

Effect of Fan Surname Eight Sequential Methods of Dynamic-Static and SIIT on the Remission in Newly Diagnosed Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To observe the clinical effect of FAN surname eight sequential methods of dynamic-static and short-term intensive insulin therapy (SIIT) on the remission in newly diagnosed type 2 diabetes mellitus (T2DM).

Methods: 124 patients with newly diagnosed T2DM were enrolled from January 2022 to April 2023. They were randomly divided into control group (n= 62) and treatment group (n= 62). The control group was treated with SIIT, and the treatment group was treated with FAN surname eight sequential methods of dynamic-static and SIIT. The treatment course of both groups was 4 weeks. The fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1C), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), (triglyceride, TG), Body mass index (BMI), fasting insulin (FINS), fasting c-peptide (FCP), homeostasis model assessment β -cell function (HOMA- β), homeostasis model assessment of insulin resistance (HOMA-IR), incidence of hypoglycemia, daily insulin dosage, efficacy of traditional Chinese medicine (TCM) syndrome and remission rate were compared in the two groups after treatment.

Results: FPG, 2hPG, TC, LDL-C, TG, HOMA-IR, and BMI of the treatment group were lower than the control group, HDL-C, FINS, FCP and HOMA- β of the treatment group were higher than the control group, with statistical significances ($P < 0.05$). And there were statistically significant differences in incidence of hypoglycemia, daily insulin dosage, efficacy of TCM syndrome and remission rate between the two groups ($P < 0.05$).

Conclusion: FAN surname eight sequential methods of dynamic-static and SIIT could remit newly diagnosed T2DM better, and reduce blood glucose, blood lipids, insulin resistance, body weight, incidence of hypoglycemia, and daily insulin dosage better. This method also improved pancreatic β -cell function and efficacy of TCM syndrome better, which is worthy of clinical application and promotion Trial registration NO. ChiCTR 2200064266).

Keywords: FAN Surname Eight Sequential Methods of Dynamic-Static; Short-Term Intensive Insulin Therapy; Remission; Newly Diagnosed Type 2 Diabetes Mellitus

Abbreviations: SIIT: Short Term Intensive Insulin Therapy; T2DM: Type 2 Diabetes Mellitus; FPG: Fasting Plasma Glucose; 2hPG: 2-Hour Postprandial Blood Glucose; HbA1C: Glycosylated Hemoglobin; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; TG: Triglyceride; BMI: Body Mass Index; FINS: Fasting Insulin; FCP: Fasting C-Peptide; HOMA- β : Homeostasis Model Assessment B-Cell Function; HOMA-IR: Homeostasis Model Assessment Of Insulin Resistance; TCM: Traditional Chinese Medicine

Introduction

On December 6, 2021, the international Diabetes federation (IDF) website released its latest global Diabetes map (IDF Diabetes Atlas) (10th Edn.),. In 2021, it is estimated that 537 million people have diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045. The countries with the largest numbers of adults with diabetes aged 20-79 years in 2021 are China, India and Pakistan. They are anticipated to remain so in 2045. According to the latest epidemiological surveys, the prevalence of diabetes in people aged 18 years and above in China is 11.2%, and the prevalence is increasing year by year [1]. The prevention and treatment of diabetes has brought heavy economic burden and social pressure to China and even the rest of the world. How to effectively control diabetes, remit newly diagnosed diabetes, induce dedifferentiated β -cells to re differentiate into mature β -cells, and restore their insulin secretion function has become an urgent problem to be solved. According to the 2021 American Diabetes Association (ADA), remission of T2DM meant that glucose could still be in the standard state or normal state without hypoglycemic drug treatment, HbA1c<6.5% was recommended as the diagnostic criteria for remission of T2DM at least 3 months of discontinuation of hypoglycemic drugs [2].

At present, the methods to remit type 2 diabetes at home and abroad mainly include lifestyle intervention, weight loss, insulin, metabolic surgery, however, there is no research report on traditional Chinese medicine (TCM) in remitting type 2 diabetes through the search of PubMed, China National Knowledge Infrastructure (CNKI) and other databases. "FAN surname eight sequential methods of dynamic-static" is a set of TCM philosophy theories gradually formed by Professor Fan Guan-Jie from the Second Clinical Medical School of Guangzhou University of Chinese Medicine in the diagnosis and treatment of diabetes. This theory takes the "core pathogenesis" as the target, takes "syndrome elements" as the basis and standard of syndrome differentiation, and takes "medicine string" dynamic combination as the prescribing idea to carry out sequential treatment for the dynamically changing "syndrome". It has formed a syndrome differentiation mode of "integration of syndrome elements, core pathogenesis, treatment rules, and medicine string". Therefore, this study innovatively used the "FAN surname eight sequential methods of dynamic-static" combined with short-term intensive insulin treatment (SIIT) to remit the newly diagnosed type 2 diabetes, and achieved good clinical effects, which are reported as follows.

