Retrospective study of Traditional Chinese Medicine treatment of type 2 diabetes mellitus

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Abstract

OBJECTIVE: To provide clinical evidence in support of Dahuang Huanglian Xiexin decoction (DHXD) to treat type 2 diabetes mellitus (T2DM) and to introduce a new treatment option for clinicians.

METHODS: Retrospective analysis was used to evaluate DHXD for the treatment of T2DM by analyzing clinical records of 183 cases. Patients with T2DM who met the inclusion criteria between January 1, 2013 and January 1, 2014 were enrolled. The effects of the treatment were evaluated by the changes in fasting blood-glucose (FBG), postprandial blood sugar (PBG), hemoglobin A1c (HbAlc), blood lipid profiles and body mass index (BMI) at 1, 2, 3 and 6 months. The changes in main symptoms were also evaluated. The dosage of Huanglian (Rhizoma Coptidis) and related factors were analyzed.

RESULTS: There was a significant improvement in mean HbA1C at 3 and 6 months after DHXD treatment compared with the baseline level (P < 0.01). There were also significant improvements in FBG, PBG, blood lipid series and BMI. DHXD also improved the main symptoms of stomach and intestine excessive heat syndrome in patients with obese T2DM. Huanglian (Rhizoma Coptidis) was the most frequently used in 678 clinical visits, the dosage of Huanglian (Rhizoma Coptidis) was related to age, BMI, DM duration, the level of blood glucose, and use of Western hypoglycemic drugs.

CONCLUSION: This study suggests that DHXD could decrease blood glucose and improve T2DM symptoms and reduce body weight. The use of DHXD may indicate a new optional treatment for T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the predominant form of DM, which accounts for 95% of the global diabetes population. The cause of T2DM has not yet been fully elucidated, although both genetic and environmental factors (obesity and sedentary lifestyles) are commonly cited. China has the world’s largest diabetes population, with more than 92.4 million people af-
The standard therapy for DM includes diet, exercise, use of oral hypoglycemic drugs, and/or subcutaneous insulin injections. Traditional Chinese Medicine (TCM) has been used to treat T2DM in China for over 2000 years. Treatment by TCM has the advantage of lower toxicity and/or fewer side effects, and herbal medicine could provide multiple therapeutic effects on multiple targets. Professor Tong Xiaolin, an expert in TCM for treating T2DM in China, reported in a syndrome analysis study involving 2518 cases of obese T2DM that stomach and intestine excessive heat syndrome is common in obese T2DM. Prof. Tong suggested a method using Dahuang Huanglian Xiexin Decoction (DHXD) to clear away the heat and direct the turbidity downward. DHXD has been established as a fundamental formula for stomach and intestine excessive heat syndrome in obese T2DM. By using large scale randomized controlled trials (RCTs), our group has confirmed that Chinese herbal medicine possesses independent anti-hyperglycemic effects. In one study with 122 cases of obese patients with T2DM, Kaiyu Qingre Jiangzhuo formula (KQJF) (modified DHXD) was given to the treatment group and metformin to the control group. The results showed no statistically significant difference between the two groups on lowering the blood glucose (P > 0.05), and no obvious adverse events were reported in the treatment group. This was the first evidence of a Chinese herbal medicine lowering blood glucose in clinical conditions.

**METHODS**

**General information**

The clinical records from Professor Tong Xiaolin were used as the database. Patients who met the inclusion criteria between January 1, 2013 and January 1, 2014 were enrolled in the study. Progress of the study is shown in Figure 1.

The diagnostic criteria were: (a) diagnosis of T2DM referred to World Health Organization (WHO) T2DM diagnostic criteria (1999); and (b) TCM syndrome differentiation referred to Guideline for TCM Diabetes Prevention and Treatment (2007). The inclusion criteria included: (a) minimum age of 18 years; (b) a confirmed diagnosis of T2DM; and (c) DHXD as the primary prescription. The baseline data were recorded as follow-up data within 6 months of blood glucose or hemoglobin A1c (HbA1c). Patients were excluded if they had type 1 diabetes mellitus or had diabetic ketoacidosis.

