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RESEARCH ARTICLE

Effects of Supersession Prescription/Metformin Combination Therapy in Overweight and Obese Individuals with Type 2 Diabetes

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Abstract

Objective: To assess the efficacy and safety of Supersession Prescription and metformin combination therapy in treatment of overweight and obese patients with T2DM.

Methods: This study was a 13-week, open-labeled, randomized parallel controlled study. Patients were randomly assigned to the treated and control groups in a 1:1 ratio. Both groups were provided metformin at the dosage of 750 mg twice daily as the primary treatment and the Supersession Prescription was given to the treated group as a supplementary treatment. Therapeutic outcomes were divided into three parts to assess different aspects of the whole effectiveness of the combination therapy and the primary outcome was body weight.

Results: A total of 80 subjects were recruited for this study and 74 finally completed. After 13 weeks of treatment, the levels of body weight, BMI, WC, WHR, HbA1C, FPG, 2hPG, HOMA-IR, TG, HDL, LDL and FFA were improved in the treated group ($P < 0.05$) and changes were significantly different in body weight, BMI, WL, HbA1C, FPG, 2hPG, LDL and FFA compared with the control group ($P < 0.05$). No serious adverse event including hypoglycemia was found in both of the two groups.

Conclusions: Supersession Prescription could produce a curative effect as a supplementary medical treatment combined with metformin and should be used while subjects could not achieve goals of weight or glucose management as well as were suffering from dyslipidemia.

Keywords

Obesity, Type 2 diabetes mellitus, Traditional Chinese medicine, Supplementary medicine

Introduction

Type 2 Diabetes (T2DM), a chronic disease characterized by elevated blood glucose which dues to islet β-cell dysfunction and insulin resistance, is often associated with a series of metabolic disorders such as hypertension and dyslipidemia. According to the World Health Organization's (WHO) latest report, the prevalence of diabetes has increased explosively in the last two decades. The number of people suffered from diabetes has risen from 108 million in 1980 to 422 million in 2014, and most are T2DM [1]. While clinical trial evidence indicates that excess body weight could make a great contribution to the development of both diabetes and the associated metabolic abnormalities [2], which perhaps due to pathologic effects of excessive adipose tissue [3], an epidemiological survey data represents that the prevalence of overweight and obesity in people with T2DM has been estimated to be even higher than 85% [4].

Individuals with T2DM could have a great increased risk of mortality caused from cardiovascular disease [5], which leads to a recommendation that the best achievable glycemic control for the individual is to reduce the risk of microvascular and possibly macrovascular disease [6]. In the meantime, obesity, as the most modifiable factor for the whole progression, itself is also a risk factor for cardiovascular disease [7-9]. As evidence

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shows that even the modest intentional weight loss could improve cardiovascular risk factors and decrease mortality significantly [10,11], thus, it seems like simultaneous treatment of obesity and T2DM is a necessary procedure for obese patients with T2DM.

While lifestyle modifications can improve glycemic control, most patients still require a sequential addition of one or more medications to achieve the target. However, many glucose-lowering medications, such as sulfonylureas and thiazolidinediones, could lead to an increase in body weight which presents a challenge to the patients who have already been struggling with weight control [12]. Fortunately, some other antihyperglycemic agents, such as metformin and liraglutide, have been shown to have neutral or even beneficial effects on body weight [13]. Metformin, an oral antidiabetes drug, is recommended as a first-line antihyperglycemic agent for the treatment of T2DM in the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines [13]. And furthermore, as a supplementary medical treatment, Traditional Chinese Medicine (TCM) has its unique advantages in dealing with these diseases.

Series of researches have been performed in recent years to explore different approaches to treat T2DM or obese patients with TCM; however, the literature about how to treat obese patients with T2DM by TCM combined with other antidiabetic agents is rare. In this study, we aimed to explore the effectiveness of Supersession Prescription, an empiric prescription inherited from deceased famous TCM doctor Peifa Yao professor, and metformin combination therapy in treatment of overweight and obese patients with T2DM, as well as to find out whether it is an available approach to manage obesity and T2DM by TCM as a supplementary therapy.

