Intervention strategy of Traditional Chinese Medicine for prediabetes(the syndrome of spleen-deficiency phlegm-dampness) based on the reversal of blood glucose and the improvement of fatigue

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Study protocol

Keywords: Prediabetes, Spleen-deficiency phlegm-dampness, Fatigue, Traditional Chinese Medicine

Posted Date: September 4th, 2019

DOI: https://doi.org/10.21203/rs.2.10293/v1

Intervention strategy of Traditional Chinese Medicine for prediabetes(the syndrome of spleen-deficiency phlegm-dampness) based on the reversal of blood glucose and the improvement of fatigue

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Abstract

Background: Prediabetes is a growing health concern,a large percentage of whom will develop full 2 type diabetes. The prominent symptom of patients with diabetes and prediabete is fatigue.The syndrome of spleen-deficiency phlegm-dampbess is the main syndrome of prediabetes.Effective intercentions on prediabetes will delay or prevent the occurrence or development of diabetes.

Methods/design: Randomized controlled trial is implemented in this study.The study term is 3 months.Participants are recruited from Binhai hospital of Tianjin of Traditional Chinese Medicine,Jinghai hospital of Tianjin of Traditional Chinese Medicine and affiliated Wuqing hospital of Tianjin university of Traditional Chinese Medicine.160 participants are randomized to treatment group(Liu Jun Zi granules) and control group(Liu Jun Zi granules emulsifier):80 participants each.Participants being included in this study must have been diagnosed as prediabetes via western medicine criteria and traditional Chinese Medicine criteria.The primary outcomes is the score of fatigue-scale 14 and the rate of blood glucose return to the normal.The secondary outcomes inludes fasting plasma glucose,2-hour post-meal blood glucose and blood lipid test.The indexes of safety include general medical examination;electrocardiogram(ECG),liver function(ALT) and renel function(BUN,Creatinine) test and record of adverse event.

Discussion: The aim of this study is to evaluate the effectiveness and safety of Liu Jun

Zi granules for the treatment of patients with prediabetes.

Trial registration: Chinese clinical trials register ChiCTR1900022736.

Key words:Prediabetes,Spleen-deficiency phlegm-dampness,Fatigue,Traditional Chinese Medicine

Background

Diabetes which threatens the health of human,has become the world's third chronic non-communicable disease,as well diabetes will be the seventh leading cause of death by 2030[1].The most recent estimate by the International Diabetes Federation(IDF) is that nearly 592 million people will have diabetes in the worldwide by the year of 2035.Ministry of Public Health of China estimates that the number of patients with diabetes will be 46 million and 54 million in prediabetes.Patients of diabetes are prone to have complications such as cardiovascular disease,blindness,kidney failure and amputation,which seriously affect the life quality of patients and lead to the growing rapidly of social and economic burdens.Prediabetes refers to the regulation of normal blood glucose developing into impaired glucose regulation which has not yet reached diagnostic criteria for diabetes.The average risk of developting diabetes is approximately 4~10 times than the normal blood glucose.The prevention of type 2 diabetes in prediabetes patients is a topic of importance in diabetes research.

The syndrome of prediabetes

The syndrome of spleen-deficiency phlegm-dampness is the main syndrome of prediabetes.MingYi Xu[2] found that the syndrome of spleen-deficiency phlegm-dampness had the highest percentage in various syndrome types,accounting for 39.44%,and the following was the syndrome of Yin deficiency and Qi stagnation acccounted for 36.62%.The result was in line with literature report.The patients with syndrome of spleen-deficiency phlegm-dampness are significantly elevated in insulin.The reason is that the deficiency in spleen leads to the dysfunction of islets which leads to hyperinsulinemia, the resistance of insulin and the risk of developing diabetes is higher.As well the Chinese medicine association branch of diabetes has established the standard of TCM diagnosis in prediabetes,which is divided into 3

types,namely the syndrome of Qi stagnation and phlegm blockade,spleen-deficiency phlegm-dampness and Yin deficiency and Qi stagnation.

