

Clinical Research of Huatan Quyu Formula on the Treatment of Type 2 Diabetes Mellitus Combined with Non-Alcoholic Fatty Liver Disease

QIN LI, ZHEXIN YU¹ AND HONGLIANG XU*

Department of Endocrinology, South Area of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Xicheng, Beijing 100053, ¹No.1 People's Hospital, Dongcheng, Beijing 100007, China

Li *et al.*: Clinical Efficacy of Huatan Quyu Granules on Type 2 Diabetes Mellitus

To observe the clinical effect of Huatan Quyu granules on type 2 diabetes mellitus combined with non-alcoholic fatty liver disease. A total of 60 patients who met the inclusion criteria were selected from the Department of Endocrinology in the Southern District of Guang'anmen Hospital from January 2018 to December 2019. Thirty patients in the control group were treated with metformin hydrochloride tablets and thirty patients in the treatment group were additionally treated with Huatan Quyu granules after given by metformin hydrochloride tablets. Patients in both groups were treated for 12 w. The blood sugar (fasting plasma glucose, 2 h post-load plasma glucose, hemoglobin A1C), the blood lipids (triglyceride, low-density lipoprotein, high-density lipoprotein, total cholesterol), homeostatic model assessment of insulin resistance and changes in traditional Chinese medicine symptoms of the two groups were compared and analyzed. The total effective rate of traditional Chinese medicine symptoms was better in the treatment group compared with in the control group ($p < 0.05$); the scores of traditional Chinese medicine symptoms, i.e., fullness in the abdomen and stomach, hidden pain under the hypochondrium, dizziness, drowsiness and tastelessness in the mouth, increased in the treatment group after treatment compared with those before treatment and the control group ($p < 0.05$). The fasting plasma glucose, 2 h post-load plasma glucose, hemoglobin A1C, fasting insulin levels, homeostatic model assessment of insulin resistance, triglyceride, total cholesterol, low-density lipoprotein were lower in the treatment group after treatment compared with those before treatment and the control group ($p < 0.05$). Huatan Quyu granules can reduce the biochemical indexes related to glucose and lipids in patients with type 2 diabetes mellitus combined with non-alcoholic fatty liver disease, alleviate insulin resistance and improve the clinical symptoms of patients. It has a good application prospect.

Key words: Huatan Quyu formula, traditional Chinese medicine, diabetes, fatty live disease

With the process of modernization, the number of diabetic patients in China has increased year by year in recent years, and according to statistics, the prevalence of Type 2 Diabetes Mellitus (T2DM) in China has increased from 10.4 % in 2013 to 11.2 % in 2017^[1]. The diabetes progress slowly and there is numerous complications, especially metabolic-related diseases, such as hyperlipidemia, hypertension, hyperuricemia and Non-Alcoholic Fatty Liver Disease (NAFLD)^[2]. Although NAFLD occurs in the liver, it has a complex interrelationship with diabetes metabolism. Many studies have shown that they are not only closely linked in the pathogenesis and promote each other's occurrence

and development, but also insulin resistance is the initiating factor and central link in the pathogenesis of both, and it is their common pathophysiological basis^[3,4]. The treatment of such disease in Western medicine is mainly based on the improvement of lifestyle combined with the use of glucose-lowering, lipid-regulating and hepatic enzymology-improving drugs, and the efficacy needs to be improved. Currently, Chinese medicine has made some progress in the treatment of T2DM combined with NAFLD. According to the dialectical treatment and holistic regulation approach, Chinese medicine cannot only treat based on symptoms, but also control the causes and reduce fat deposition in the liver, thus delaying the progression of the disease. This study is guided

