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Effects of Huanglian Jiedu Decoction Combined with Acarbose on Vascular Endothelial Function in Patients with Type 2 Diabetes Mellitus

Jing Guan [1,*]

[1.] Jiangsu Provincial Hospital of Traditional Chinese Medicine, Liyang Branch, 121 West Back Street, 213300 Liyang, Jiangsu, China

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* **Correspondence**

Jing Guan

Jiangsu Provincial Hospital of Traditional Chinese Medicine, Liyang Branch, 121 West Back Street, 213300 Liyang, Jiangsu, China

E-mail: 15795047124@163.com

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Abstract

Objective: To investigate the effects of Huanglian Jiedu Decoction combined with acarbose on vascular endothelial function in patients with type 2 diabetes mellitus (T2DM). **Methods:** 45 patients with T2DM who were treated with Huanglian Jiedu Decoction combined with acarbose in our hospital from January 2022 to June 2023 were included as the combination group, and 45 patients with T2DM treated with acarbose were enrolled as the control group during the same period. Both groups were treated for 2 months. The clinical efficacy of the two groups was compared. Data of vascular endothelial function index, insulin secretion function index and blood glucose level in the two groups were collected, and the occurrence of adverse reactions in the two groups during treatment was statistically collated. **Results:** The total effective rate of the combination group was higher than that of the control group ($p < 0.05$). The levels of endothelin-1 (ET-1), fasting blood glucose, 2 h postprandial blood glucose, glycated hemoglobin, fasting insulin (FINS) and insulin resistance (HOMA-IR) in both groups were decreased after treatment, and these indexes were lower in the combination group than the control group ($p < 0.05$). The levels of nitric oxide (NO), endothelial nitric oxide synthetase (eNOS) and islet beta cell function index (HOMA-β) in the two groups were increased after treatment, which were higher in the combination group than the control group ($p < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($p < 0.05$). **Conclusion:** Huanglian Jiadu Decoction combined with acarbose is effective in the treatment of T2DM, which can improve the endothelial function and insulin secretion function, and effectively control the blood glucose level, without causing serious adverse reactions.

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1 Introduction

Type 2 diabetes mellitus (T2DM), also known as non-insulin dependent diabetes, accounts for more than 90% of diabetes patients, which mainly results from aberrant secretion of pancreatic islet β cells and insulin resistance at different degrees. Long-term hyperglycemia may induce renal, retinal and cardiovascular diseases, which seriously threaten the life and health of patients [1,2]. Hence, effectively improving dysfunction of pancreatic islet β cells and insulin resistance is the key to treat T2DM.

At present, acarbose is often used clinically to treat T2DM, and is a α-glycosidase inhibitor of the brush border of small intestinal parietal cells, which can inhibit the activity of glycosidase, block the formation of α -glycosidase, decelerate the absorption of carbohydrates by the human body, and thus reduce the blood glucose level [3]. However, as the disease progresses, diabetes patients taking acarbose are prone to abdominal distension, diarrhea and other adverse reactions [4]. In recent years, the combination of traditional Chinese medicine (TCM) and Western medicine has been gradually applied to the clinical treatment of T2DM. In TCM, T2DM belongs to "wasting and thirst disorders". Professor Pei proposed that the wasting and thirst disorders occurs when the liver fails to govern the free flow of qi, qi stagnation transforms into fire pattern, and the body fluids is heated and damaged, and the treatment should be based on the basic principles of soothing the liver and relieving depression, strengthening the spleen and harmonizing the stomach, and moving blood and circulating qi [5]. Huanglian Jiedu Decoction is a representative prescription for clearing heat and removing toxins, which is composed of *Coptis chinensis*, *Scutellaria baicalensis*, Fructus Gardeniae, Phellodendri Chinensis Cortex, etc. The components together can clear heat, detoxify, circulate blood, eliminate stasis, and unblock the three jiao [6]. It has been reported that Huanglian Jiedu Decoction treatment significantly improvements in glycemic control and lipid profiles in patients with T2DM and without increased adverse events [7,8]. Based on network pharmacology and molecular docking analysis, there are 65 active components involved in 197 T2DM-related targets that are identified in Huanglian Jiedu Decoction formula, among which quercetin, wogonin, baicalein, kaempferol, and oroxylin A were 5 high affinity active components in Huanglian Jiedu Decoction [9]. Although the effect of Huanglian Jiedu Decoction on the T2DM has been reported, the curative effect of Huanglian Jiedu decoction combined with Western medicine in the treatment of T2DM is still to be discussed.