The main symptom of prediabetes

The prominent symptom of patients with diabetes and prediabetes is fatigue,bringing the perplex to patients and affecting the quality life of patients.It has been proved[3] that patients with diabetes are more likely to be fatigue than the healthy people with a rate of more than 50%.Fatigue is the persistent symptome of diabetes patients,affecting the quality of their life and functional state[4-5].Huifang Zhang[6] found that the frequency symptoms in patients with prediabetes was fatigue,accounting for 32.9%.Huaping Li[7] found that the symptoms among 101 cases of prediabetes was fatigue(66.3%),followed by soreness and weakness of waist and knees(61.4%),irritable(60.4%) and tired(50.5%).Therefore,it can be seen that alleviating and improving the fatigue symptoms of prediabetes should be arouse the attention of clinical researchers.

Progress of prediabetes

Effective intervention on the syndrome of spleen-deficiency phlegm-dampness of prediabetes patients can alleviate the fatigue symptom.Ying Zhou[8] found that adopting the method of invigorating spleen and phlegm can reduce the levels of blood glucose and lipid,improve the resistance of insulin and relieve clinical symptoms.Gang Xu[9] adopted the prescription of Jianpi clearing damp phlegm to treat prediabetes and found that this treatment can effectively reduce the blood sugar levels,the incidence of disease and improve the quality life of patients.

Constituents of Liu Jun Zi granules

Liu Jun Zi granules are consisted of codonopsis pilosula(12g),rhizoma atractylodis macrocephalae(12g),poria cocos(18g),pericarpium citri reticulatae(12g),pinellia ternate(12g) and honey-fried licorice root(6g).

Methods/study design

Study setting and overview

The research will be carried out in the three clinical centers in Tianjin,China(Binhai hospital of Traditional Chinese Medicine,Jinghai hospital of Traditional Chinese

Medicine， Affiliated Wuqing hospital of Tianjin university of Traditional Chinese Medicine),aimming to recurit 160 patients with prediabetes.Potential participants will be recruited from inpatient and outpatient services in each center.They will be assigned to 2 groups after they have been provided with a complete description of the study and written informed consent.(Fig.1)

