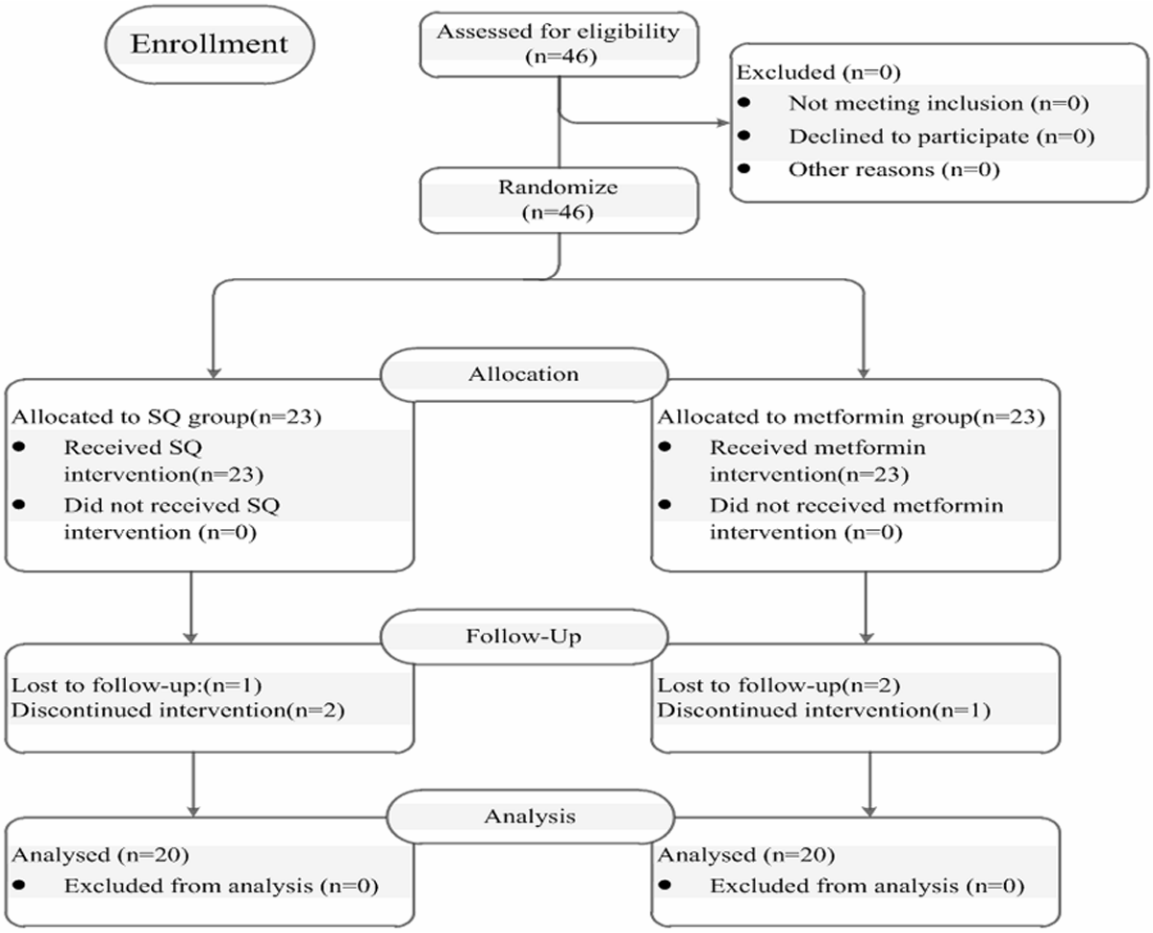

Figure 1. Study flow diagram.

resulting in increased vascular damage and weakened vascular protection and repair. This results in macrovascular disease, ultimately. Previous studies have shown that antioxidants, including glutathione (GSH) [7], vitamins C-E, and vitamins B1-B2 [8], along with anti-AGEs drugs, can control blood glucose and oxidative stress in T2DM patients, to some extent [9-12]. Antioxidants, however, are still in the research stage. They are not yet widely used in patients with diabetic macroangiopathy.