This study compared the clinical efficacy of Huanglian Jiedu Decoction combined with acarbose on T2DM patients and their effects on endothelial function and insulin secretion function, thereby providing a reference for the clinical treatment of T2DM.

2.2 Information and methods

2.1 General information

45 patients with T2DM who were treated with Huanglian Jiedu Decoction combined with acarbose in our hospital from January 2022 to June 2023 were included as the combination group, and 45 patients with T2DM treated with acarbose were enrolled as the control group during the same period.

2.2 Diagnostic criteria

(1) Diagnostic criteria of Western medicine: T2DM meets the diagnostic criteria in the Chinese Guidelines for the Prevention and Treatment of Type 2 diabetes (2013 Edition): a. fasting blood glucose (FBG) > 7.0 mmol/L; b. postprandial blood glucose > 11.1 mmol/L [10]; (2) Diagnostic criteria of TCM: T2DM meets the diagnostic criteria in the Diagnostic Criteria of TCM for diabetes [11]. According to the syndrome differentiation of TCM, the diabetes is characterized by

yin deficiency and exuberant heat, with the primary symptoms of dry throat and mouth, and excessive thirst and drinking, and the secondary symptoms of vexation, fear of heat, preference for cold drinks, and reddish urine. The tongue is red in color, the coating is yellow and greasy, and the pulse is thin and wiry.

2.3 Inclusion criteria

(1) Meet the diagnostic criteria of TCM and Western medicine; (2) Diagnosisd for the first time without hypoglycemic treatment; (3) Informed of the research content and cooperate in data collection.

2.4 Exclusion criteria

(1) Diabetes ketoacidosis; (2) Hyperthyroidism; (3) Allergy to the drug in this study; (4) Hematological system diseases; (5) Epilepsy; (6) Malignant tumors; (7) Previous history of gastrointestinal surgery; (8) Severe dysfunction of organs such as the heart, liver, and kidneys; (9) Pregnant and lactating women.

2.5 Treatment methods

The control group adopted acarbose (50 mg/time, 3 times/day; 50 mg × 45 tablets; National medicine permission number (NMPN): H20020202; Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.). The combination group received modified Huanglian Jiedu Decoction and acarbose as the control group. The decoction consists of 12 g *Coptis chinensis*, 12 g *Scutellaria baicalensis*, 12 g Fructus Gardeniae, and 9 g Phellodendri Chinensis Cortex, but some other medicinal materials were additionally added for specific patients; for example, 30 g *Astragalus membranaceus*, 15 g *Atractylodis macrocephalae* Rhizoma and 15 g Codonopsis Radix for patients with qi deficiency; 15 g *fresh* Radix Rehmanniae and 15 g Radix Scrophulariae for patients with yin deficiency; 15 g *Poria cocos* and 15 g Rhizoma Dioscoreae for spleen deficiency; 20 g Radix Trichosanthis and 15 g Radix Ophiopogonis for patients with great thirst; and 6 g Fructus Amomi and 20 g Endothelium Corneum Gigeriae Galli for patients eating less but abdominal distension. The above medicinal materials were decocted with water to obtain 200 mL decoction that was taken orally in the morning and at night (100 mL each time).

2.6 Observation indexes

Data of vascular endothelial function index, insulin secretion function index and blood glucose level in the two groups were collected. The changes of symptoms and the occurrence of adverse reactions in the two groups during treatment were collated based on the medical records.

(1) Clinical efficacy: the clinical efficacy was compared between the two groups after two months of treatment. The efficacy was evaluated according to the relevant standards in the Guiding Principles for Clinical Research of New Chinese Medicines (Trial). Significantly effective: FBG level decreased by more than 40% or has returned to normal; Effectiveness: FBG level decreased by 20%-40%; Invalidity: FBG level decreased by less than 20% or higher than previous levels [12]. Total effective rate = (number of significant effective cases + number of effectiveness cases)/total cases × 100%.