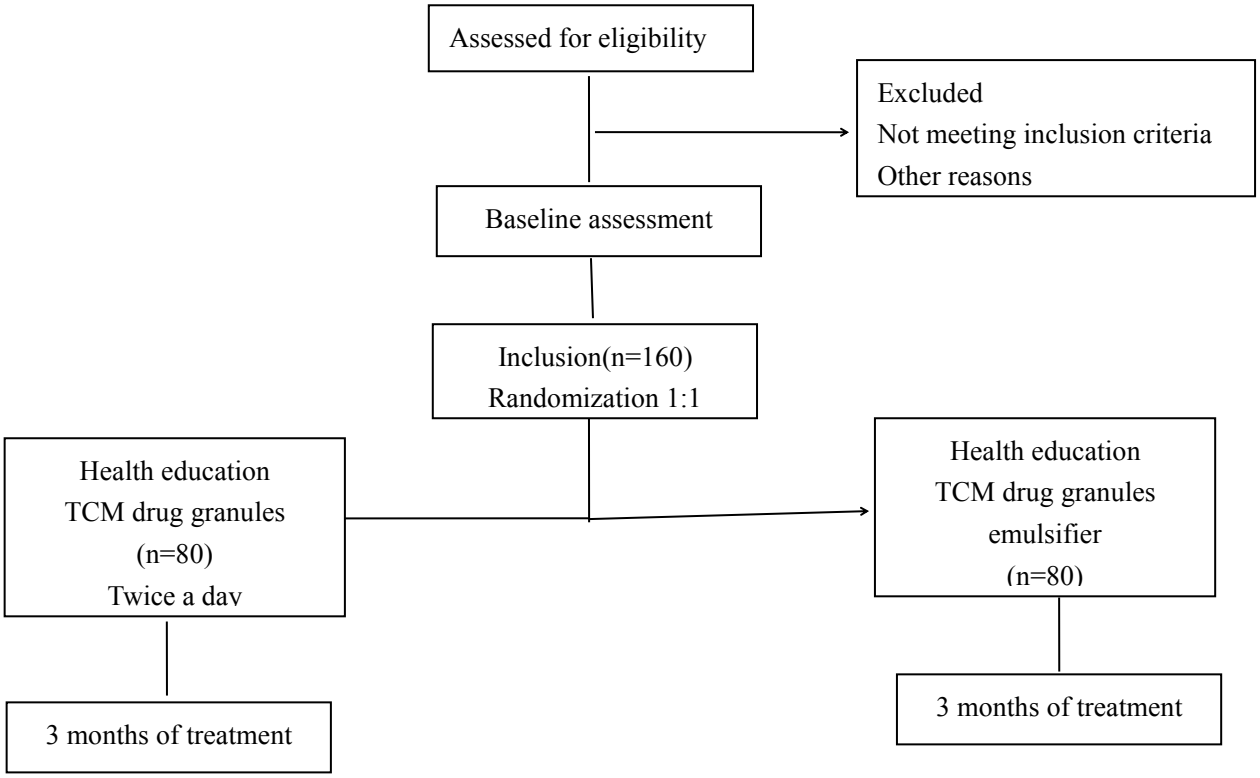

Fig.1

Study flow diagram

Objectives

The syndrome of spleen-deficiency phlegm-dampness of prediabetes patients with fatigue as research object,combining integration of TCM intervention and lifestyle education,in order to form comprehensive intervention and controllment strategy for the prevention of prediabetes.

Research type

This is a randomized controlled clinical trial.Ethical approval is given by the Ethics Committee of Tianjin University of Traditional Chinese Medicine with the following reference number :TJUTCM-EC20170007.The trial is registered at the Chinese Clinical Trial Registry (Registration ID:ChiCTR1900022736).Tianjin university of TCM is held responsible for the organization and coordination of the trial sites and

staff.The participating institutions include Binhai hospital of Tianjin of Traditional Chinese Medicine,Jingihai hospital of Tianjin of Traditional Chinese Medicine and affiliated Wuqing hospital of Tianjin university of TCM.

Screening of participants

160 prediabetes patients(the syndrome of spleen-deficiency phlegm-dampness)will be divided into the treatment group and the control group(1:1).Participants should be included according to diagnosis criteria and inclusion criteria.

Intervention

Health education:Researchers will develop health diet and general lifestyle for each participant.According to different labor intensity and bodity form,stipulate basically different staple food will be intaken:the daily staple food should be controlled at 250~300g for the light physical labor or overweight of participant ;the daily staple food should be controlled at 300~350g for the ordinary participant;the daily staple food should be controlled at 350~450g for the moderate manual worker.As well,the required calories will be supplemented by non-staple food except staple food.Daily rest,activities and work will be included in reasonable exercise.

Drug intervention:The period of drug intervention is 3 months.All participants have to visit researchers each month.The interventions are as follows:Liu Jun Zi decoction as the main prescription,TCM drug granules for the treatment group and TCM drug granules emulsifier for the control group.The drug granules and their emulsifier are formulated with the national standard of TCM.Their emulsifier is basically consistent with TCM formula based on the characteristics of odor,color,shape and so on.

Randomization

According to a random sequence table(generated by SAS8.2),participants who satisfied the inclusion criteria will be allocated randomly into one of the two groups with a ratio of 1:1.

Blindness

Double-blinding method is adopted in this study.Emulsifier agents have the same appearance,shape,color and packaging with drug granules,so researchers and participants can not know the kind of medication and group.

Sample Size

Using the score of fatigue-scale 14 and the rate of blood glucose return to the normal as the criteria,the sample size is estimated by PASS 2008.