*Address for correspondence

E-mail: gamyy1987@163.com

by the basic theory of Chinese medicine and based on clinical manifestations. We found that phlegm and blood stasis is the common types of T2DM. Therefore, we proposed to use the Huatan Quyu granules based on method of “removing phlegm and lowering turbidity, activating blood circulation and eliminating blood stasis” and to observe the effects on the glucose and lipids metabolism, insulin resistance and Traditional Chinese Medicine (TCM) symptoms in patients with T2DM combined with NAFLD. All the cases in this trial were patients who were treated in the Department of Endocrinology of the Southern District of Guang’anmen Hospital, China Academy of Chinese Medical Sciences. Patients with T2DM combined with NAFLD who met the inclusion criteria were randomly divided into the treatment group and the control group and thirty cases in each group. There were 21 males and 9 females in the treatment group, with an age range of (30-64) y, and the mean age was (53.24±8.51) y; there are 19 males and 11 females in the control group, with an age range of (30-65) y, and the mean age was (52.78±9.07) y. General data such as diabetes course, laboratory physical and chemical indexes and main TCM symptoms can be compared between the two groups ($p>0.05$). Western medicine diagnostic criteria including the T2DM combined with NAFLD meets the diagnostic criteria of diabetes proposed by World Health Organization (WHO) (1999 edition) and the diagnostic criteria of “Guidelines for the Diagnosis and Treatment of NAFLD”^[5] (2006 revised edition). TCM syndrome differentiation standard including the syndrome of mutual obstruction of phlegm and blood stasis was formulated with reference to “Guidelines for Clinical Research of New Chinese Medicines” (2002 edition)^[6] and “Internal Medicine of TCM (2nd edition)”^[7]. Main symptoms including the obesity, fullness in the abdomen and stomach, hidden pain under the hypochondrium; secondary symptoms including the dizziness, drowsiness, tastelessness in the mouth or dry mouth but do not want to drink; tongue and pulse including the fat tongue, dark color or with petechiae and bruise on the sides, thick and greasy tongue coating; smooth or fine pulse. If all the main symptoms are present; or two of the main symptoms are accompanied by any two of the secondary symptoms; if the tongue and pulse are basically similar, the syndrome of mutual obstruction of phlegm and blood stasis is diagnosed. Meet the above-mentioned Western medicine diagnostic

criteria and TCM syndrome differentiation criteria; age between (25-65) y old, and have no communication barriers or history of mental illness; have not received treatment with similar TCM preparations within the past 1 mo and have not participated in other clinical trials within the past 3 mo. Voluntarily participate in this study and sign the informed consent. Type 1 diabetes or other special types of diabetes; specific types of liver diseases caused by factors such as fatty liver that is caused by other known causes, alcoholism, various types of viral hepatitis, autoimmune liver disease, hereditary liver disease, drugs; diabetic ketosis or co-infection and other emergency states within the past 1 mo; severe underlying diseases such as cardiovascular and cerebrovascular diseases, tumors, etc.; planned pregnancy or pregnancy or lactation. Those who are allergic to the ingredients of TCM in this study. Treatment methods including the patients in both groups were given the same health education diet and exercise interventions related to diabetes and non-alcoholic fatty liver, and they controlled staple food intake and increased exercise. The control group was given metformin hydrochloride tablets (Sino-American Shanghai Squibb Pharmaceutical Co., Ltd., H20023370), 1.0 g/time, 2 times/d. The treatment group was additionally given Huatan Quyu granules (main components: Cortex Mori 15 g, Rhizoma *Alisma* 10 g, *Salvia miltiorrhiza* (*S. miltiorrhiza*) 15 g, *Coptis chinensis* (*C. chinensis*) 10 g, cooked Rhubarb 6 g, (produced by Beijing Kangrentang Pharmaceutical Co., Ltd., 3 g/bag), 1 dose a day, one time in the morning and one in the evening with warm water. Patients in both groups were treated for 12 w. Efficacy indexes including the Physicochemical indexes include blood glucose (Fasting Plasma Glucose (FPG), 2 h post-load Plasma Glucose (2hPG), Hemoglobin A1C (HbA1C)), blood lipids (Triglyceride (TC), Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Total Cholesterol (TG)), Fasting Insulin Levels (FINS), and insulin resistance index was calculated (Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)=FPG×FINS/22.5), which were tested once before and after treatment; the evaluation of TCM symptoms scores refer to the “Guidelines for clinical research on new Chinese medicines”, and patients’ TCM clinical symptoms and signs were scored as 0, 2, 4 and 6 points for each degree of absence, mild, moderate and severe; the efficacy evaluation criteria of TCM symptoms were