(2) Endothelial function: the endothelial function of two groups was compared before and 2 months after treatment between the two groups. 5 mL elbow vein blood was collected from patients on an empty stomach in the morning and placed in a test tube, followed by centrifugation (3000 r/min) for 5 min and storage in a −20 ℃ refrigerator for later use. The levels of endothelin-1 (ET-1), nitric oxide (NO), and endothelial nitric oxide synthase (eNOS) was measured by using their detection kit, as per the instructions of each reagent kit (ET-1 kit, ml025101, Shanghai Enzyme-Linked Biotechnology Co., LTD, Shanghai, China; NO, ab65328, Abcam, Cambridge, MA, USA; eNOS, ml025095, Shanghai Enzyme-Linked Biotechnology Co., LTD, Shanghai, China).

(3) Blood glucose levels: the blood glucose levels were compared before and 2 months after treatment between the two groups. After fasting for 8 h, 2 mL venous blood was taken, where FBG was measured using the venous glucose oxidase method. The affinity chromatography was used to determine the level of glycated hemoglobin (HbA1c). After 2 h of eating, 2 mL venous blood was harvested to measure the 2-hour postprandial blood glucose using the venous glucose oxidase method.

(4) Insulin secretion function: the insulin secretion function was contrasted between the two groups before and 2 months after treatment. 4 mL fasting elbow vein blood was obtained from patients in the morning, and centrifuged (3500 r/min) for 10 min. The supernatant underwent measurement of fasting serum insulin (FINS) levels using radioimmunoassay. Insulin resistance index (HOMA-IR) = FBG × FINS/22.5; Insulin beta cell function index (HOMA-β) = (fasting insulin × 20)/(FBG − 3.5) [13].

(5) Adverse reactions: the adverse reactions such as diarrhea, abdominal distension, and impaired liver function that may occur during treatment were collected and compared between the two groups.

2.7 Statistical method

Statistical analysis was conducted using SPSS 26.0. The count data were presented as percentage (%), and compared using chi square test. The measurement data were analyzed using Kolmogorov-Smirnov method for normality, which conformed to normal distribution were expressed in the form of mean ± standard deviation. Independent sample t-test was performed for comparison between two groups, paired sample t-test for comparison before and after treatment within the same group, quartile M (P_{25}-P_{75}) for comparison of variables that did not conform to normal distribution, Mann-Whitney U test for comparison between two groups, and Wilcoxon sign rank sum test for comparison between two different time points within the same group. Bilateral $p < 0.05$ indicated statistically significant differences.

3 Results

3.1 Comparison of general information between the two groups

As shown in Table 1, the general information of patients was collected and compared, and there was no significant difference in general information between the two groups ($p > 0.05$), which was comparable.

3.2 Comparison of clinical efficacy between the two groups

The total clinical efficacy was higher in the combination group than the control group ($p < 0.05$, Table 2).

3.3 Comparison of vascular endothelial function between the two groups before and after treatment

There was no evident difference in ET-1, NO and eNOS levels between the two groups before treatment ($p > 0.05$). After treatment, ET-1 level was reduced and NO and eNOS levels were increased, and the changes were more evident in the combination group than the control group ($p < 0.05$, Table 3).

3.4 Comparison of blood glucose level between the two groups before and after treatment

Before treatment, there was no significant difference in FBG, 2-hour postprandial blood glucose, and HbA1c level between the two groups ($p > 0.05$). These indexes were diminished after treatment ($p < 0.05$), and were lower in the combination group than the control group ($p < 0.05$, Table 4).

Table 1 Comparison of general information between the two groups (mean ± standard deviation).

Group	Case	Sex [case (%)]		Age (years)	Average course of disease (month)	BMI (kg/m^2)
		Male	Female			
Combination group	45	28 (62.22)	17 (37.78)	47.93 ± 8.89	34.58 ± 14.49	24.71 ± 2.15
Control group	45	32 (71.11)	13 (28.89)	48.04 ± 10.23	32.22 ± 13.68	24.67 ± 2.12
t/X^2		0.800		−0.055	0.793	0.086
p		0.371		0.956	0.430	0.931

Group	Case	Complicated with high blood pressure [case (%)]	Education background [case (%)]		
			Elementary and junior high school education	Senior high school education	Junior college or above education
Combination group	45	9 (20.00)	7 (15.56)	15 (33.33)	23 (51.11)
Control group	45	12 (26.67)	8 (17.78)	20 (44.44)	17 (37.78)
t/X^2		0.559		1.681	
p		0.455		0.432	

Table 2 Comparison of clinical efficacy between the two groups [case (%)].