In recent years, studies have confirmed that TCM has made remarkable progress in reducing blood glucose, regulating blood lipids, and improving oxidative stress and diabetic macroangiopathy [13, 14].

SCP is a Traditional Chinese Medicine compound consisting of Ginseng (Renshen), Radix Astragali (Huangqi), Rhizoma Dioscoreae (Shanyao), Fructus Corni (Shanzhuyu), Radix Rehmanniae (Shengdihuang), Radix Salviae Miltiorrhizae (Danshen), Radix Trichosanthis (Tianhuafen), and cooked Rhubarb (Dahuang). Modern pharmacological studies have shown that Ginseng, Radix Astragali, Rhizoma Dioscoreae, and Radix Trichosanthis could significantly improve hyperglycemia [15]. Many clinical trials have confirmed that, compared with metformin, the TCM compound could also reduce weights and glucose levels of diabetic patients, to some extent [16]. In addition, the chemical components of ginseng, including ginsenosides and polyethylene compounds, have shown antioxidant effects [17]. *In vivo* experiments with T2DM rats have shown that astragalus can enhance the total antioxidant capacity by increasing the activity of antioxidant enzymes, such as catalase and SOD, removing harmful superoxide anions and hydroxyl radicals [18]. Rehmannia not only can effectively reduce fasting blood glucose levels of diabetic rats, but some of its extracts have higher

Table 1. Background data and baseline characteristics (X±S)

Characteristic	Shenqi group	Metformin group	*P* value
Sex			
Male	11	8	0.342
Female	9	12	
Age (years)	52.55±7.54	51.85±7.84	0.775
BMI (kg/m^2)	23.79±2.37	24.92±3.39	0.230
FPG (mmol/L)	8.39±2.04	7.88±1.84	0.407
2hPBG (mmol/L)	12.86±2.04	12.41±1.65	0.445
TC (mmol/L)	4.78±0.47	4.67±0.33	0.380
LDL-C (mmol/L)	2.80±0.24	2.88±0.23	0.380
HbA1c (%)	6.54±0.94	6.38±0.87	0.580
SOD (U/gHb)	63.06±6.93	62.24±4.12	0.653
NO (mmol/l)	4.46±0.94	4.53±0.73	0.239
ROS (umol/ml)	0.69±0.16	0.67±0.18	0.758
MDA (umol/l)	176.76±28.00	174.12±31.83	0.681
T-AOC (mmol/l)	2.23±0.20	2.25±0.20	0.425

Notes: Shenqi group: the intervention group. metformin group: the control group. BMI: body mass index. FPG: fasting plasma glucose. 2hPBG: 2 h plasma blood glucose. TC: total cholesterol. LDL: low-density lipoprotein. HbA1c: HemoglobinA1c. SOD: super oxide dimutase. NO: nitric oxide. ROS: reactive oxygen species. MDA: malondialdehyde. T-AOC: total antioxidant capacity. Gender data was analyzed by Chi-square test and the rest of the data was analyzed by t-tests. Compared with pre-treatment figures between groups, *P*>0.05.

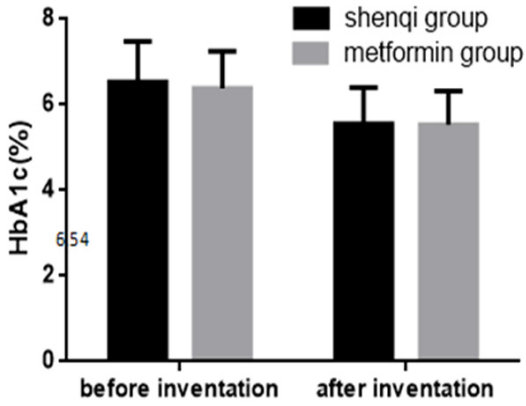

Figure 2. Changes of HbA1C in two groups.

immune activity and antioxidant capacity [19]. Therefore, SCP provides certain hypoglycemic and antioxidant effects in theory.