**Information collection and standardization**

A full medical history was recorded, including general information about diabetes, related diabetic complications, diagnosis, therapeutic treatments and prescribed herbal medicine.
medication, whether hypoglycemic drugs were used, and whether the patient was suffering from any other disease. All the information was inputted into Visual FoxPro software (vers 6.0, Microsoft Corporation, Redmond, Washington D.C., USA), and cases which met the inclusion criteria were transferred to an Excel table and screened out. EpiData 3.1 software (vers 3.1, EpiData Association, Odense, Denmark) was used to document the detailed medical histories. Because of variations in the way the medical histories were expressed, they were scrutinized for errors and, where necessary, the language was standardized. The criteria used for standardizing word choice were based on the normative textbooks.³⁻⁴ For example, "sleep disorder", "sleeplessness", and "insomnia" were unified as "insomnia"; "Da Huang", "Jiu Da Huang", "Jiu Jun" were unified as "Da Huang"; "gliclazide" and "Da Mei Kang" were unified as "gliclazide".

**TCM therapy method**

Stomach and intestine excessive heat syndrome was identified in patients according to symptoms of dry mouth, bad breath, dry stool, red or yellow tongue coating, and rapid pulse. The therapeutic method used was "clear away the heat and direct the turbidity downward".¹² DHXD was established as the primary prescription, which was composed of Dahuang (Radix et Rhizaoma Rhei Palmata) and Huanglian (Rhizaoma Coptidis), Tianma (Rhizoma Gastrodiae) and Gouteng (Ramulus Uncariae Rhynchophyllae cum Unci) were added for hypertension, Weilingxian (Radix et Rhizaoma Clematidis Chinensis) was added for hyperuricemia, and Yinchen (Herba Artemisiae Capillaris) and Wuweizi (Fructus Schisandrae Chinensis) were added for fatty liver. Patients took decoction twice daily, and evaluations were performed at 1, 2, 3 and 6 months return visits. HBAlc, BMI, FBG, P BG, cholesterol (CHO), triglyceride (TG), high-density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) changes were measured before and after the treatment.

**Statistical analysis**

Statistical analyses were performed with SPSS software (vers 17.0, SPSS Institute, Chicago, IL, USA). Frequencies of main symptoms were summarized by numbers (n) or percentages (%). Quantitative indicators were presented as the mean ± SD, P < 0.05 or P < 0.01 was considered to be statistically significant, and comparisons of before and after treatment were tested using the t-test or non-parametric test. Subjective symptoms were recorded and baseline symptoms scored "2". After the treatment, alleviated symptoms scored "1", disappeared symptoms scored "0", no symptom improvement or worse symptoms scored "3". If no obvious symptom appeared when first seeing a doctor, "0" was scored. If symptoms began to appear after treatment, "2" was scored. If symptoms were aggravated, then "3" was scored.³⁻³

**Subjects**

Study subjects were outpatients at Guang’anmen Hospital. All patients gave informed consent and the study was approved by the Ethics Committee of Guang’anmen Hospital of China Academy of Chinese Medical Sciences.

**RESULTS**

**Study population**

A total of 183 patients with 678 clinical visits were included. The treatment group was composed of 122 men (66.7%) and 61 women (33.4%) with a mean age of (48 ± 13) years (range 18-79 years). The level of HBAlc less than 7 appeared 24.29% (43/177), 7 to 8 appeared 30.50% (54/177), 8 to 9 appeared 20.34% (36/177), the level of HBAlc more than 9 appeared 24.86% (44/177). Of 183 patients, 49 patients combined with insulin, 52 patients combined with Metformin, 32 combined with Acarbose, 15 combined with Repaglinide, 10 combined with Gliclazide, 8 combined with Rosiglitazone.

**Change in HBAlc**

Patients may have different follow-up times according to the severity of their symptoms and indicators in this retrospective study. The number of patients at 0, 1, 2, 3 and 6 months were 177, 78, 56, 177 and 126, respectively. Mean HBAlC at 0, 1, 2, 3 and 6 months was 8.0% ± 1.7%, 7.8% ± 1.5%, 7.7% ± 1.0%, 7.1% ± 1.1% and 6.8% ± 1.1%, respectively. There were significant differences between 0 and 3 months (P < 0.01) and between 0 and 6 months (P < 0.01), but only decreasing trends between 0 and 1 month and between 0 and 2 months (P > 0.5), indicating that DHXD had a beneficial effect on improving HBAlc and that a time-effect relationship existed. Results were also analyzed from the perspective of different uses of Western hypoglycemic drugs, and BMI or DM duration. The results showed that HBAlc had a decreasing trend at all follow-up points and showed significant differences at 6 months compared with 0 months (P < 0.01 or P < 0.05), and the curative effect increased as time progressed (Tables 1-3).