calculated by the nimodipine method. Safety indexes general physical examination was performed on enrolled patients, vital signs and the occurrence of adverse events during drug administration were recorded, and changes in the blood routine, routine urine, liver function and kidney function were detected before and after the enrollment. The Statistical Package for the Social Sciences (SPSS) 26.0 software package was used for statistical analysis. The measurement data were expressed as mean±standard deviation ($\bar{x}\pm s$), the enumeration data were tested by Chi-square (χ^2) test, and the measurement data were tested by t test and the difference was statistically significant ($p<0.05$). The total effective rate of TCM symptoms was 86.7 % in the treatment group and 50.0 % in the control group; the difference between the two groups was statistically significant ($p<0.05$) as shown in Table 1. The scores and total scores of symptoms, i.e., abdominal and stomach fullness, hidden pain under the hypochondrium, dizziness, drowsiness and tastelessness in the mouth, increased in the treatment group after treatment compared with before treatment and the control group, ($p<0.05$); there was no statistical difference between the two groups in the scores of physical obesity ($p>0.05$) as shown in Table 2. The FPG, 2hPG, HbA1c, FINS, HOMA-IR, TC, TG and LDL were lower in the treatment group after treatment compared with before treatment and the

control group ($p<0.05$), and the decrease in the treatment group was more significant than that in the control group ($p<0.05$); there was no statistical difference in HDL between the two groups ($p>0.05$) as shown in Table 3. During the whole trial period, two cases in the treatment group showed gastrointestinal reactions, which were characterized by thin stools and increased frequency, and the symptoms gradually decreased after adherence to the medication. In the control group, one case showed abdominal fullness and two cases showed nausea. There were no abnormalities in the blood routine, urine routine, liver function, kidney function and electrocardiogram before and after treatment in the two groups. It is suggested that the clinical medication of the two groups is safe and reliable. T2DM and NAFLD are modern medical concepts, so there is no corresponding disease name in Chinese medicine. However, to judge from the symptoms and clinical manifestations, some words such as “Xiaodan”, “Xiaoke”, “Ganzhuo” and “Jiju” in ancient classics are similar to T2DM and NAFLD. With the process of modern socialization, people spend a lot of time staying indoors, eat too many foods high in fat and sugar, and do less and less physical activities. This type of lifestyle gradually damages the spleen and stomach so that the spleen and stomach can't function properly.

TABLE 1: COMPARISON OF THE EFFICACY OF TCM SYMPTOMS [CASE (%)]

Group	Number	Significantly effective	Effective	Ineffective	Total efficacy
Treatment	30	9 (30.0)	17 (56.7)	4 (13.3)	26 (86.7)*
Control	30	4 (13.3)	11 (36.7)	15 (50.0)	20 (50.0)

Note: Compared with the control group after treatment, * $p<0.05$

TABLE 2: COMPARISON OF TCM SYMPTOMS SCORES BEFORE AND AFTER TREATMENT BETWEEN TWO GROUPS ($\bar{x}\pm s$)

Symptoms	Treatment group (n=30)		Control group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
Obesity	4.23±1.43	3.91±1.19	4.34±1.42	4.21±1.08
Abdominal and stomach fullness	4.67±1.63	2.84±1.02 Δ^*	4.54±1.46	3.97±1.14
Hidden pain under the hypochondrium	3.69±1.27	2.14±0.97 Δ^*	3.58±1.25	3.41±1.18
Dizziness	2.92±0.92	1.25±0.84 Δ^*	2.87±0.97	2.26±0.86
Drowsiness	4.17±1.43	2.26±1.01 Δ^*	4.23±1.31	3.98±1.14
Tastelessness in the mouth	3.53±1.12	1.43±0.84 Δ^*	3.47±1.34	3.06±0.90
Total scores	24.21±3.14	13.72±2.01 Δ^*	23.84±3.06	20.89±2.43