Previous clinical studies have shown that control rates of SCP on HbA1c and blood glucose levels in type 2 diabetes patients are in accord with those of metformin, with good efficacy and safety. Moreover, in other studies, SCP has shown extensive regulation of gene expression [20], inhibition of β cell apoptosis [21], repair of cell damage [22], improvement of insulin resistance [23], regulation of glycolipid metabolism, reduction of lipotoxicity [24], inhibition of inflammatory response in the body [25], anti-oxidative stress reduction [26], protection of endothelial cells, and repair of vascular damage [27].

To the best of our knowledge, few studies have focused on the effects of TCM compounds on glycemic control and oxidative stress. Therefore, the purpose of the current study was to clarify the effects of SCP on early blood glucose control and improvement of oxidative stress injuries in patients with newly diagnosed T2DM. The aim of the current study was to discover a new therapy, controlling blood glucose and long term macrovascular complications at the root.

Methods

Trial design

This study was designed as a randomized controlled trial (RCT). The program was approved by the Ethics Committee of Sichuan Traditional Chinese Medicine (TCM) Regional Ethics Review Committee Chengdu University of TCM Teaching Hospital Ethics Committee (Code2016KL-049). This study was registered on the China Clinical Trial Registration Platform: ChiCTR-800018880.

Participants

Diagnosis of T2DM refers to 2017 American Diabetes Association (ADA) diabetes medical diagnosis standards. Forty-six volunteers with newly diagnosed T2DM were recruited, from October 2018 to December June 2019, at the Department of Endocrinology and Inpatient Department of the Teaching Hospital of Chengdu University of TCM. Inclusion criteria: Aged between 18 and 70 years; HbA1c≤7.5%; Voluntarily signed a written informed consent agreement. Exclusion criteria: Type 1 diabetes, gestational diabetes, or special types of diabetes; Pregnancy or lactation; Diabetes complicated by acute or severe complications, including liver and kidney dysfunction, cardiovascular and cerebrovascular accidents, history of oncology, acute complications or infections; Hi-

Table 2. Comparison of glycemic and HbA1c between groups (X±S)

Group	Case	Time	FPG (mmol/l)	2hPBG (mmol/l)	HbA1c (%)
Shenqi group	20	Before	8.40±2.04	12.86±2.01	6.54±0.94
		After	7.20±1.47*	11.11±1.82*	5.55±0.85*
Metformin group	20	Before	7.88±1.84	12.41±1.65	6.38±0.87
		After	6.60±1.25*,#	10.65±1.51*,#	5.53±0.79*,#

Notes: Shenqi group: The intervention group. Metformin group: the control group. FPG: fasting plasma glucose. 2hPBG: 2 h plasma blood glucose. HbA1c: HemoglobinA1c. Intra-group comparison was calculated by paired t-test, *P<0.05, independent t-test values were used for inter-group comparisons #P>0.05.

ghly allergic constitution and any allergy history to TCM.

Interventions

SCP was obtained from the Chinese Pharmacy of the Hospital of Chengdu University of TCM. Metformin was purchased from Sino-US Shanghai Squibb Pharmaceutical Co., Ltd. Qualified volunteers were randomly assigned to the Shenqi group or metformin group. Both groups during the trial received diet and exercise therapy, according to the *Chinese Diabetes Medical Nutrition Treatment Guide*. Subjects in the Shenqi group took SCP, 1/3 dose, with 150 mL boiled water, 30 minutes before meals. Subjects in the metformin group took at a dose of 850 mg metformin during dinner or after dinner. Other hypoglycemic agents were not allowed during the intervention.