Hypothesis:After treatment the score of fatigue-scale is 6 in the group of Liu Jun Zi granuals and 7 in the group of Liu Jun Zi granuals emulsifier,standard deviation is 1.5,the error of I type is 0.05,the degree of master is 80%,the calculated sample size is 124.Considering the abscission is 10%,136 cases are needed in total,68 cases each group.

Hypothesis:After treatment the rate of blood glucose return to the normal is 36% in the group of Liu Jun Zi granuals and 16% in the group of Liu Jun Zi granuals emulsifier,the error of I type is 0.05,the degree of master is 80%,the calculated sample size is 144.Considering the abscission is 10%,158 cases are needed in total,79 cases each group.

Therefore,it can be seen that the total number of qualified subjects is less than 160 in the 2 groups,80 particapants each group.

Patients identification and enrollment

Diagnosis criteria

western medicine diagnostic criteria

① History:the history of prediabetic and meeting the diagnosis for prediabetes ;②clinical manifestations(guidelines for the prevention and controllment of diabetes in 2007):symptoms:general atypical clinical symptoms,such as mouth sweet to drink,appetite,abdominal enlargement,absominal distension,fatigue,etc.Most prediabetes patients are found in physical examination or other diseases;physical signs:multiform obesity or overweight,such as manifested as waist-hip ratio and physical index abnormality,and other signs are not obvious;③(Guidelines for Clinical Diagnosis and Treatment of Diabetes in 2010,ADA):impaired fasting glucose(IFG)(FPG 5.6~6.9mmol/L)&/or impaired glucose tolerance(IGT)(FPG<5.6mmol/L & OGTT 2hPG 7.8~11.1mmol/L).

③Symptoms of Traditional Chinese Medicine(Guidelines to the clinical practice and evidence-based medicine for prediabetes):the syndrome ofspleen-deficiency

phlegm-dampness

Inclusion criteria

①Patients who meet the diagnostic criteria for the prediabetes with the syndrome of spleen-deficiency phlegm-dampness;

②Patients with moderate or severe fatigue were included evaluated by the self-rating scale;

③Aged from 30 to 75 years old;

④No participating in clinical studies of other interventions within 2 weeks before inclusion;

⑤Completed and submitted informed consent form voluntarily.

Exclusion criteria

① The history of diabetes(except gestational diabetes) ;

②Recent cardiovascular events,mental diseases,severe liver and renal insuffciency;

③Endocrine diseases such as hyperthyroidism;

④Taking glucocorticoid,β receptor blockers,thiazide diuretics and nicotinic acid;

⑤Pregnancy,preparation of pregnancy and lactating women;

⑥Participating in clinical trial of other drugs recently.

Rejection criteria

①No taking medicine according to the protocol

②Data is incomplete.

Suspension criteria

① Serious adverse events,complications and special physiological changes;

②Poor compliance;

③Reluctance to continue this study;

④Incomplete information which will influence the study;

⑤Unblinded abnormally;

⑥National laws,ministry of science and technology or other authorities decided to terminate the study.

Follow up

The follow-up period is 1 month.

Outcomes measures

Primary outcomes

①The score of Fatigue Scale-14(FS-14)

FS-14 contains 14 items that are related to the problem of fatigue.The first 8 items reflect physical fatigue;6 items from 9 to 14 reflect the mental fatigue.According to whether the content is consistent with the actual situation,participants should answer yes or no.The highest score of the total FS-14 is 14,namely the highest score of physical fatigue is 8 and the highest score of mental fatigue is 6.The higher the score,the fatigue is more severe.

②The rate of blood glucose return to normal

Reversion rate=cases of blood glucose return to normal/total cases of each group×100%

Secondary outcome measures

①Height,weight,BMI,waist-hip ratio;

② The value of fasting plasma glucose(FPG);the value of 2-hour post-meal blood glucose(2hPG);

③ Total Cholesterol(TC),Triglyceride(TG),High Density Lipoprotein-Cholesterol(HDL-C),Low Density Lipoprotein -Cholesterol(LDL-C)

Safety index

①General medical examination

②Functional examination:ECG,ALT,BUN,Cr.