**Change in blood glucose levels**

The number of patients at 0, 1, 2, 3 and 6 months were 167, 70, 53, 148 and 107 patients, respectively. Mean FBG at 0, 1, 2, 3 and 6 months was (9.2 ± 2.6), (8.6 ± 2.0), (8.7 ± 1.9), (8.2 ± 2.2) and (7.8 ± 1.8) mmol/L, respectively. There were significant differences between 0 and 3 months (P < 0.01) and between 0 and 6 months (P < 0.01), but only decreasing trends between 0 and 1 month (P > 0.05) and 0 and 2 months (P > 0.05), indicating that DHXD is beneficial in controlling FBG. The FBG decreased with patients who used DHXD alone and also with those who used DHXD plus the original dosage of hypoglycemic
drugs. Before and after treatments were analyzed at 3 and 6 months and showed remarkable differences ($P < 0.01$ or $P < 0.05$). The FBG of patients who reduced the dosage of hypoglycemic drugs during the treatment had a decreasing trend, but did not show any significant difference ($P > 0.05$) (Table 4). The number of patients at 0, 1, 2, 3 and 6 months with PBG results were 91, 42, 22, 68 and 39, respectively. The mean PBG at 0, 1, 2, 3 and 6 months was $(14.3 \pm 4.6)$, $(13.7 \pm 5.0)$, $(14.5 \pm 4.4)$, $(11.7 \pm 3.7)$ and $(11.4 \pm 3.4)$ mmol/L, respectively. There were significant differences between 0 and 3 months and between 0 and 6 months ($P < 0.01$), but only decreasing trends between 0 and 1 month and between 0 and 2 months ($P > 0.05$), indicating that DHXD has a beneficial effect on controlling PBG, and as time progressed, the effect increased.

**Change in body mass index (BMI)**

The mean BMI of obese patients (BMI $> 28$ kg/m$^2$) during the study period were $(30.2 \pm 2.5)$, $(29.6 \pm 2.4)$ and $(28.9 \pm 1.7)$ kg/m$^2$ at 0, 3 and 6 months, respectively. There was a significant difference in BMI between 0 and 6 months ($P < 0.05$), but not between 0 and 3 months ($P > 0.05$). In overweight patients (BMI 24-28 kg/m$^2$), mean BMIs were $(26.2 \pm 1.3)$, $(25.8 \pm 1.3)$ and $(25.4 \pm 1.3)$ kg/m$^2$ at 0, 3 and 6 months, respectively. There were significant differences in BMI between 0 and 3 months ($P < 0.05$) and between 0 and 6 months ($P < 0.01$).

**Change in blood lipid profiles**

Seventy-four patients with CHO $> 5.17$ mmol/L were analyzed, and the means were $(6.03 \pm 0.75)$, $(5.54 \pm 0.94)$ and $(5.55 \pm 1.12)$ mmol/L at 0, 3 and 6 months, respectively. There were significant differences between 0 and 3 months and between 0 and 6 months ($P < 0.01$). Seventy-nine patients with TG $> 1.70$ mmol/L were analyzed, and the means were $(3.2 \pm 1.7)$, $(2.6 \pm 1.3)$ and $(2.6 \pm 1.5)$ mmol/L at 0, 3 and 6 months, respectively. There were significant differences between 0 and 3 months and 0 and 6 months ($P < 0.05$). Fifty-nine patients with LDL-C $> 3.10$ mmol/L were analyzed, and the means were $(3.85 \pm 0.76)$, $(3.49 \pm 0.97)$ and $(3.42 \pm 1.02)$ mmol/L at 0, 3 and 6 months, respectively. There were significant differences between 0 and 3 and between 0 and 6 months ($P < 0.05$) and 3 and 6 months ($P > 0.05$).

| Table 1 HbA1c comparison from the use of western drugs (%) $\pm$ s |
|---------------------------|---------------------------|---------------------------|---------------------------|
| Use of western drugs      | HbA1c 0 month             | HbA1c 3 month             | P value                   |
| No use (n=69)             | 7.7±1.4 (n=67)            | 6.9±0.9 (n=67)            | 0.031                     |
| Reduce dosage (n=30)      | 7.7±1.9 (n=34)            | 6.9±1.1 (n=34)            | 0.09                      |
| Original dosage (n=80)    | 8.3±1.8 (n=73)            | 7.3±1.3 (n=73)            | 0.000                     |

Notes: $P < 0.051$; $P < 0.01$, compared with 0 month. HbA1C: hemoglobin A1c.

| Table 2 HbA1c comparison from the level of BMI (%) $\pm$ s |
|---------------------------|---------------------------|---------------------------|---------------------------|
| BMI (kg/m$^2$)            | HbA1c 0 month             | HbA1c 3 month             | P value                   |
| 18-24 (n=50)              | 7.6±1.7 (n=48)            | 7.0±1.2 (n=48)            | 0.038                     |
| 24-28 (n=84)              | 8.0±1.7 (n=82)            | 7.0±1.0 (n=81)            | 0.000                     |
| ≥ 28 (n=47)               | 8.5±1.6 (n=47)            | 7.5±1.2 (n=47)            | 0.001                     |