Efficacy indicators

Primary efficacy indicators: FBG and 2hPBG were detected via the glucose oxidase method at week 0 and week 12. Fingertip blood was monitored at 2, 4, 6, 8, and 10 weeks. HbA1c and blood lipid levels were measured before baseline and 12 weeks after intervention. HbA1c was detected by colorimetry and lipid mass spectrometry was measured with a biochemical analyzer at 0 and 12 weeks.

Secondary efficacy indicators: Secondary efficacy indicators were indexes of oxidative stress, including superoxide dimutase (SOD), nitric oxide (NO), reactive oxygen species (ROS), total antioxidant capacity (T-AOC), and malondialdehyde (MDA).The first four were detected by enzyme-linked immunosorbent assay (ELISA) at 0 and 12 weeks. The last one was detected using the colorimetric method at 0 and 12 weeks.

Safety indicators: Safety indicators included basic vital signs (body temperature, respiration, blood pressure, and heart rate), 12-lead ECG, blood and urine routine examinations, liver and kidney function tests (ALT, AST, Cr, and BUN), and malnutrition events.

Statistical analysis

SPSS 21.0 was used for statistical analysis. Measurement results were calculated by t-tests and expressed as mean ± standard deviation. Chi-square tests were used to analyze count data. Paired design t-tests were used for comparisons of differences before and after treatment with the same group. Independent sample t-tests were used for comparisons of differences between groups. Incidence of adverse events between the two groups was calculated with X^2 tests or Fisher's exact probability method. P<0.05 indicates statistically significant differences.

Results

Study flow diagram outcomes

Forty-six newly diagnosed T2DM patients met the study requirements. The random number table was generated by SAS software. Patients were randomly distributed to the Shenqi group and metformin group with a 1:1 ratio. A total of 6 patients did not complete the study. Of these, 2 patients had poor adherence to the study protocol, 1 patient due had incomplete data, and 3 patients left for personal reasons (**Figure 1**). There were no significant differences in baseline characteristics between the groups before intervention (**Table 1**).

Comparison of HbA1C between groups

HbA1C was observed in both groups at 0 and 12 weeks. Results show that the mean HbA1c was decreased in the two groups (**Figure 2**). HbA1c was decreased from 6.54±0.94% to 5.55±0.85% in the Shenqi group (*P<0.05) and from 6.38±0.87% to 5.53±0.79% in the metformin group (*P<0.05, **Table 2**). Differences were not significant (#P>0.05). Results indicate that SCP and metformin could decrease HbA1c,

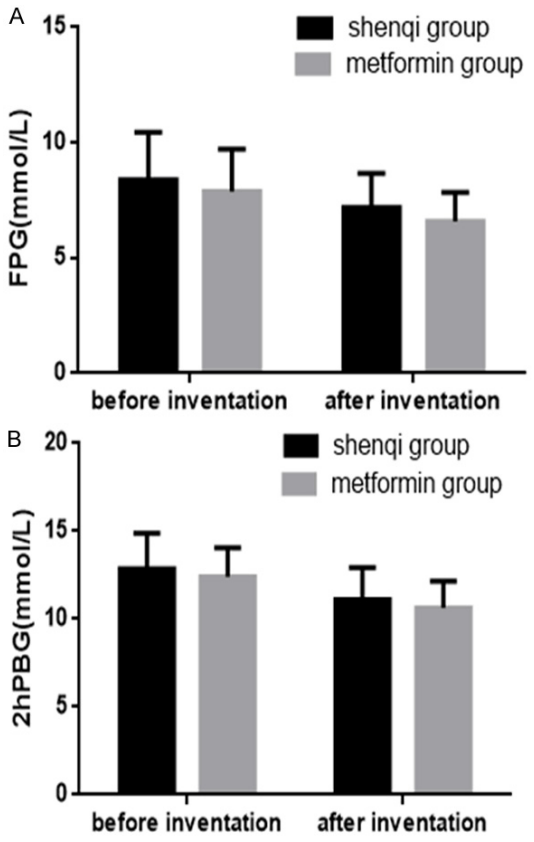

Figure 3. Changes of FPG and 2hPG in two groups. A. Changes of FPG before and after treatment. B. Changes of 2hPBG before and after treatment.