Note: Compared with before treatment, $\Delta p<0.05$ and compared with the control group after treatment, * $p<0.05$

TABLE 3: COMPARISON OF BLOOD GLUCOSE, BLOOD LIPIDS AND INSULIN-RELATED INDEXES ($\bar{x}\pm s$)

	Treatment group (n=30)		Control group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
FPG (mmol/l)	8.37±1.45	7.05±1.29 ^{Δ*}	8.51±1.51	7.43±1.23 ^Δ
2hPG (mmol/l)	10.21±2.26	8.87±1.27 ^{Δ*}	10.49±2.34	9.12±1.71 ^Δ
HbA1c (%)	7.18±0.65	6.24±0.43 ^{Δ*}	7.21±0.59	6.78±0.52 ^Δ
FINS (mU/l)	15.24±4.02	11.57±3.18 ^{Δ*}	15.96±4.32	14.37±4.13
HOMA-IR	6.02±2.34	4.03±1.69 ^{Δ*}	6.13±2.48	5.59±2.75
TC (mmol/l)	6.16±1.42	4.34±1.02 ^{Δ*}	6.29±1.27	5.78±1.17
TG (mmol/l)	3.32±0.84	1.96±0.71 ^{Δ*}	3.17±0.87	2.94±0.81
HDL (mmol/l)	0.96±0.24	1.19±0.37	0.99±0.22	1.01±0.29
LDL (mmol/l)	4.32±0.86	3.17±0.73 ^{Δ*}	4.31±0.79	3.83±0.85

Note: Compared with before treatment, ^Δp<0.05 and compared with the control group after treatment, *p<0.05

The metabolism of nutrients such as sugar and fat slow down, and the surplus is laid down as the phlegm and fat. Both of them are stored in the liver. Liver governs stagnation, regulates Qi and helps spleen to function properly. Nowadays, we are living a fast-paced and high-pressured society, where many things can trigger mood swings. However, the violent mood swings will contribute to the liver-depression and the spleen-deficiency. There is a vicious circle between them and the accumulation of phlegm aggravates. The accumulation of phlegm in the interior hinders the circulation of Qi and blood, and further causes blood stasis. The interplay of dampness, phlegm coagulation and blood stasis are not only a pathological product but also a pathogenic cause, leading to the malfunction of the liver and spleen, thus inducing a series of metabolic imbalance. Therefore, the liver and spleen are mainly responsible for the pathogenesis of T2DM combined with NAFLD, and phlegm, dampness, heat and stasis are the main pathological factors. Mutual obstruction of phlegm and stasis runs through the occurrence and development of the disease. Therefore, the method of “resolving phlegm and lowering turbidity, activating blood circulation and resolving stasis” is proposed for the treatment of this disease. In this study, Huatan Huoxue granules are composed of Cortex Mori, Rhizoma *Alisma*, *S. miltiorrhiza*, *C. chinensis* and Rhubarb. Among them, Cortex Mori and Rhizoma *Alisma* resolve the phlegm, disperse stagnation, remove dampness and reduce turbidity; *S. miltiorrhiza* is bitter and slightly cold. It can promote blood circulation, eliminate blood stasis, dispel stagnation and generate new blood. If the phlegm and blood stasis are blocked for a long time, it is easy to turn heat into toxin. Therefore, *C. chinensis* and Rhubarb cannot only clear away heat and dry dampness, but also clear the internal organs, relieve