Material and Methods

Diagnostic Criteria

The diagnostic criteria for type 2 diabetes mellitus (T2DM) were referred to the 1999 World Health Organization (WHO) [3,4]. The diagnostic criteria for newly diagnosed T2DM were as follows: those who met the above diagnostic criteria for T2DM were newly diagnosed and did not receive hypoglycemic medication. The diagnostic criteria for hypoglycemia was according to the Guideline for the prevention and

treatment of type 2 diabetes mellitus in China (2020 edition) [5]. According to the 2021 American Diabetes Association (ADA), remission of T2DM meant that blood glucose could still be in the standard state or normal state without hypoglycemic drug treatment, HbA1c<6.5% was recommended as the diagnostic criteria for remission of T2DM at least 3 months of discontinuation of hypoglycemic drugs [2]. The diagnosis criteria of Traditional Chinese Medicine (TCM) syndrome types were formulated according to Guiding Principles for Clinical Research of New Traditional Chinese Medicine (2002 edition) [6], and combined with Professor Fan Guan-Jie's unique clinical experience in the diagnosis and treatment of T2DM [7]:

1. Syndrome of kidney qi deficiency: the waist and knees are weak, tired and weak, and urinate frequently;
2. Syndrome of deficiency of both qi and yin: can eat and diarrhea, the limbs are weak, the mouth is dry or thirsty, the tongue is weak, and the coating is thin;
3. Syndrome of stagnation of liver qi: irritable or depressed, irregular menstruation in women;
4. Syndrome of blood heat depression: red face, red lips, red tongue;
5. Syndrome of lung stomach dryness and heat syndrome: overeating, easy hunger, thirsty and polydipsia, dry stool, the smooth and firm pulse;
6. Syndrome of malnutrition of heart spirit: upset, dreamy, restless sleep;
7. Syndrome of internal retention damp-heat: dry mouth, but does not want to drink too much, or does not want to eat too much, yellow urine, yellow greasy fur;
8. Syndrome of blood stasis syndrome: dark tongue, thick varicose veins at the bottom of the tongue, or accompanied by numbness of limbs and abnormal pain sensation.

The quantitative scores of specific symptoms were formulated according to Guiding Principles for Clinical Research of New Traditional Chinese Medicine (2002 edition), mild symptoms were recorded as 1 point, moderate symptoms were recorded as 2 points, and severe symptoms were recorded as 3 points. The criteria for evaluating the efficacy of TCM syndromes was also formulated according to above Guiding Principles.

Inclusion Criteria

Subjects must meet all of the following requirements:

1. Newly diagnosed T2DM patients with HbA1c \geq 9.0% or fasting plasma glucose (FPG) \geq 11.1 mmol/L, accompanied by obvious hyperglycemia symptoms
2. Age 18~70 years old
3. Normal liver and renal function

Exclusion Criteria

1. Type 1 diabetes mellitus, gestational diabetes mellitus, and other special types of diabetes mellitus
2. Acute complications of diabetes mellitus or serious chronic complications of diabetes mellitus
3. Age >70 or <18 years
4. High risk of hypoglycemia
5. Severe visceral organ diseases
6. The islet β -cell function was poor (fasting C-peptide < 1.0 ug/L)
7. Allergic to insulin or Chinese herbal decoction
8. Accompanied by novel coronavirus pneumonia
9. Impaired liver function or renal function
10. Unable to cooperate.

Suspension Criteria

The criteria for suspension for participation are as follows:

1. Poor compliance with investigators
2. Incomplete data that might affect analysis of the results
3. Voluntary withdrawal
4. Using other medications which were not listed in the trial protocol that might affect analysis of the results.

Study Design

The study was a randomized, double-blind trial that was conducted at Huangshi Hospital of Traditional Chinese Medicine in Hubei Province, China. Study participants or legal representatives of family members signed the informed consent, which abides by the principles of the Declaration of Helsinki and the regulations on quality management of clinical trials in China. The study protocol was approved by the Ethics Committee (approval number HSZYPJ-2021-001-01) and registered with the Chinese Clinical Registry (ChiCTR 2200064266).

Patients

In this prospective, randomized, double-blind study, 124 patients with newly diagnosed T2DM hospitalized in endocrinology department of Huangshi Hospital of Traditional Chinese Medicine were enrolled from January 2022 to April 2023. All patients were provided written informed consent.

Intervention

The control group was treated with American PARADIGM 712 Medtronic insulin pump treatment (Continuous subcutaneous insulin infusion CSII) for 2 weeks, and then it was treated with Insulin

glargine injection combined with insulin aspart injection 4 times a day for 2 weeks. On the basis of the control group, the treatment group was treated orally with FAN surname eight sequential methods of dynamic-static Chinese herbal decoction. According to the above eight TCM syndrome types, the following eight treatment rules were formulated [3]:

- a. Tonifying kidney and consolidating origin, 10g of Rhizoma Cibotii (Gouji), 10g of Radix Dipsaci (Xuduan), 30g of Fructus Ligustri Lucidi (Nvzhenzi), 30g of Herba Ecliptae (Mohanlian);
- b. Replenishing qi and nourishing yin, 15g of Radix Astragali (Huangqi), 15g of Radix Rehmanniae Recens (Shengdihuang), 15g of Cortex Lycii (Digupi);
- c. Soothing the liver and regulating qi, 10g of Radix bupleuri (Chaihu), 30g of Radix Paeoniae Alba (Baishao), 10g of Herba Menthae (Bohe), 30g of Cortex Moutan Radicis (Danpi);
- d. Clearing heat and moistening dryness, 30g of Gypsum Fibrosum (Shigao), 30g of Radix Puerariae (Gegen), 10g of Rhizoma Anemarrhena (Zhimu), 15g of Fructus Forsythiae (Lianqiao); Clearing heat and Purgation, 5g of Radix et Rhizoma Rhei (Dahuang), 10g of Fructus Aurantii Immaturus (Zhishi), 15g of Fructus Cannabis (Huomaren);
- e. Nourishing heart and calming mind, 30g of Caulis Polygoni Multiflori (Shouwuteng), 10g of Radix Polygalae (Yuanzhi), 15g of Semen Ziziphi Spinosae (Suanzaoren);
- f. Clearing heat in the Ying System, Cooling blood: 15g of Radix Ophiopogonis (Maidong), 10g of Radix Scrophulariae (Xuanshen), 15g of Radix Paeoniae Rubra (Chishao), 15g of Cortex Moutan Radicis (Danpi);
- g. Clearing heat and removing dampness, medicinal 10g of Rhizoma Atractylodis (Cangzhu), 10g of Cortex Phellodendri (Huangbo), 30g of Semen Coicis (Yiyiren), 30g of Herba Plantaginis (Cheqiancao), 15g of Herba Artemisiae Scopariae (Yinchen);
- h. Activating blood circulation and removing blood stasis: 15g of Radix Salviae Miltiorrhiza (Danshen), 15g of Herba Lycopi (Zelan), 10g of Rhizoma Sparganii (Sanleng), 10g of Rhizoma Curcumae (Ezhu), 10g of Rhizoma Ligustici Chuanxiong (Chuanxiong).

These eight treatment rules combined with each other to implement sequential treatment of dynamic-static. The method of decoction of traditional Chinese medicine was to add proper amount of water and decocted traditional Chinese medicine to 200ml each time, repeated it three times, and then mixed all traditional Chinese medicine in water and drank it three times after breakfast, lunch and dinner. At the same time, peripheral blood glucose of two groups was monitored daily on an empty stomach, 2h after breakfast, before lunch, 2h after lunch, before dinner, 2h after dinner, and bedtime. The peripheral

blood glucose was detected using ONETOUCH verioVue blood glucose meter (model AW 06856104A) produced by Johnson & Johnson. The treatment course of two groups was 4 weeks (outpatient follow-up of discharged patients), all hypoglycemic drugs were stopped immediately after treatment. The FPG, 2hPG, TC, HDL-C, LDL-C, TG, BMI, FINS, FCP, HOMA- β , HOMA-IR, efficacy of TCM syndrome, and daily insulin dosage of two groups were observed after treatment. After 3 months of drug withdrawal, HbA1C was observed and the remission rate of newly diagnosed T2DM was compared between two groups.

Sample Size

The sample size was calculated according to the parameters $\alpha=0.05$ (two-sided test) and $\beta=0.1$. By comparing the clinically effective rates of the two groups with the sample size estimation formula, we determined that we needed to recruit at least 60 participants in each group to achieve sufficient statistical power. Since the withdrawal rate was less than 15%, a total of 166 participants were ultimately needed in the two groups, with 83 participants in each group.

Randomization

Patients meeting the eligibility criteria were randomized into two groups (control group or treatment group) in a ratio of 1:1. Eligible patients were allocated to receive medication in individually numbered packs.

Outcomes and Measurements

The fasting plasma glucose (FPG), 2 hours postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1C), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) low density lipoprotein cholesterol (LDL-C), triglyceride (TG), Body mass index (BMI), fasting insulin (FINS), fasting c-peptide (FCP) were detected by Automatic Biochemical Immunoanalyzer (Model: BS-2000M) from Shenzhen Mindray Bio-Medical Electronics limited company. Evaluation index of islet β -cell function: Homeostasis model assessment β cell function (HOMA β)calculated by homeostasis model assessment (HOMA), $HOMA-\beta = 20 \times FINS / (FPG - 3.5)$, homeostasis model assessment insulin resistance (HOMA-IR) = $FPG \times FINS / 22.5$ [8].

Safety Monitoring

The safety indices included blood routine test, urine routine test, stool routine test, liver function, kidney function, electrocardiogram and blood glucose monitoring. Once adverse events occurred, they would be handled immediately and documented using case report forms.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS,version 23.0). Measurement data were expressed as the mean \pm standard deviation ($\pm S$), the independent sample Student's t-test was used for comparison between groups for normal distribution, non-parametric Mann-Whitney U test was used for comparison between groups for non-normal distribution. Paired t-test was used for intra-group comparison, and Wilcoxon signed-rank test was used for non-normal distribution. Categorical data were expressed as frequency and percentage, Chi-square test was used for comparison between groups, $P < 0.05$ was considered statistically significant.