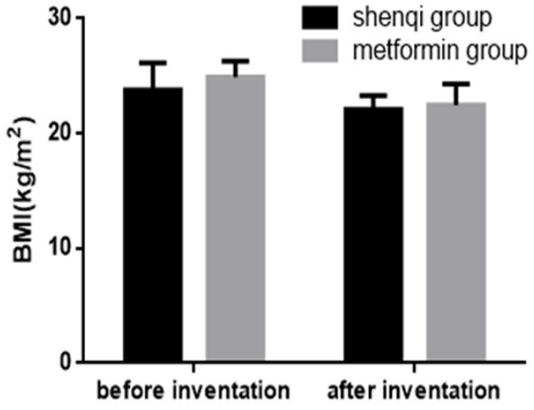

Figure 4. Changes of BMI in two groups.

with no statistically significant differences observed.

Comparison of FPG and 2hPBG between groups

FPG and 2hPBG were measured before and after intervention. After 12 weeks, FPG and 2hPBG in both groups were significantly reduced (**Figure 3A**, **3B**). FPG was decreased by 1.20 mmol/L and 2hPBG was decreased by 1.75 mmol/L in the Shenqi group ($^{*}P<0.05$, **Table 2**). Moreover, in the metformin group, FPG was decreased by 1.28 mmol/L and 2hPBG was decreased by 1.76 mmol/L ($^{*}P<0.05$, **Table 2**). There were no significant differences in levels of FPG and 2hPBG between the groups before and after treatment ($^{\#}P>0.05$).

Comparison of BMI between the groups

BMI was measured at 0 and 12 weeks. BMI levels ranged between 23 kg/m^2 and 25 kg/m^2. After intervention, both groups were significantly reduced ($^{*}P<0.05$, **Figure 4**). Metformin reduced BMI more obviously ($^{\#\#}P<0.05$, **Table 3**).

Comparison of lipid profiles (TC, LDL-C) between the groups

TC and LDL-C were monitored at 0 and 12 weeks during the trial. In both groups, levels of TC and LDL-C were significantly lower after treatment ($^{*}P<0.05$, **Figure 5A**, **5B**). There were no significant differences in TC and LDL-C between Shenqi and metformin groups ($^{\#}P>0.05$, **Table 3**).

Comparison of antioxidant results between groups

Antioxidant indicators before and after treatment in the two groups are shown in **Table 4**. After 12 weeks of observation, SOD levels of both groups increased ($^{*}P<0.05$, **Table 4**). However, SOD levels of the Shenqi group were more evident ($^{\#\#}P<0.05$, **Figure 6A**). Compared with pre-intervention in the two groups, levels of NO were increased ($^{*}P<0.05$, **Table 4**). There were little significant differences between the two groups ($^{\#}P>0.05$, **Figure 6B**). After treatment, in both groups, ROS decreased ($^{*}P<0.05$, **Table 4**). There was no significant difference between the two groups ($^{\#}P>0.05$, **Figure 6C**). Levels of T-AOC were increased in both groups ($^{*}P<0.05$, **Table 4**). Elevated levels of T-AOC in the SQ group were superior to those in the metformin group ($^{\#\#}P<0.05$, **Figure 6D**). Mean MDA concentrations in both groups were reduced ($^{*}P<0.05$, **Table 4**), but the reduction in the SQ group was more outstanding than in the metformin group ($^{\#\#}P<0.05$, **Figure 6E**).