Materials and Methods

Subjects

Individuals matching any of the following criteria were diagnosed as T2DM [14]: 1) The glycosylated Hemoglobin (HbA1c) ≥ 6.5%; 2) The Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL); 3) The 2h post-prandial Plasma Glucose (2hPG) ≥ 11.1 mmol/L (200 mg/dL). Adult subjects with T2DM were screened and enrolled if they were also matching the criteria of overweight or obesity [15], i.e. Body Mass Index (BMI) of ≥ 25 kg/m^2, as well as were agreed to participate in this trial. Subjects were excluded if they had any cardiocerebral vascular events occurring in the last six months or complicated with other severe diseases, such as malignant tumor, mental disorders, etc.

All patients enrolled in this study were outpatients from the department of internal medicine of TCM, Longhua Hospital of Shanghai University of TCM. The study was conducted between September 2014 and March 2016 according to the guidelines and principles of Good Clinical Practices standards and the Declaration of Helsinki [16]. Written informed consent was obtained from all subjects prior to inclusion in this trial, and patients were free to withdraw from the study at any time.

Interventions

This study was a 13-week, open-labeled, randomized parallel controlled study. Patients were randomly assigned to the treated and control groups in a 1:1 ratio with a computer-generated randomization schedule emerged by SPSS 22.0.

Before treatment, all the patients underwent a drug-clearing period for one week. Hypoglycemic agents including insulin that had been used before randomization were discontinued. The patients were asked to achieve a calorie restriction during the whole study while the daily energy requirement was determined as 1500 kcal/d for women and 1800 kcal/d for men [15].

Patients in both groups were provided metformin at the dosage of 750 mg twice daily as a primary treatment and the Supersession Prescription was given to the treated group as a supplementary treatment. The prescription included Chinese herbal medicine of Cang Zhu (Rhizoma Atractylodes) 18 g, Bai Zhu (Rhizoma Atractylodis Macrocephalae) 18 g, Dan Shen (Radix Salviae Miltiorrhizae) 15 g, Hu Zhang (Polygonum cuspidatum) 12 g, niao Bu Su (Septemlobate Kalopanax Branchlet) 15 g, Huang Qin (Scutellaria Baicalensis) 12 g and Wu Yao (Linderae Radix) 12 g to strengthen spleen and remove turbidity as well as to eliminate phlegm and dissipate toxin. All of these herbs were provided and manufactured into decoction by the pharmacy of Longhua Hospital. Patients were provided the Supersession Prescription decoction at the dosage of 200 ml one dose twice daily. Treatment continued for 13 weeks in both of the two groups.

Outcomes

Therapeutic outcomes were divided into three parts to assess different aspects of the whole effectiveness of the combination therapy and the primary outcome was body weight. Indexes of body weight, BMI, Weight Loss (WL), Waist Circumference (WC), Hip Circumference (HC) and Waist-To-Hip Ratio (WHR) were gauged to estimate the body weight changes. While indexes of HbA1c, FPG, 2hPG, Fasting Insulin (FINS) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were measured to evaluate the reduction in plasma glucose as well as the improvement in beta cell function. Triglyceride (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL), Low Density Lipoprotein Cholesterol (LDL) and Free Fatty Acids (FFA) were also checked to explore the effects on lipid metabolism.