Group	Case	Significantly effective	Effectiveness	Invalidity	Total effective rate
Combination group	45	26 (57.78)	15 (33.33)	4 (8.89)	41 (91.11)
Control group	45	10 (22.22)	27 (60.00)	8 (17.78)	37 (82.22)
Z					-3.238
p					0.001

Table 3 Comparison of vascular endothelial function between the two groups before and after treatment (mean ± standard deviation).

Group	Case	ET-1 (ng/L)		NO (μmol/L)		eNOS (mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	45	91.89 ± 8.36	71.58 ± 6.14 *	44.82 ± 5.05	66.29 ± 5.38 *	5.18 ± 1.01	12.36 ± 1.94 *
Control group	45	92.36 ± 7.61	79.95 ± 5.88 *	43.29 ± 4.55	53.87 ± 5.95 *	5.27 ± 1.13	7.69 ± 1.07 *
t		−0.276	−6.604	1.514	10.390	−0.399	14.140
p		0.784	<0.001	0.134	<0.001	0.691	<0.001

Note: compared to before treatment within the same group, * $p < 0.05$.

Table 4 Comparison of blood glucose level between the two groups before and after treatment (mean ± standard deviation).

Group	Case	FBG (mmol/L)		2-hour postprandial blood glucose (mmol/L)		HbA1c (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	45	11.32 ± 1.66	6.47 ± 1.02 *	14.96 ± 1.31	9.10 ± 0.86 *	8.20 ± 1.20	6.36 ± 1.19 *
Control group	45	11.83 ± 0.87	8.09 ± 0.79 *	14.72 ± 1.28	11.70 ± 1.00 *	8.22 ± 1.26	7.07 ± 1.19 *
t		−1.832	−8.434	0.885	−13.236	−0.077	−2.821
p		0.071	<0.001	0.379	<0.001	0.939	0.006

Note: compared to before treatment within the same group, * $p < 0.05$.

3.5 Comparison of insulin secretion function between the two groups before and after treatment

FINS, HOMA-IR and HOMA-β levels had no apparent difference between the two groups before treatment ($p > 0.05$). After treatment, FINS and HOMA-IR levels were dwindled while HOMA-β level was elevated, and the changes were more remarkable in the combination group than the control group ($p < 0.05$, Table 5).

3.6 Comparison of adverse reactions between the two groups

There was no significant difference in the total incidence of adverse reactions (diarrhea, abdominal distension, impaired liver function) between the two groups ($p > 0.05$, Table 6).

Table 5 Comparison of insulin secretion function between the two groups before and after treatment (mean ± standard deviation).

Group	Case	FINS (μU/mL)		HOMA-IR		HOMA-β	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	45	16.54 ± 4.13	10.14 ± 3.19 *	8.42 ± 2.82	3.01 ± 1.31 *	43.60 ± 11.84	71.30 ± 17.84 *
Control group	45	16.94 ± 3.83	13.65 ± 3.61 *	8.92 ± 2.14	4.93 ± 1.47 *	41.04 ± 10.07	60.80 ± 17.72 *
t		-0.479	-4.878	-0.942	-6.528	1.105	2.801
p		0.633	<0.001	0.349	<0.001	0.272	0.006

Note: compared to before treatment within the same group, * $p < 0.05$.

Table 6 Comparison of adverse reactions between the two groups [case (%)].

Group	Case	Diarrhea	Abdominal distension	Impaired liver function	Total incidence
Combination group	45	1 (2.22)	0 (0.00)	1 (2.22)	2 (4.44)
Control group	45	1 (2.22)	2 (4.44)	1 (2.22)	4 (8.89)
χ^2					0.179
p					0.673

4 Discussion

To improve the clinical efficacy of patients with T2DM, this study explored the efficacy of Huanglian Jiedu Decoction combined with acarbose in the treatment of patients with T2DM, and confirmed the combination therapy might have better efficacy in the treatment of patients with T2DM.

According to the results of this study, Huanglian Jiedu Decoction combined with acarbose in the treatment of T2DM can effectively improve insulin secretion and reduce blood glucose levels, and was more effective than acarbose alone. Acarbose belongs to oligosaccharides, which combined with α glucosidase can effectively inhibit the activity of the enzyme, decelerate the rate of starch decomposition into glucose and sucrose, reduce the absorption of glucose and sucrose and lower blood glucose, thereby alleviating the toxic effect of high blood glucose on pancreatic β cells and promoting the recovery of pancreatic β cell secretion function [14]. Huanglian Jiedu Decoction is primarily composed of *Coptis chinensis*, *Scutellaria baicalensis*, Fructus Gardeniae, Phellodendri Chinensis Cortex, etc. Among them, *Coptis chinensis* can clear heat and dry dampness, *Scutellaria baicalensis* can reduce fire and detoxify, Fructus Gardeniae can reduce fire and alleviate vexation, and Phellodendri Chinensis Cortex can reduce fire and relieve bone-steaming sensation.