Table 3. Comparison of BMI and lipid profiles between groups (X±S)

Group	Case	Time	BMI (kg/m^2)	TC (mmol/l)	LDL-C (mmol/l)
Shenqi group	20	Before	23.79±2.37	4.78±0.47	2.80±0.24
		After	22.08±1.21*	4.31±0.55*	2.54±0.13*
Metformin group	20	Before	24.92±1.39	4.67±0.33	2.88±0.23
		After	22.48±1.84$^{*,\#\#}$	4.19±0.22$^{*,\#}$	2.51±0.11$^{*,\#}$

Notes: Shenqi group: the intervention group, metformin group: the control group. BMI: body mass index. TC: total cholesterol. LDL: low density lipoprotein. Intra-group comparison was calculated by paired t-tests $^{*}P<0.05$. Independent t-tests were used for inter-group comparisons. $^{\#}P>0.05$, $^{\#\#}P<0.05$.

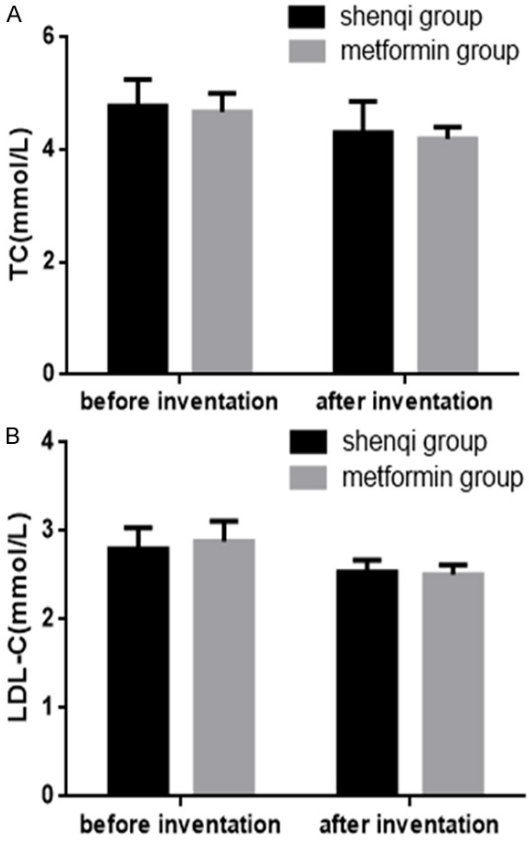

Figure 5. Changes of TC and LDL-C in two groups. A. Changes of TC before and after treatment. B. Changes of LDL-C before and after treatment.

Adverse events

Both groups of patients were well-tolerated, with no serious treatment-related adverse events occurring throughout the trial. In the Shenqi group, 3 subjects suffered with short term nausea and anorexia or other upper gastrointestinal adverse symptoms (15.0%, **Table 5**). One subject suffered from temporary bloating and diarrhea (5.0%, **Table 5**). Two subjects suffered from temporary constipation (10%, **Table 5**). Four cases suffered with upper gastrointestinal adverse reactions (20.0%, **Table 5**), 3 cases suffered from transient bloating and diarrhea (15.0%, **Table 5**), and 1 case suffered from temporary constipation (5.0%, **Table 5**) in the metformin group. In summary, the occurrence rate of diarrhea and upper gastrointestinal adverse symptoms in the metformin group was significantly higher than that of the Shenqi group ($^{*}P<0.05$, **Table 5**).

Discussion

In the current study, HbA1c decreased from 6.54% to 5.55% in the Shenqi group. In the metformin group, HbA1c decreased from 6.38% to 5.53%. FPG and 2hPBG were decreased in both groups. Similar efficacy levels were attained in decreasing blood glucose and HbA1c (%) in *SQ* and metformin groups. In view of the therapeutic effects, FPG and 2hPBG reduction effects were significant in both groups. It should be noted that subjects were newly diagnosed patients and blood glucose was poorly controlled by dietary exercise adjustments prior to enrollment. Results show that SCP has significant hypoglycemic effects. After 12 weeks of treatment, FPG and 2hPBG were significantly reduced. Results of the metformin group in reducing blood glucose levels also met expected requirements, indicating that results were stable. Outcomes of this study are in accordance with the research of Xiaoxu Fu et al. [28], which showed a significant reduction in blood glucose and glycated hemoglobin after treatment with *SCP*.