All the indicators were measured at the beginning of the treatment as well as at the endpoint, and the index

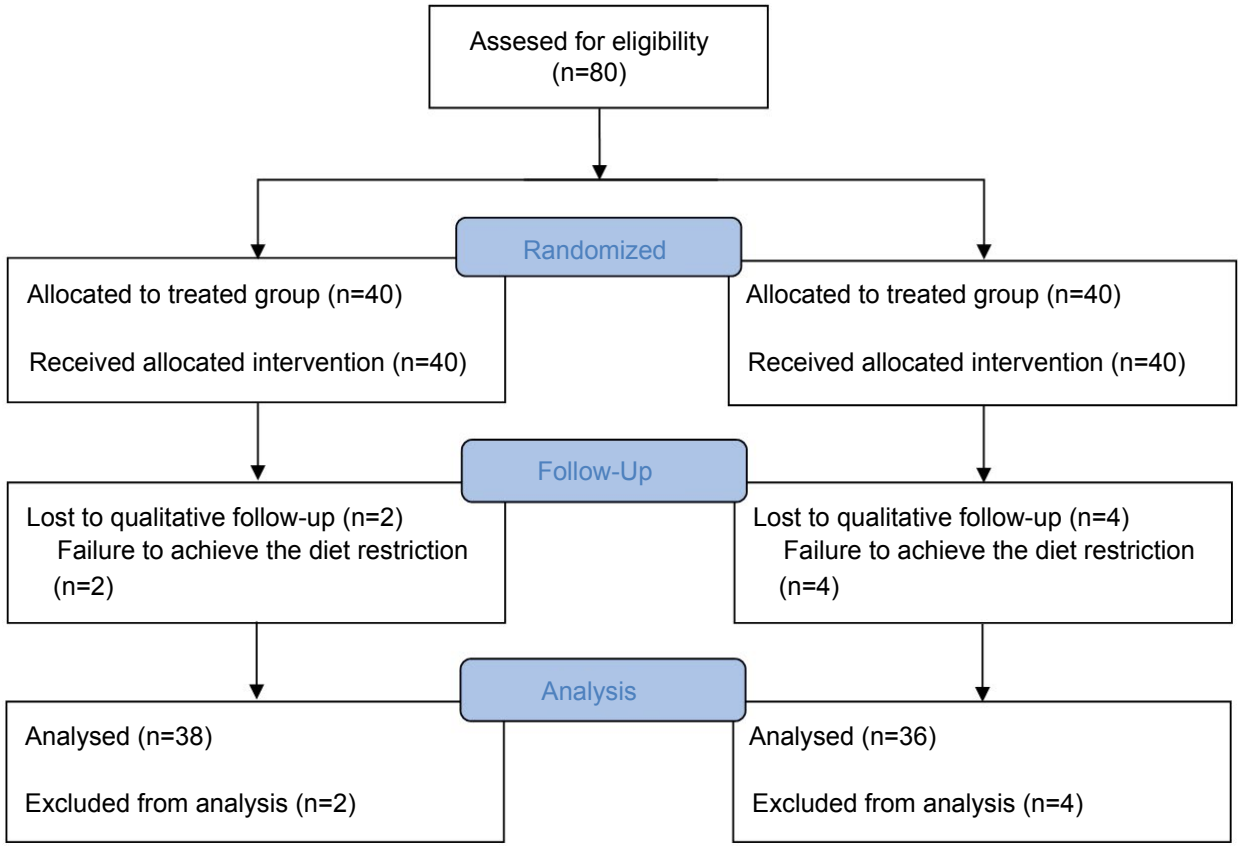

Figure 1: The CONSORT flow diagram.

of body weight was gauged additionally once a week at the first five weeks as well as at the ninth week.

Safety monitoring included adverse events, vital signs and blood biochemical tests. Hypoglycemic episodes were observed in detail as a major indicator of adverse reactions in the therapeutic period.

Statistical analysis

Sample size calculation was performed for the primary outcome, body weight, and the sample size was calculated according to the following formula [17]:

$$n_2 = (1+1/c)\,[\sigma\,(z_{1-\alpha/2} + z_{1-\beta})/\,(\mu_1-\mu_2)]^2;\ n_1 = cn_2$$

$$\mu_1 = 4,\ \mu_2 = 3,\ \sigma = 1.5,\ c = 2,\ \alpha = 0.05,\ 1-\beta = 0.80$$

As a result, body weight reduction in the treated group and the control group was estimated to be 4 kg and 3 kg, respectively, and the Standard Deviation (SD) was supposed to be 1.5 in both of the two groups. As the subjects were assigned to either the treated group or the control group in a 1:1 ratio, the calculation indicated that a sample size of 36 subjects per group would yield a power of 80% with a 5% two-sided significance level. To allow for a 10% withdrawal rate, 40 subjects for each group should be recruited.