Results

Characteristics of Patients

A total of 166 Patients were assessed for eligibility in this trial, 42 patients were excluded for many reasons.124 patients underwent randomized,62 patients each were assigned to either the control group or treatment group. 100 patients completed the experiments successfully, there were 12 patients in treatment group and control group withdrew from the trial, respectively (Figure 1). There were no significant differences in gender, age, FPG, 2hPG, HbA1C, TC, HDL-C, LDL-C, TG, BMI, FINS, FCP, HOMA- β , HOMA-IR and other general data between the two groups ($P > 0.05$) (Table 1).

Table 1: Comparison of baseline data between the two groups ($\bar{x} \pm S$).

Variables	Treatment group (50 cases)	Control group (50 cases)	P value
Age (years)	53.24 \pm 9.49	53.76 \pm 9.31	0.783
FPG (mmol/L)	12.03 \pm 0.92	12.01 \pm 1.09	0.924
2hPG (mmol/L)	19.73 \pm 1.02	19.78 \pm 0.97	0.783
HbA1C (%)	11.38 \pm 1.33	11.68 \pm 1.27	0.252
TC (mmol/L)	7.21 \pm 0.79	7.22 \pm 0.92	0.928
HDL-C (mmol/L)	0.61 \pm 0.10	0.62 \pm 0.10	0.537
LDL-C (mmol/L)	6.27 \pm 0.84	6.23 \pm 0.95	0.796
TG (mmol/L)	4.71 \pm 0.81	4.67 \pm 1.04	0.832
BMI (kg/m ²)	26.02 \pm 1.23	26.19 \pm 1.31	0.516
FINS (mIU/L)	6.75 \pm 0.93	6.82 \pm 0.86	0.717
FCP (ng/mL)	1.49 \pm 0.24	1.47 \pm 0.25	0.640
HOMA- β	16.00 \pm 2.78	16.37 \pm 3.46	0.558
HOMA-IR	3.61 \pm 0.58	3.63 \pm 0.49	0.893

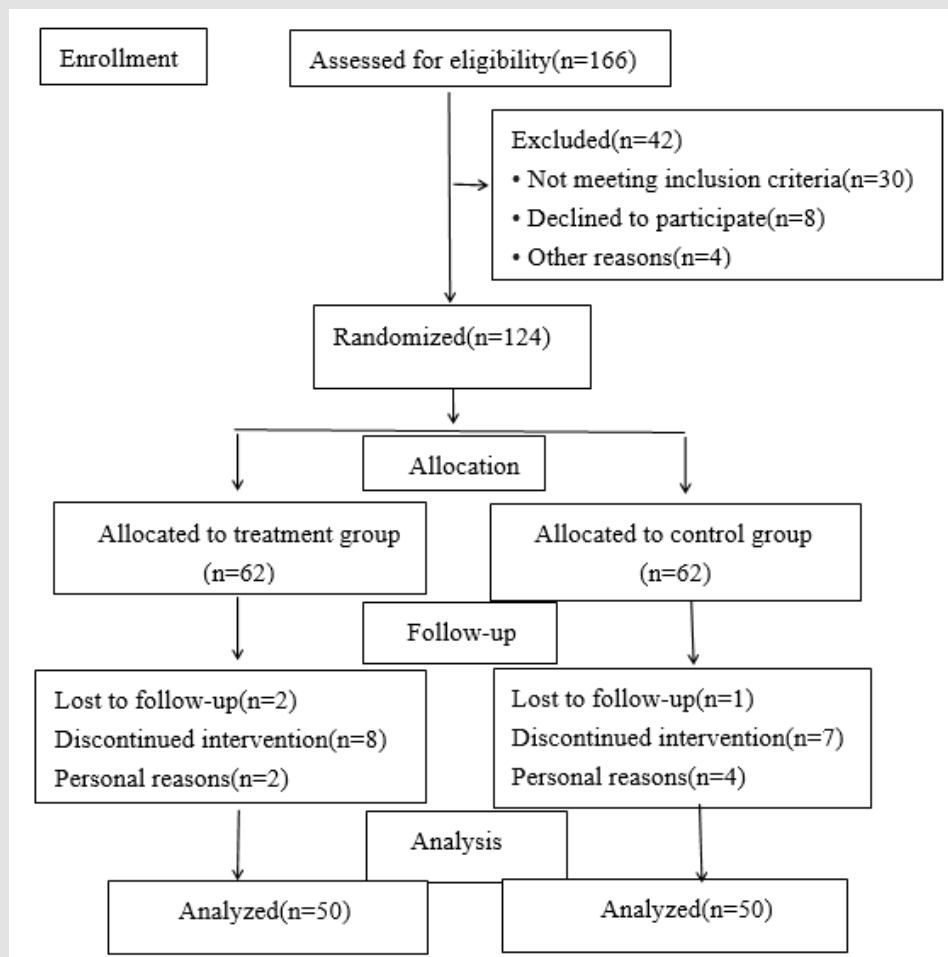


Figure 1: Study Flowchart of FAN Surname Eight Sequential Methods of Dynamic-Static and Siit on The Remission in Newly Diagnosed Type 2 Diabetes Mellitus.