These herbs together have the function of clearing heat and removing toxins [15]. In an animal study, it was found that the Huanglian Jiedu Decoction may play a therapeutic role by promoting GLUT4 protein expression and translocation in adipose and skeletal muscle tissue of T2DM rats [16]. Modern pharmacology has revealed that berberine in Huanglian Jiedu Decoction can diminish blood glucose by increasing insulin receptor expression, and can also exert hypoglycemic effects through improving insulin resistance, inhibiting α glycosidase activity, etc. [17]. Sun et al. found that berberine can regulate the gut-brain axis, upregulate the expression of glucagon like peptide-1 (GLP-1) receptor mRNA, enhance the effect of gastrointestinal hormones, and mediate glucose metabolism, consistent with the results of this study [18]. Baicalein can regulate the InsR/IRS-1/PI3K/Akt signaling pathway, suppress gluconeogenesis and increase the activity of pyruvate kinase (PK) and glucokinase (GCK), thus promoting glycolysis and reducing blood glucose [19]. In addition, *Scutellaria baicalensis* aqueous extract can also exert hypoglycemic effects by regulating the interaction between ileac farnesoid X receptor (FXR)-mediated intestinal microbiota and bile acid (BA) metabolism [20]. Hence, Huanglian Jiedu Decoction combined with acarbose in the treatment of T2DM can effectively improve insulin secretion and reduce blood glucose levels, which was more effective than acarbose alone.

Hyperglycemia can increase the permeability of endothelial cells, allowing extracellular fluid to enter the cells and causing an increase in osmotic pressure, which result in edema and hypoxia of endothelial cells and ultimately affect the structure and function of endothelial cells [21]. This study selected ET-1, NO, and eNOS as three indicators to evaluate the degree of endothelial injury in patients. NO and eNOS are important vasorelaxation factors synthesized by endothelial cells, the downregulation of which indicates a decrease in vascular activity; ET-1 is an active peptide that constricts blood vessels, the higher expression level of which signifies more severe damage to endothelial function [22]. Herein, Huanglian Jiedu Decoction combined with acarbose can effectively improve the endothelial function of T2DM patients, which was superior to acarbose alone. Acarbose can reduce postprandial hyperglycemia in patients with hyperglycemia, improve insulin resistance, reduce the release of inflammatory factors, and enhance endothelial function [23]. Modern pharmacology has demonstrated that geniposide in Huanglian Jiedu Decoction can act on pancreatic β cells, activate GLP-1, improve glucose-stimulated insulin secretion, increase levels of heme oxygenase-1 and Bcl-2 proteins, promote the breakdown of thioredoxin-interacting proteins (Txnip), and inhibit Txnip-mediated oxidative stress and high glucose-induced endothelial damage [24]. Accordingly, Huanglian Jiedu Decoction combined with acarbose in the treatment of T2DM can effectively mitigate the degree of endothelial injury and reduce blood glucose levels, which was more effective than acarbose alone.

The results of this study unraveled that Huanglian Jiedu Decoction combined with acarbose had good safety and can reduce the occurrence of abdominal distension. Huanglian Jiedu Decoction can modulate the dysregulated gut microbiota, restore the balance between beneficial and pathogenic bacteria, alleviate intestinal inflammatory reactions, and reduce the occurrence of abdominal distension, thereby diminishing the incidence of adverse events caused by Western medicine [25].

Nevertheless, there are limitations in this study to be addressed. For example, the number of included cases is relatively small, and the cases are all patients in our hospital, resulting in a lack of large-scale random sampling and incomplete representativeness. In the future, further exploration is needed based on expanded sample size, so as to provide more

advanced evidence to support the application of Huanglian Jiedu Decoction combined with acarbose.

Collectively, Huanglian Jiedu Decoction combined with acarbose has good efficacy in the treatment of T2DM, which can improve the endothelial function and insulin secretion function, and effectively control the blood glucose level, without causing serious adverse reactions.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

The author, J.G., confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

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