turbidity and detoxification. In addition, Rhubarb can also promote blood circulation and dredge channels, which improve the abilities to remove phlegm and eliminate blood stasis. It coordinates the whole recipe to achieve the effects of removing phlegm and dampness, promoting blood circulation and removing blood stasis, thereby restoring the functions of liver and spleen, smoothing the movement of Qi of the whole body. As a result, the dampness is removed, the phlegm is resolved and the blood stasis and channels are unblocked. Modern pharmacological researches have shown that alkaloids and flavonoids in mulberry can inhibit the activity of α -glucosidase, reduce the decomposition efficiency of oligosaccharides, inhibit the activity of glucoamylase and regulate the metabolism of glucose in the liver. Secondly, it inhibits the absorption of glucose in the intestine, activates the insulin signaling pathway Phosphatidylinositol 3-Kinase (PI3K)/protein kinase B in the skeletal muscle of diabetic mice and improves insulin sensitivity. It not only has multi-channel hypoglycemic effects, but also has good curative effects in lowering blood lipids and anti-atherosclerosis^[8]. The aqueous extract of Rhizoma *Alisma* can improve the metabolism of fat in the liver, reduce lipid deposition, inhibit the proliferation of preadipocytes, and reduce the steatosis and damage of HepG2 cells in NAFLD. It also has the liver protective activity, and its aqueous decoction can inhibit transaminase elevation and hepatosplenomegaly, and reduce hepatic fatty lesions, inflammatory necrosis and collagen deposition^[9]. The tanshinol in *S. miltiorrhiza* can significantly reduce thrombin-induced platelet aggregation; salvianolic acid A can increase the content of cyclic adenosine monophosphate in platelets, reduce blood viscosity, significantly inhibit platelet aggregation and have antithrombotic activity; *S. miltiorrhiza*

also can reduce damage to hepatocyte morphology, promote the recovery of liver function, and has significant hepatoprotective effect^[10]. Berberine can block insulin resistance caused by free fatty acids by increasing the expression of insulin receptor substrate-1 and PI3K proteins; berberine can also promote the secretion of glucagon-like peptide-1, increase insulin levels and the number of pancreatic β -cells to achieve hypoglycemic effect^[11,12]. Rhubarb extract can regulate blood lipids, reduce TC and TG, improve the ratio of thromboxane to prostaglandins, reduce blood viscosity, improve microcirculation and increase local blood supply^[13]. Metformin is the first-line drug for the treatment of T2DM combined with NAFLD^[14]. In this study, patients with metformin were selected as the control group. It can not only inhibit liver glycogenolysis and gluconeogenesis, increase carbohydrate uptake in peripheral tissues, improve insulin resistance and thus effectively reduce blood sugar; it can also reduce liver damage caused by lipid accumulation in liver tissues by participating in lipid metabolism. However, for patients with T2DM and NAFLD with a longer course of disease, it is difficult to achieve the desired effect with single-agent therapy. In this study, Huatan Quyu Granule was used as the treatment group for observation. The results showed that the FPG, 2hPG, HbA1c, FINS and HOMA-IR of the two groups were lower after treatment compared with before treatment ($p < 0.05$), but compared with those treated with Western medicine alone, after supplemented with Huatan Quyu granules, the FPG, 2hPG, HbA1c, FINS, HOMA-IR, TC, TG and LDL were significantly lower in the treatment group compared with in the control group ($p < 0.05$). The treatment group can significantly improve the patient's TCM symptoms scores, especially for abdominal and stomach fullness, hidden pain under the hypochondrium, dizziness, drowsiness and tastelessness in the mouth, and no adverse drug reactions were observed. In conclusion, Huatan Quyu Granules combined with Western medicine in the treatment of this disease can effectively reduce the biochemical indexes related to glucose and lipids in patients with T2DM combined with NAFLD, alleviate insulin resistance, and improve clinical symptoms of patients. It has a positive curative effect and high safety.

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Conflict of interests:

The authors declared no conflict of interests.

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