Primary Outcome

There were no significant differences in FPG, 2hPG, TC, HDL-C, LDL-C and TG between the two groups before treatment ($P > 0.05$); After treatment, FPG, 2hPG, TC, LDL-C and TG of the two groups were lower than before treatment, HDL-C of the two groups was higher than before treatment, and FPG, 2hPG, TC, LDL-C and TG of the treatment group were lower than the control group, HDL-C of the treatment group was higher than the control group, with statistical significances ($P < 0.05$). (Table 2) There were no signif-

icant differences in FINS, FCP, HOMA- β , HOMA-IR and BMI between the two groups before treatment ($P > 0.05$). After treatment, FINS, FCP and HOMA- β of the two groups were higher than before treatment, HOMA-IR and BMI of the control group were higher than before treatment, HOMA-IR and BMI of the treatment group were lower than before treatment, FCP and HOMA- β of the treatment group were higher than control group, FINS, HOMA-IR and BMI of the treatment group were lower than control group, with statistical significances ($P < 0.05$) (Tables 3 & 4).

Table 2: Comparison of FPG, 2hPG, blood lipids between the two groups before and after treatment.

Group	Time	FPG (mmol/L)	2hPG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)
Control group	Pre-treatment	12.01±1.09	19.78±0.97	7.22±0.92	0.62±0.10	6.23±0.95	4.67±0.98
	Post-treatment	7.78±0.57 ^{*)}	10.56±1.32 ^{*)}	5.83±0.82 ^{*)}	1.79±0.18 ^{*)}	4.63±0.67 ^{*)}	2.85±0.73 ^{*)}
Treatment Group	Pre-treatment	12.03±0.92	19.73±1.02	7.21±0.79	0.61±0.10	6.27±0.84	4.71±0.81
	Post-treatment	5.63±0.32 ^{*)#)}	8.69±0.53 ^{*)#)}	3.65±0.47 ^{*)#)}	3.71±0.35 ^{*)#)}	3.12±0.57 ^{*)#)}	1.56±0.26 ^{*)}

Note: *P<0.05 vs. before intervention in the same group; #P<0.05 vs. control group.

Table 3: Comparison of FINS, HOMA-β, HOMA-IR Between the Two Groups After Treatment.

Group	Time	FINS (mIU/L)	FCP (ug/L)	HOMA-β	HOMA-IR	BMI (kg/m ²)
Control Group	Pre-treatment	6.82±0.86	1.47±0.25	16.37±3.46	3.63±0.49	26.23±1.23
	Post-treatment	13.64±0.99 ^{*)}	2.78±0.32 ^{*)}	64.91±10.34 ^{*)}	4.71±0.45 ^{*)}	29.09±1.87 ^{*)}
Treatment Group	Pre-treatment	6.75±0.93	1.49±0.24	16.00±2.78	3.61±0.58	26.18±1.03
	Post-treatment	8.70±0.75 ^{*)#)}	3.97±0.46 ^{*)#)}	83.43±14.37 ^{*)#)}	2.18±0.22 ^{*)#)}	23.23±1.05 ^{*)#)}

Note: *P<0.05 vs. before intervention in the same group; #P<0.05 vs. control group.

Table 4: Comparison of HbA1c and remission between the two groups after treatment.

Group	Case (n)	HbA1C (%)	Remission [n (%)]
Control group	50	7.44±1.6	34 (68.00)
Treatment group	50	5.90±0.94 ^{*)}	42 (84.00) ^{*)}

Notes: *P<0.05 vs. control group.

Secondary Outcome

After treatment, here were significant differences in incidence of hypoglycemia, and daily insulin dosage between the two groups

(P<0.05) (Table 5). After treatment, there was significant difference in efficacy of TCM syndrome between the two groups (P<0.05) (Table 6).

Table 5: Comparison of Incidence of Hypoglycemia and Daily Insulin Dosage Between the Two Groups After Treatment.

Group	Case (n)	Incidence of hypoglycemia	Daily insulin dosage (U)
Control group	50	9(18.00)	34.57±2.10
Treatment group	50	2(4.00) ^{*)}	26.96±1.99 ^{*)}

Table 6: Comparison of Efficacy of TCM Syndrome Between the Two Groups After Treatment.

Group	Case (n)	Healing	Obvious effective	Effective	Ineffective	Total effective rate [n (%)]
Control Group	50	3	9	24	14	36 (72.00)
Treatment Group	50	24	17	7	1	49 (98.00) ^{*)}

Note: *P<0.05 vs. control group.

Adverse Events

After treatment, there were no significant differences in Subcutaneous induration, Abdominal distension, vomiting, diarrhea, im-

paired liver function and impaired renal function between the two groups (P>0.05). (Table7).

Table 7: Summary of Adverse Events Between the Two Groups After Treatment [case (%)].