All normally distributed data were presented as mean ± SD, while non-normal data were presented as median and Interquartile Range (IQR). Parametric Student's t-test or non-parametric Wilcoxon test was used to compare variables according to their distribution characteristics and a *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0.

Table 1: The general characteristics of all the 80 patients.

	Control	Treated
N (M/F)	36 (15/21)	38 (16/22)
Age (Year)	35.5 ± 6.0	36.2 ± 6.6
Height (cm)	172.1 ± 5.2	170.6 ± 5.5
Weight (kg)	84.6 ± 7.2	83.7 ± 7.5
BMI (kg/m²)	28.5 ± 1.7	28.7 ± 1.6
WC (cm)	90.3 ± 3.6	90.3 ± 4.0
HC (cm)	99.8 ± 3.3	99.1 ± 3.6
WHR (%)	0.91 ± 0.04	0.91 ± 0.05
HbA1c (%)	7.35 ± 0.89	7.28 ± 1.02
FPG (mmol/L)	7.69 ± 1.03	7.76 ± 0.97
2hPG (mmol/L)	12.02 ± 1.77	11.81 ± 2.07
FINS (μIU/mL)	19.10 ± 7.36	19.24 ± 8.82
HOMA-IR	6.53 ± 2.61	6.64 ± 3.19
TG (mmol/L)	2.46 ± 0.98	2.52 ± 1.00
TC (mmol/L)	5.38 ± 1.08	5.28 ± 0.97
HDL (mmol/L)	1.35 ± 0.30	1.32 ± 0.27
LDL (mmol/L)	3.22 ± 0.93	3.30 ± 0.87
FFA (mmol/L)	0.69 ± 0.14	0.68 ± 0.16

BMI: Body Mass Index; WC: Waist Circumference; HC: Hip Circumference; WHR: Waist-To-Hip Ratio; HbA1c: Glycosylated Hemoglobin; FPG: Fasting Plasma Glucose; 2hPG: 2h Post-Prandial Plasma Glucose; FINS: Fasting Insulin; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TG: Triglyceride; TC: Total Cholesterol; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; FFA: Free Fatty Acids

Results

A total of 80 subjects were recruited for this study as proposed, however, six were excluded due to failure to achieve the diet restriction. Thus, 74 subjects (in which 38 in the treated group and 36 in the control group) finally completed this study and analyses were performed in this cohort. Figure 1 illustrated the above process in a CONSORT flow diagram.

The general characteristics of the patients are presented in Table 1. No significant difference was identified between the two groups in all the parameters such as gender, age, height and weight before treatment.

Comparisons of body weight

Table 2 presents the results of comparisons on the aspect of body weight.

After 13 weeks of treatment, indexes of body weight and BMI displayed significantly curative effects in the treated group ($P < 0.05$), but none of them revealed in the control group. Analyses presented statistically significant differences between the two groups ($P < 0.05$), favoring the treated group, while the result of WL was consistent.

The levels of WC and WHR were significantly decreased in both of the two groups ($P < 0.05$), however, the changes between the two groups did not show any significant difference. In the meantime, there was no significant change in HC was found within each group as well as between them.

As the primary outcome in the body weight indexes, changes in body weight were presented in Figure 2. The levels of body weight constantly decreased in both of the two groups within the first five weeks. However, there was no statistically significant difference between before vs. after treatment within each group as well as between treated and control groups at any time point. Significantly curative effect appeared at the ninth week in the treated group ($P < 0.05$) and sustained throughout the next four weeks. However, the difference between the two groups was significant only at the endpoint of the treatment ($P < 0.05$). No significantly curative effect was found in the control group during the whole study.