Notes: $P < 0.01$; $P < 0.05$, compared with 0 month. HbA1C: hemoglobin A1c; BMI: Body mass index.

| Table 3 HbA1c comparison from the duration of diabetes (%) $\pm$ s |
|---------------------------|---------------------------|---------------------------|---------------------------|
| DM duration (years)       | HbA1c 0 month             | HbA1c 3 month             | P value                   |
| 0-1 (n=44)                | 7.7±1.9 (n=43)            | 6.7±1.4 (n=43)            | 0.001                     |
| 1-2 (n=16)                | 7.9±1.5 (n=15)            | 7.0±1.5 (n=15)            | 0.091                     |
| 2-5 (n=44)                | 7.9±1.2 (n=45)            | 7.2±1.0 (n=44)            | 0.005                     |
| 5-10 (n=36)               | 7.9±2.0 (n=35)            | 7.2±0.9 (n=36)            | 0.064                     |
| ≥10 (n=43)                | 8.4±1.8 (n=41)            | 7.5±1.3 (n=40)            | 0.011                     |

Notes: $P < 0.01$; $P < 0.05$, compared with 0 month. HbA1C: Hemoglobin A1c; DM: diabetes mellitus.

| Table 4 Comparison between FBG and different dosages of combined hypoglycemic drugs (mmol/L) $\pm$ s |
|---------------------------|---------------------------|---------------------------|---------------------------|
| Use of western drugs      | FBG 0 month               | FBG 3 month               | P value                   |
| No use (n=69)             | 8.9±2.0 (n=63)            | 7.8±1.4 (n=60)            | 0.000                     |
| Reduce dosage (n=30)      | 8.2±2.2 (n=32)            | 7.5±1.4 (n=27)            | 0.144                     |
| Original dosage (n=80)    | 9.7±3.0 (n=68)            | 8.6±2.7 (n=57)            | 0.026                     |

Notes: compared with 0 month, $P < 0.01$; $P < 0.05$. FBG: fasting blood-glucose.
0.05), which indicated that DHXD had beneficial effects on decreasing CHO, TG and LDL-C. Forty-two patients with HDL-C (< 1.10 mmol/L) were analyzed, and the means were (0.91 ± 0.12), (0.98 ± 0.22) and (1.02 ± 0.24) mmol/L at 0, 3 and 6 months, respectively. There was a significant difference between 0 and 6 months ($P < 0.05$), but only a decreasing trend between 0 and 3 months ($P > 0.05$).

**Change in main symptoms**

The frequencies of main symptoms showed that the highest frequency was 163 cases for greasy tongue coating, followed by 152 for yellow tongue coating and 132 for red tongue. The subjective symptoms with high frequency were dry mouth and thirst, fatigue, insomnia, loose and smelly stool, irritability and hyperhidrosis. Of 183 cases, 89.07% of patients suffered greasy tongue coating, 83.06% yellow tongue coating, 72.13% red tongue, and 42.08% dry mouth and thirst. With regards to the effectiveness of the treatment for relieving the main symptoms, dry stool was obviously alleviated with remission rates at 3 and 6 months of 95.08% and 90.16%, respectively. Remission rates of dry mouth and thirst were 85.71% and 61.04% at 3 and 6 months, respectively. Remission rates of fatigue were 61.43% and 80% at 3 and 6 months, respectively (Table 5).

**The use of Huanglian (Rhizoma Coptidis) and related factors**

Huanglian (Rhizoma Coptidis) was the most frequently used herb in 678 clinical visits, the frequency reached 87.02%. We investigated factors affecting the dosage of Huanglian (Rhizoma Coptidis) from five levels: ≥ 30 g, 15-29 g, 9-14 g, 6-8 g and < 6 g. From the perspective of age, we can see the oldest people (mean age) were using 9 to 14g, and the youngest people (mean age) were using more than 30 g. From the perspective of BMI, the decrease of BMI caused consequent dosage reduction of Huanglian (Rhizoma Coptidis). Huanglian (Rhizoma Coptidis), and the highest BMI patients were using more than 30g dosage of Huanglian (Rhizoma Coptidis). Huanglian (Rhizoma Coptidis). The patients with longest DM duration (mean) used 9 to 14 g, and patients with the shortest DM duration (mean) used 6 to 8g, suggesting that DM duration was short and the blood glucose was easy to control, so the amount of the Huanglian (Rhizoma Coptidis) was relatively less. With the increase of blood glucose (HbA1c,FBG and PBG), the amount of Huanglian (Rhizoma Coptidis) was consequently increasing, the highest level of blood glucose were using more than 30 g dosage of Huanglian (Rhizoma Coptidis). Moreover, the different dosages of Huanglian (Rhizoma Coptidis) when using different use of western drugs were analyzed. The means dosages were (17 ± 9), (19 ± 10) and (20 ± 11) g when no use of western drugs, reduced dosage of western drugs, and increased dosage of western drugs, respectively, suggesting that doctors could increase the dosage of Huanglian (Rhizoma Coptidis) under the condition that reduced dosage of western drugs, and when the patient did not use Western hypoglycemic drugs, the dosage of Huanglian (Rhizoma Coptidis) could be decreased (Table 6).