Adverse events	Treatment group (50 cases)	Control group (50 cases)	P value
Subcutaneous induration	2 (4.00%)	4 (8.00%)	0.674
Abdominal distension	3(6.00%)	1(2.00%)	0.610
Vomiting	1(2.00%)	1(2.00%)	1.000
Diarrhea	1(2.00%)	1(2.00%)	1.000
Impaired liver function	1(2.00%)	12.00%)	1.000
Impaired renal function	1(2.00%)	1(2.00%)	1.000

Discussion

The Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition) pointed out that type 2 diabetes (T2DM) is the main type of diabetes in China, accounting for more than 90%, and the survey results from 2015 to 2017 showed that newly diagnosed diabetes patients accounted for 54% of the total number of diabetes [4]. It has long been thought that T2DM is a lifelong disease, especially the famous United Kingdom Prospective Diabetes Study (UKPDS) results showed that the blood glucose of patients with T2DM was progressive regardless of treatment method, and had to increase the intensity of treatment [8]. This was even stronger understanding that T2DM was a “progressive” disease [9]. However, recent clinical practice has shown that some T2DM patients can stop hypoglycemic drugs after taking certain interventions and their blood glucose level is still normal or close to normal. At present, most scholars use the term “remission” to describe sustained metabolic improvement of diabetic patients to a near-normal state. This concept has attracted wide attention from scholars at home and abroad [10]. In 2009, the American diabetes Association (ADA) issued a consensus statement suggesting that the status of diabetes free from drug treatment should be referred to as “remission” with reference to the oncology academic language, and further divided into partial remission, complete remission and prolonged remission.

The partial remission referred to the glycosylated hemoglobin A1c(HbA1c) <6.5% (48 mmol/mol),fasting plasma glucose (FPG) reached 5.6~6.9 mmol/L (100-125 mg/dl) on the premise of cessation of hypoglycemic drugs for more than 1 year; complete remission referred to normal glucose metabolism (HbA1c<5.7%, FPG<5.6 mmol/L) on the premise of cessation of hypoglycemic drugs for at least 1 year. Prolonged remission meant complete remission solutions lasted for more than 5 years [11]. In 2019, Association of British Clinical Diabetologists (ABCD) and Primary Care diabetes Society(P-CDS) suggested that diabetes patients who stopped taking hypoglycemic drugs for more than 6 months, FPG<7.0 mmol/L, HbA1c<6.5%, could be defined as remission [12]. In September 2021, the Consensus of Chinese Expert on the Remission of Type 2 Diabetes Mellitus was officially published in the Chinese Journal of diabetes [13]. The definition of T2DM remission adopted the “Definition and Interpretation of Type 2 diabetes remission “ of ADA in 2021 [2]: T2DM re-

mission means that glucose can still be in the standard state or normal state without hypoglycemic drug treatment. It is suggested that HbA1c<6.5% should be taken as the diagnostic standard of T2DM remission after cessation of glucose-lowering pharmacotherapy for at least 3 months. However, in some cases, such as the presence of hemoglobin variation, diseases affecting the survival time of red blood cells, and non-standard HbA1c detection methods. HbA1c can not reflect the true glucose level, so FPG<7.0mmol/L or HbA1<6.5% estimated by continuous glucose monitoring (CGM) can be used as an alternative standard for T2DM remission. Mechanisms of T2DM remission are associated with correction of obesity or significant reduction of body weight, fatty liver and fatty pancreas, insulin resistance and hyperinsulinemia, correction of hyperglycemia, and dedifferentiation and transdifferentiation of pancreatic islet β -cells [14].

Diabetes remission previously known as diabetes reversal. There are several methods to remit T2DM. Firstly, Intensive lifestyle interventions are the basic methods. Interventions such as diet and exercise therapy can achieve weight loss, thus improving insulin sensitivity and protecting the function of pancreatic islets β -Cells, thus promoting the transformation of pre-diabetes to normal glucose metabolism [15]. Secondly, Weight loss drugs. Orlistat is the only approved weight loss drug in China, and was approved as an over-the-counter weight loss drug in 2007. For T2DM patients with a BMI of ≥ 27 kg/m², short-term use (12-24 weeks) of Orlistat can be used as an auxiliary method for T2DM remission [14]. A Chinese study showed that 18% of T2DM patients returned to normal blood glucose after 6 months of orlistat treatment, compared with zero remission in the placebo group [15]. In the Look AHEAD study [16], Orlistat was recommended as a weight loss drug to promote weight improvement in combination with intensive lifestyle intervention. Thirdly, Short-term intensive insulin therapy (SIIT).

In 1997, (Ilkova, et al. [17]) took the lead in newly diagnosed type 2 diabetes with short-term insulin intensive treatment (SIIT), 13 patients after 2 weeks of Continuous subcutaneous insulin infusion (Continuous subcutaneous insulin infusion, CSII) after treatment, Among them, 9 patients could maintain FPG<7.8 mmol/L and 2h postprandial blood glucose (2hPG) <10 mmol/L for 9-36 months only through regular exercise and dietary intervention. A total of 138 newly diagnosed T2DM patients with severe hyperglycemia (mean HbA1c

was 10.0%) were treated with 2-week intensive short-term insulin therapy aiming to normalize blood glucose. 72.6%, 67.0%, 47.1% and 42.3% of subjects maintained remission at 3, 6, 12 and 24 months after treatment, respectively, accompanied by improved insulin secretion in the first phase [18-20]. A meta-analysis of 7 studies showed that short-term intensive insulin therapy (SIIT) could improve pancreatic β -cell function and IR in patients with newly diagnosed T2DM [21]. Fourthly, Non-insulin hypoglycemic drugs. For T2DM patients who do not reach the HbA1c standard and have not effectively implemented intensified lifestyle interventions, short-term (8-12 weeks) adjuvant use of non-insulin drug combination therapy with significant weight improvement can help remit T2DM. Glucagon-like peptide-1 receptor agonist (GLP-1RA) and its combined treatment regimen.