Comparisons of glucose metabolism

Table 3 presents the results of comparisons on the aspect of glucose metabolism.

As the most important outcome in the glucose metabolism indexes, HbA1c significantly decreased in both

Table 2: Comparisons on the aspect of body weight.

Group	Time	Weight (kg)	BMI (kg/m^2)	WL (%)	WC (cm)	HC (cm)	WHR (%)
	Before	84.6 ± 7.2	28.5 ± 1.7	-	90.3 ± 3.6	99.8 ± 3.3	0.91 ± 0.04
Control	After	83.2 ± 7.8	28.1 ± 1.9	2.7 ± 2.1	87.5 ± 2.5	99.2 ± 4.4	0.88 ± 0.04
	*P	0.444	0.335		< 0.001	0.55	0.026
	Before	83.7 ± 7.5	28.7 ± 1.6	-	90.3 ± 4.0	99.1 ± 3.6	0.91 ± 0.05
Treated	After	79.2 ± 6.9	27.2 ± 1.4	6.0 ± 1.0	86.1 ± 4.0	98.8 ± 4.4	0.87 ± 0.06
	*P	0.007	< 0.001		< 0.001	0.771	0.003
	#P	0.022	0.02	< 0.001	0.083	0.667	0.431

*P value refers to comparison between before vs. after treatment within each group; #P value refers to comparison between treated and control groups after treatment; BMI: Body Mass Index; WL: Weight Loss; WC: Waist Circumference; HC: Hip Circumference; WHR: Waist-To-Hip Ratio.

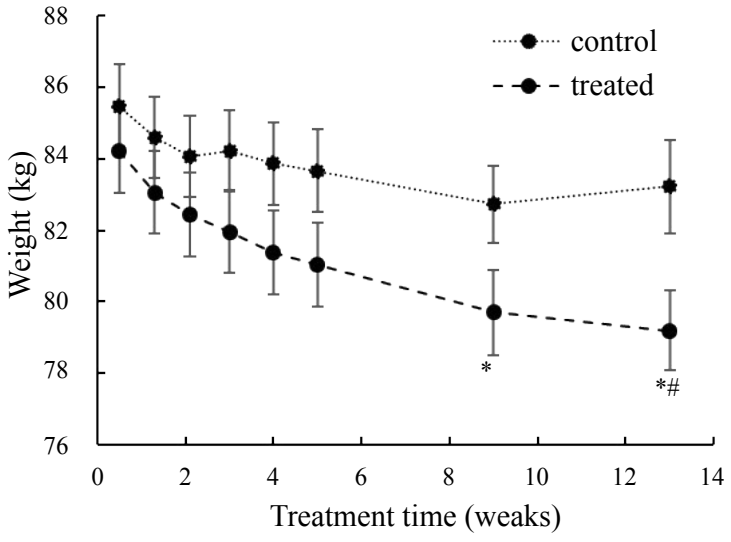

Figure 2: Changes in body weight during the study.

*$P < 0.05$, P value refers to comparison between before vs. after treatment within each group. #$P < 0.05$, P value refers to comparison between treated and control groups after treatment.

Table 3: Comparisons on the aspect of glucose metabolism.

Group	Time	HbA1c (%)	FPG (mmol/L)	2hPG (mmol/L)	FINS (μIU/mL)	HOMA-IR
	Before	7.35 ± 0.89	7.69 ± 1.03	12.02 ± 1.77	19.10 ± 7.36	6.53 ± 2.61
Control	After	6.95 ± 0.75	7.05 ± 0.98	10.95 ± 2.34	17.81 ± 7.89	5.57 ± 2.55
	*P	0.039	0.007	0.027	0.465	0.109
	Before	7.28 ± 1.02	7.76 ± 0.97	11.81 ± 2.07	19.24 ± 8.82	6.64 ± 3.19
Treated	After	6.44 ± 0.83	6.50 ± 1.06	9.91 ± 1.99	16.40 ± 8.53	4.75 ± 2.64
	*P	< 0.001	< 0.001	< 0.001	0.153	0.006
	#P	0.008	0.025	0.043	0.464	0.178

*P value refers to comparison between before vs. after treatment within each group; #P value refers to comparison between treated and control groups after treatment; HbA1c: Glycosylated Hemoglobin; FPG: Fasting Plasma Glucose; 2hPG: 2h Post-Prandial Plasma Glucose; FINS: Fasting Insulin; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

Table 4: Comparisons on the aspect of lipid metabolism.