More than 60% of diabetes cases have been closely related to obesity [29]. However, diabetes with obesity is an independent risk factor for cardiovascular failure. Thus, weight control is particularly important. Current research data shows that, concerning lifestyle intervention, BMIs of the Shenqi group and metformin group showed a downward trend. There were no significant differences in BMI index between the two groups. In addition, TC and LDL-C levels in the two groups were effectively decreased. There were no significant differences between the two groups.

Table 4. Comparison of antioxidant results between groups (X±S)

Group	Case	Time	SOD (U/gHb)	NO (mmol/l)	ROS (umol/ml)	T-AOC (mmol/L)	MDA (umol/L)
Shenqi group	20	Before	63.06±6.93	4.46±0.94	0.69±0.16	2.23±0.20	176.76±28.00
		After	79.91±5.57*	5.64±1.42*	0.54±0.18*	2.55±0.10*	144.53±13.83*
Metformin group	20	Before	62.24±4.12	4.53±0.73	0.67±0.18	2.25±0.20	174.12±31.83
		After	73.15±3.86*,##	5.81±1.27*,#	0.56±0.19*,#	2.72±0.14*,##	164.47±17.09*,##

Notes: Shenqi group: the intervention group, metformin group: the control group. SOD: Super Oxide Dismutase. NO: Nitric oxide. ROS: Reactive oxygen species. T-AOC: Total anti-oxidant capacity. MDA: Malondialdehyde. Intra-group comparison was calculated by paired t-tests. *P<0.05. Independent t-tests were used for intergroup comparisons. #P>0.05, ##P<0.05.