**DISCUSSION**

**TCM therapy of type 2 diabetes**

The epidemic growth rate of obesity and an increasing elderly population contribute to the prevalence of DM. TCM has a long history of being used to treat DM in China. Clinical practice has shown a bright future for
Analysis of results
The study aim was to provide clinical evidence to support DHXD for treating T2DM. All participating patients were diagnosed with T2DM, and there were more men than women (122 vs. 61). Most patients (>70%) were middle-aged with a BMI higher than 24 kg/m², an HbA1C that ranged from 7% to 9%, and DM duration of less than 10 years. These data reflect the clinical characteristics of our study population. Patients with T2DM in the early stages began developing excessive heat where there was a history of over-eating and a sedentary lifestyle, which generally combined with the clinical appearance of obesity and fatty liver, hyperlipidemia, hypertension and hyperuricemia.

To analyze the factors related to the effects of herbal medicine, we conducted subgroup analysis. From the perspective of mean HbA1c, HbA1c levels of obese patients were higher than that of overweight and normal-weight patients, which may be related to greater body weight. Patients with reduced sensibility to the effects of herbal medicine and who had difficulties controlling their blood glucose levels had increased HbA1C. We also analyzed the relationship between DM duration and HbA1C, indicating an increased trend that DHXD treatment could be more effective in the early stages of T2DM (<10 years). We also analyzed the FBG levels of patients taking Western hypoglycemic drugs who had reduced the dosage during treatment and found a decreased trend in FBG levels, though this was not statistically significant (P > 0.05). This result indicates that herbal and Western medicines have a synergistic effect in decreasing FBG, but again it was not statistically significant — probably owing to the large dosage reductions of the Western drugs and the fewer number of cases. With regards to BMI, the results showed a decreased trend in BMI levels with treatment, indicating that DHXD has effects on reducing body weight. In addition, the results also showed that DHXD helped correct lipid metabolism disorders by decreasing levels of CHO, TG and LDL-C, and increasing levels of HDL-C. Furthermore, the results demonstrated that DHXD effectively improved the symptoms of fatigue, dry mouth, thirst and dry stool. However, red tongue and yellow tongue coating were only slightly improved. But
because they may be general symptoms caused by the generation of heat syndrome, they could not improve in the short term. Huanglian (Rhizoma Coptidis) was the most frequently used herb in 678 clinical visits, the dosage of Huanglian (Rhizoma Coptidis) was related to age, BMI, DM duration, the level of blood glucose, and use of western hypoglycemic drugs. With the increase of BMI, DM duration and the level of blood glucose, the dosage of Huanglian (Rhizoma Coptidis) was generally increased, but the increase of age caused consequent dosage reduction of Huanglian (Rhizoma Coptidis). Moreover, DM duration was short and the blood glucose was easy to control, so the amount of the Huanglian (Rhizoma Coptidis) was relatively less.

Limitations

Several limitations exist, including: (a) the retrospective nature of the study, (b) the complex pharmacologic ingredients of the treatments, (c) the use of clinic medical records to collect information on patients, and (d) the unequal number of patients at every follow-up because of the different timings of patient return visits. DHXD was found to decrease FBG, PBG and HbA1C in patients with T2DM, reduce body weight, correct disorders of lipid metabolism, and improve diabetic symptoms, which may indicate a new optional treatment for DM.

REFERENCES


13 Liu GF. Experience of stomach and intestine as center to treat type 2 diabetes by professor Tong XL. Zhong Yi Yao Xin Chuan Za Zhi 2012; 24(2): 139-141.


25 Tong XL. The application of “Combination of symptoms, syndrome and disease” to Treat Diseases. Zhong Yi Za Zhi 2010; 51(4): 300-303.