A meta-analysis [22] based on placebo-controlled studies showed that GLP-1RA treatment of exenatide reduced body weight to 1.69 kg, liraglutide treatment to 2.51 kg, and lirisenatide treatment to 0.90 kg in T2DM patients. The combination therapy of Metformin, Sodium Glucose Co transporter 2 (SGLT2) inhibitor and GLP-1RA resulted in the most weight loss and the least hypoglycemia compared to other combination therapies for T2DM patients, the incidence of cardiovascular and cerebrovascular diseases and all-cause mortality was the lowest [23]. Fifth, metabolic surgery strategies. Metabolic surgery can affect food intake, digestion and absorption, cause changes in gastrointestinal hormones and /or intestinal flora, achieve weight loss and improve metabolic abnormalities, and ultimately remit T2DM [24]. Common metabolic operations include Roux-en-Y gastric bypass surgery (RYGB), laparoscopic sleeve gastrectomy (LSG) and laparoscopic adjustable gastric banding (LAGB) and so on. A 10-year Italian study [25] showed that metabolic surgery could improve the remission rate of T2DM in obese patients with poor blood glucose control. A 3-year follow-up study [26] found that 40% and 29% of T2DM patients treated with RYGB and LAGB achieved complete or partial T2DM remission, respectively, while those treated with lifestyle intervention alone had no T2DM remission. At present, Western medicine is the main method to remit T2DM at home and abroad, however, there is no research report on traditional Chinese medicine (TCM) in remitting type 2 diabetes through the search of PubMed, China National Knowledge Infrastructure (CNKI) and other databases.

Diabetes belongs to the category of "Xiaoke" disease in traditional Chinese medicine (TCM). Xiaoke is a disease characterized by yin deficiency and internal heat caused by congenital endowment deficiency, improper diet, emotional disorder, fatigue and internal injury. The main symptoms are polydipsia, polyuria, fatigue, emaciation or sweet urine. The name of "diabetes" was first found in the inner Canon of Yellow Emperor [26]. With the continuous improvement of modern medical technology, the improvement of people's living standards and the gradual strengthening of their awareness of health, the diagnosis time of T2DM is significantly earlier than before. The typical "three more and one less" symptoms are not common. The newly diagnosed T2DM, as the initial stage of generalized diabetes, has a complex and

diverse pathogenesis, which is mixed with deficiency and excess. Different doctors have played a role in discussing its etiology and pathogenesis from the perspectives of the five zang organs, qi, blood, yin and yang, phlegm, blood stasis, dampness and so on [27]. Professor Fan Guanjie of the Second Clinical College of Guangzhou University of Chinese Medicine learned from Professor Lv Renhe, a master of traditional Chinese medicine, and inherited the academic ideas and clinical treatment experience of Shi Jinmo, Qin Bowei, Zhu Chenyu and other famous Chinese medicine practitioners from their academic origins.

Professor Fan has been engaged in the clinical work of traditional Chinese medicine for a long time, and has his unique experience in the diagnosis and treatment of diabetes in traditional Chinese medicine. On this basis, he has gradually formed a set of syndrome differentiation and treatment methods, that is, the original theory of traditional Chinese medicine of "FAN surname eight sequential methods of dynamic-static" [7]. Its specific connotation is taking the overall concept and syndrome differentiation and treatment as the leading ideology, taking the dynamic grasp of the internal laws of the core pathogenesis as the thinking mode, and taking the relatively fixed and dynamic changes of traditional Chinese medicine clusters as the characteristics of treatment, constantly enriching the understanding of traditional Chinese medicine on the basic theory, etiology and pathogenesis, syndrome differentiation rules, and therapeutic methods and prescriptions from practice. Among them, "dynamic" means to change, which means to break the fixed thinking and treat flexibly and dynamically whether we understand the etiology and pathogenesis of diseases or the properties of traditional Chinese medicine; "Static" is opposite to "dynamic", which means fixed and unchanging, that is, to grasp the regularity of things; "Order" means order and rule; "Sequential" refers to continuity. "Sequential" reflects that the method of recognizing diseases and treating according to syndrome differentiation is a coherent and orderly process. The "eight methods" refer to the formulation of the key points of syndrome differentiation corresponding to the main syndrome. The five major methods of regulating the internal organs, namely, tonifying the kidney, soothing the liver, moistening the lung, nourishing the heart, and invigorating the spleen, are taken as the basic major methods.