Group	Time	TG (mmol/L)	TC (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	FFA (mmol/L)
	Before	2.46 ± 0.98	5.38 ± 1.08	1.35 ± 0.30	3.22 ± 0.93	0.69 ± 0.14
Control	After	1.91 ± 0.91	5.19 ± 0.86	1.45 ± 0.28	2.85 ± 0.72	0.63 ± 0.16
	*P	0.012	0.401	0.156	0.059	0.111
	Before	2.52 ± 1.00	5.28 ± 0.97	1.32 ± 0.27	3.30 ± 0.87	0.68 ± 0.16
Treated	After	1.71 ± 0.67	4.86 ± 0.91	1.53 ± 0.33	2.39 ± 0.74	0.48 ± 0.14
	*P	< 0.001	0.051	0.002	< 0.001	< 0.001
	#P	0.299	0.11	0.23	0.009	< 0.001

*P value refers to comparison between before vs. after treatment within each group; #P value refers to comparison between treated and control groups after treatment; TG: Triglyceride; TC: Total Cholesterol; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; FFA: Free Fatty Acids.

of the two groups (P < 0.05) after 13 weeks of treatment, while the results of FPG and 2hPG were consistent. Comparisons of these indexes between groups presented significant differences (P < 0.05) favoring the treated group.

In both of the two groups, there was no significant change in FINS during this study, but an improvement in HOMA-IR was displayed in the treated group (P < 0.05) in which was not displayed the control group. However, comparisons between the two groups showed no significant difference in both of the two indexes.

Comparisons of lipid metabolism

Table 4 presents the results of comparisons on the aspect of lipid metabolism.

After 13 weeks of treatment, reductions in TG were significantly different in both of the two groups (P < 0.05), however, changes between the two groups did not present a significant difference. Analyses also confirmed that there was no significant difference in TC reduction within each group as well as between the two groups.

Significant improvements in HDL, LDL and FFA were confirmed in the treated group (P < 0.05), however, reductions between groups were significantly greater only in LDL and FFA (P < 0.05). None of these indexes presented any significant change in the control group.

Adverse reactions

Levels of routine blood, liver and kidney function in both groups examined before and after treatment were all in the normal range. There were three patients in the control group that felt bloating and diarrhea as well as two in the treated group. All the gastrointestinal symptoms were recovered at the first week. Besides, no hypoglycemic episodes and other serious side effect were found in both of the two groups.

Discussion

The aim of this current study was to compare the effects of combination therapy and metformin, in order to see if Supersession Prescription could produce a curative effect as a supplementary medical treatment combined with metformin.

As a result, this trial demonstrated that treatment of overweight and obese individuals with type 2 diabetes with combination therapy resulted in a 6.0% reduction in body weight, compared with a reduction of 2.7% with metformin intervention alone. Individuals treated with combination therapy were more than twice as treated with metformin intervention alone as likely to lose ≥ 5% of their initial body weight, which was associated with a significantly improved glucose control, resulting in reduced mortality in patients with diabetes [18,19]. Similar BMI reduction was confirmed after a 13-week treatment, while modest improvements in WC and WHR were also observed.