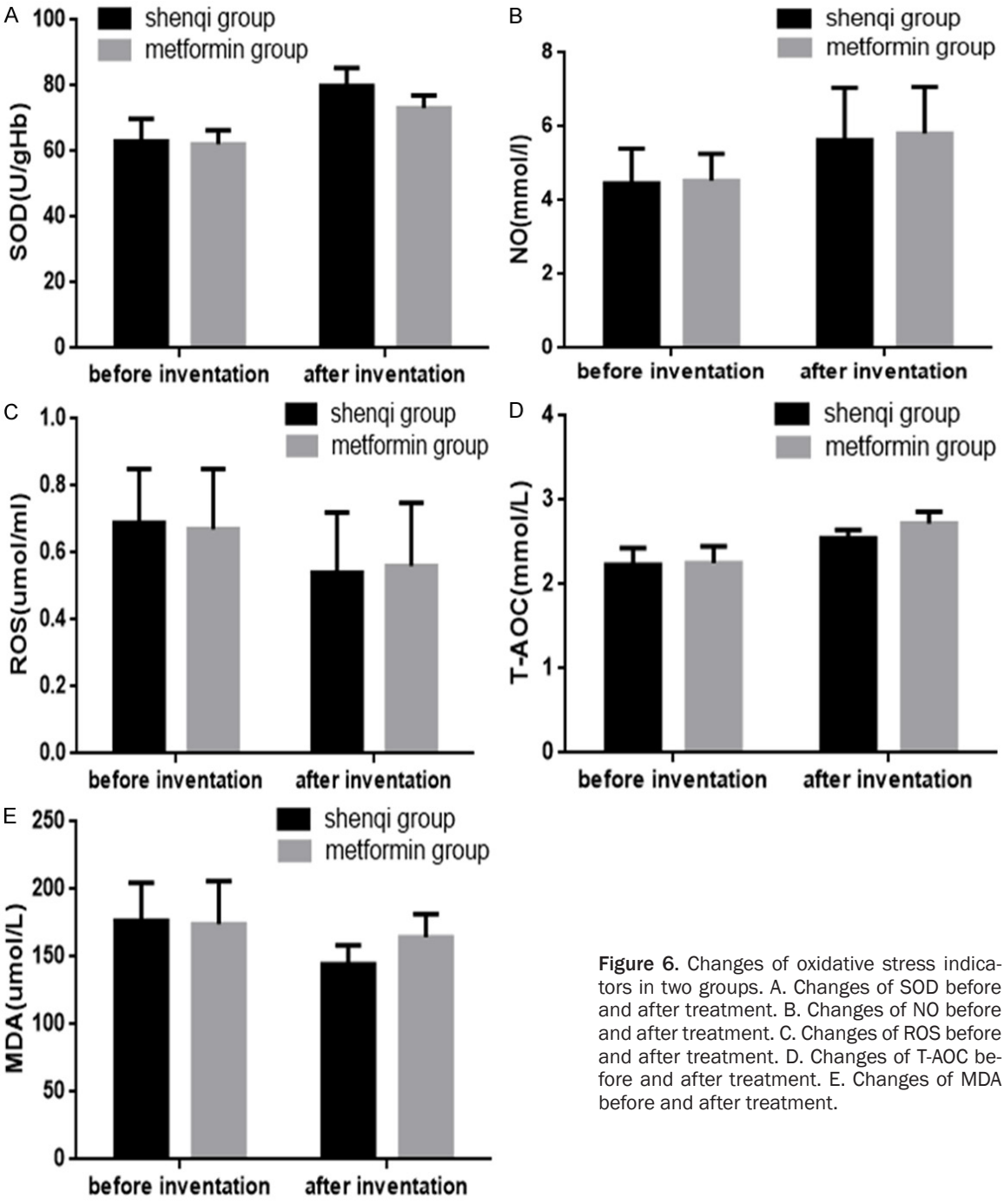

Figure 6. Changes of oxidative stress indicators in two groups. A. Changes of SOD before and after treatment. B. Changes of NO before and after treatment. C. Changes of ROS before and after treatment. D. Changes of T-AOC before and after treatment. E. Changes of MDA before and after treatment.

Table 5. Comparison of the occurrence rates of adverse effects after the 12-week treatment (n%)

Group	Case	Upper gastrointestinal Adverse	Bloating and diarrhea	Constipation
Shenqi group	20	3 (15%)	1 (5%)	2 (10%)
Metformin group	20	4 (20%)*	3 (15%)	1 (5%)

Notes: *P<0.05.

Previous studies have shown that SCP reduces weight. This may be related to insulin resistance and lipid metabolism correction [30]. A previous study found that SCP can lower serum oxidized low density lipoprotein levels and reduce total cholesterol and triglyceride levels [31]. Others also observed that SCP can upregulate gene expression of adiponectin-related mRNA, to some extent, increase adiponectin secretion, and reduce FFA, ox-LDL, and blood lipid levels [32]. Results suggest that SCP regulates lipid metabolism.

Compared with oxidative stress indicators before and after treatment, changes in the Shenqi group were significant. Levels of SOD, NO, and T-AOC were all remarkably increased, while levels of ROS and MDA were reduced. Results show that SCP can effectively improve oxidative stress responses in the body. Present results also confirmed that some specific herbs of the SCP compound may reduce levels of oxidation products through various channels and targets.

No serious adverse reactions were observed in either group during treatment. The metformin group had a higher incidence of gastrointestinal side effects and diarrhea due to adverse effects of the drug itself. However, compared with the metformin group, the Shenqi group had a lower incidence of adverse reactions. Therefore, results suggest that SCP has better safety and tolerance.

However, there were several limitations to the current study. Due to the particularity of the Traditional Chinese Medicine preparation, a double-blind trial is difficult to carry out. Moreover, research concerning the molecular mechanisms of SCP are incomplete, requiring further examination.

In conclusion, the current study demonstrates that SCP has the same effect of lowering blood glucose levels and HbA1c as metformin. In addition, SCP lowers BMI, regulates blood lipids, and improves oxidative stress. SCP significantly reduced gastrointestinal adverse reactions, compared with metformin and other drugs, improving patient tolerance and medication compliance.

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Disclosure of conflict of interest

None.

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