Then, according to the continuous evolution and integration of syndromes, the remaining 3 methods are regulating blood (clearing heat and cooling blood, activating blood circulation and removing blood stasis), regulating qi, and smoothing the three energizers. The "eight methods" take the meaning of the eight trigrams and can evolve into ever-changing therapeutic methods. At the same time, a relatively fixed traditional Chinese medicine string corresponding to the eight methods is formed as the basic medicine for clinical treatment. On the basis of summing up years of clinical experience, Professor Fan Guanjie proposed the idea of understanding the core pathogenesis from the "core symptoms", and believed that syndrome differentiation should be good at finding the most characteristic symptoms and tongue vessels from the four diagnostic materials, and quickly and

accurately established its core pathogenesis [28]. Based on years of clinical practice, Professor Fan summarized the core symptoms corresponding to the eightcore pathogenesis of diabetes [7].

Syndrome of kidney qi deficiency : the waist and knees are weak, tired and weak, and urinate frequently; Syndrome of deficiency of both qi and yin: can eat and diarrhea, the limbs are weak, the mouth is dry or thirsty, the tongue is weak, and the coating is thin; Syndrome of stagnation of liver qi: irritable or depressed, irregular menstruation in women; Syndrome of blood heat depression: red face, red lips, red tongue; Syndrome of lung stomach dryness and heat syndrome: over-eating, easy hunger, thirsty and polydipsia, dry stool, the smooth and firm pulse;)Syndrome of malnutrition of heart spirit: upset, dreamy, restless sleep; Syndrome of internal retention damp-heat: dry mouth, but does not want to drink too much, or does not want to eat too much, yellow urine, yellow greasy fur; Syndrome of blood stasis syndrome: dark tongue, thick varicose veins at the bottom of the tongue, or accompanied by numbness of limbs and abnormal pain sensation. The theory of "FAN surname eight sequential methods of dynamic-static" takes "core pathogenesis" as the target, takes "syndrome element" as the basis and standard of syndrome differentiation, and "drug string" dynamic combination as the way to organize prescriptions.

It conducts sequential treatment for dynamically changing "syndromes", forming a syndrome differentiation model of "syndrome—element core pathogenesis—treatment rule—drug string" integration. As early as 2011, it was reported that Professor Fan Guanjie used "FAN surname eight sequential methods of dynamic-static" pure Chinese medicine to treat newly diagnosed type 2 diabetes, which could make newly diagnosed type 2 diabetes patients stop taking medicine, or even reverse it [29]. Subsequently, the research showed that "FAN surname eight sequential methods of dynamic-static" Chinese medicine had clear effect in treating patients with T2DM. Besides, it was beneficial in improving the clinical symptoms, losing weight, increasing the curve area of insulin and decreasing the level of blood-lipid [30]. The theory of traditional Chinese medicine of the philosophy of "FAN surname eight sequential methods of dynamic-static" has become increasingly mature, and more than 100 academic papers have been published. This theory is also to meet the needs of the new era and upgrade the theory of traditional Chinese medicine. It is the first time to collide traditional Chinese philosophical thoughts such as Confucianism, Taoism, Neo Confucianism, and Psychology, as well as mainstream philosophical thoughts such as contemporary Western structuralism, cognitive philosophy, positivism, and humanism with traditional Chinese medicine [31].

In this study, the results showed that FPG, 2hPG, TC, LDL-C and TG of the treatment group were lower than the control group ($P<0.05$), HDL-C of the treatment group was higher than the control group ($P<0.05$), It was suggested that the treatment group could lower blood glucose and regulate blood lipid better than the control group. FCP and HOMA- β of the treatment group were higher than control

group ($P<0.05$), FINS, HOMA-IR and BMI of the treatment group were lower than the control group ($P<0.05$). It was suggested that the treatment group could improve the function of islet β cells, reduce insulin resistance and lose weight better than the control group. There were significant differences in time of blood glucose reaching standard, Incidence of hypoglycemia and daily insulin dosage between the two groups ($P<0.05$). It was suggested that the treatment group had lower incidence of hypoglycemia and less daily insulin dosage than the control group. There was significant difference in efficacy of TCM syndromes between the two groups ($P<0.05$). It was suggested that the treatment group was better than the control group. There were significant differences in HbA1c and remission between the two groups ($P<0.05$). It was suggested that the remission rate of newly diagnosed type 2 diabetes in the treatment group was higher than that in the control group. There are still some limitations in this study. Firstly, the sample size was not large enough, because the time of clinical research was limited [32], which affected the number of clinical cases collected; Secondly, this study was a single center randomized controlled study, not a multicenter study, so the results might be biased to some extent. In the future, we will cooperate with many medical institutions to expand the sample size for further research to verify the results.

Conclusion

FAN surname eight sequential methods of dynamic-static and SIIT could better remit newly diagnosed T2DM, could better reduce blood glucose, blood lipids, insulin resistance, body weight, time of blood glucose standard, incidence of hypoglycemia, and daily insulin dosage, could better improve pancreatic β cell function and efficacy of TCM syndrome, which is a promising integrative therapy for newly diagnosed T2DM.

Trial Protocol

The full trial protocol can be accessed by contacting the corresponding author.

Author Contributions

Fan GJ and Liu HJ were the originator and chief designer of the study. Chen F, Lin YP and Xiao J were responsible for the formulation of the clinical plan. Huang R and Wan QQ performed the statistical analysis for this article. Yan H, Huang QY, and Feng D and Wan JJ provided the data for this manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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