The weight loss in the treated group was significant as early as the ninth week, while a constant decline was maintained for the next four weeks, with no evidence of weight regain. In the meantime, body weight reached a near-maximal reduction at the ninth week in the control group and presented a slight increase at the endpoint of the treatment. These results provided an indication that Supersession Prescription could strengthen the

therapeutic effect as well as could prolong the duration of therapeutic effect as a supplementary medicine combination with metformin in the treatment of obesity. Stability of long-term curative effect was not assessed in this study due to no follow-up data was available.

In this study, treatment with combination therapy provided a reduction of 0.8% in HbA1c superior to that of 0.4% with metformin, and the results of FPG and 2hPG were consistent. Attention should be paid as this degree of reduction was meaningful to long-term risk of micro- and macro-vascular complications [20,21]. Improvements in FNIS and HOMA-IR were modest, which were mostly due to the limited number of participants and the large heterogeneity among them as researches reported that metformin could make amelioration on insulin sensitivity [22,23]. Deficiency of treatment time might also play an important role on this procedure. These findings indicated that Supersession Prescription could be considered as an effective treatment option for combination therapy with metformin while subjects could not achieve glycemic control with metformin therapy alone.

Comparisons on the aspect of lipid metabolism presented certain therapeutic effects in both of the two groups, however, changes were greater in the treatment group which might be largely due to the reduction in body weight as subcutaneous and visceral adipose tissue, especially the latter one, was strongly associated with lipidemia [24,25]. As serum lipids were also markers of cardiovascular risk, Supersession Prescription should be suggested as a supplementary remedy to patients with dyslipidemia.

Safety analyses showed that there was no difference between the two groups in the overall incidence of adverse events, and most were gastrointestinal symptoms which were well-known adverse effects reported with metformin [26,27]. Importantly, there was no serious adverse event including hypoglycemia during this study which means Supersession Prescription could be used in a wide range of different conditions such as impaired glucose tolerance.

Compared with the previous research, this study provided an available approach to manage body weight, blood glucose and serum lipids at the same time which might be good news to patients with multiple metabolic abnormalities such as metabolic syndrome. In the meantime, Supersession Prescription was clearly defined as a supplementary therapy in this research which might provide it a wide range of application prospect. As we all know that TCM has not been allowed to be used as medical treatment in many countries as herbal preparations are complex and contain a serious of active ingredients which are unidentified and may even work together, resulting in unclear mechanisms and instable efficacy, however, it is accepted as an assistant in the course of health protection in most places.

In this study, Supersession Prescription, in conjunction with a standardized drug intervention, resulted in clinically meaningful improvements in body weight, HbA1c and other cardiovascular risk factors, which were associated with a reduced risk of mortality. Thus, a hypothesis was provided that combination therapies with TCM, such as Supersession Prescription, might have the potentiality to become an effective option for the management of body weight, blood glucose and serum lipids at the same time. And then, further assumptions were proposed that other comprehensive treatment, such as acupuncture and catgut embedding [28-30], could also provide adjuvant therapy to patients with multiple metabolic abnormalities.

Limitations should be acknowledged that sample size was small in this study in which some differences between groups might not have been detected due to insufficient statistical power. And more importantly, 13-week duration of treatment is obviously not adequate to fully assess the long-term efficacy. As long-term continuous treatment and short-term repeated treatment may provide different outcomes in some way, the optimal treatment duration still need to be explored in further studies. Dietary restriction was performed in this study, however, efficacy on satiation was not evaluated which was reported with some other remedies [31-33]. And furthermore, the mechanism of curative effect by Supersession Prescription was still unclear which means more studies were needed to explore.

In recent years, series of researches have been performed to explore different approaches to treat overweight and obese patients with T2DM, however, the current epidemic of obesity and obesity-related diabetes continues to be of increasing. New approaches to prevention and treatment are needed, and a controllable and stable curative treatment of TCM might provide an effective assistance to the current standardized intervention strategy.

Conclusion

In this research, Supersession Prescription could produce a curative effect as a supplementary medical treatment combined with metformin and should be used while subjects could not achieve goals of weight or glucose management as well as were suffering from dyslipidemia.

Competing Interests

All authors declare that they have no competing interests.

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