③Adverse events

Health-economic indicators

Cost-effectiveness analysis;incremental cost-effectiveness analysis

Study procedure

The study will have three phases.During the first phase,participants will be screened using the inclusion and exclusion criteria.Information on the implementatiaon of the study and the objectives of the research will be given to the each subject by trained staff and/or health care providers.Enrollment and Traditional Chinese Medicine treatment will be scheduled in the following months for eligible participants.The

detailed procedure is displayed in Fig.2.

	Study Period				
	Phase 1	Phase 2	Phase 3		
	Screening	Inclusion	Post-allocation		
Timepoint(month)	Month -1	Month 0	Month 1	Month 2	Month 3
ENROLLMENT Presentation of study Informed consent Randomized allocation (Group 1 or 2)	X	 X X			
INTERVENTION Health Education TCM drug granules TCM drug granules emulsifier			 Group 1+2 Group 1 Group 2	 Group 1+2 Group 1 Group 2	 Group 1+2 Group 1 Group 2
ASSESSMENTS Primary outcome the score of FS-14		 Baseline measures	 X	 X	 X
Secondary outcomes Height,weight,BMI FBG,2hPG TC/TG/LDL/HDL		 Baseline measures	 X X	 X X	 X X

Fig 2

Adverse Event Monitoring

Report of adverse event

When adverse event happens,researchers should fill out the “SAE form” and report it to project office immediately.

Record of adverse event

Adverse event report form should be filled according to the real circumstances,some information such as occurrence time,severity,duration,adopted measure must be recorded as well.

Relationship between adverse event and investigational drugs

Judgement the relationship between the adverse reactions and the administration time;judgement the relationship between suspected and known adverse reactions of investigational drug;whether suspected adverse reactions disappear or mitigate after discontinuation;whether the same reaction occurred again after taking investigational drug once more.

Security evaluation criterion

Safe without any adverse drug reaction;

Relative safe with mild adverse drug reactions and unnecessary treatment;

Having moderate adverse drug reactions and necessary treatment;

Stopping to take investigational drugs due to adverse reactions.

Data management and statistical analysis

Analysis parameters

All parameters will be analyzed by SPSS 11.0 and SAS6.12 sofeware package.

Mathematical statistics analysis and expression

Comparison between groups:t-test for normal distribution of measurement data;the chi-square test test for enumeration data;Wilcoxon rank sum test for non-normal distribution of measurement data.

Documents conservation and summary

The documents such as informed consent,signature of participants and other materials are requested to conserve clearly according to GCP by every unit after the study.Reseachers should preserve the materials of clinical trial.

Management of investigational drug

TCM drug granules and emulsifier are supplied by Baokang Hospital of Tianjin

university of TCM.Based on double-blind method,the package of emulsifier should be consistent with the investigational drug.

Trial management

Change of protocol

All modifications of protocol must be preserved and any changes of the protocol,including ICF,should get the approval of ethics committee.

CRF tracking

All signed ICF should be handed over even if some of them are unqualified;any questions of CRF and comments must be submitted directly to the organizer.

Researcher's responsibility

Researchers should understand the details of protocol and adhere to it strictly.They should have enough time to complete the study on schedule and respomsibility to explain the process of study and consent form to participants.When the participants happen adverse events,they should be treated suitably and related data should be recorded accurately and completely in primitive medical record and CRF.

Bias control

When participants decide to participate in this study,they stop to take any other western medicine or TCM drugs which has similar effects as the investigated agent.Researchers pay attention to contamination and disturbance in the study aimming to prevent occurence of bias.

Declarations

Trial Status

The patient with prediabetes in this trial are recruited from May 12,2019.The recruitment of patients are expected to be completed on May,2020.As well :the program of clinical research 1.0,informed consent 1.0,case report form 1.0,investigator's brochure 1.0 and resume of principal investigator 1.0 are used for this trial.

Ethics approval and consent to participate

The current protocal is version 1.0,28 June 2017..Ethical approval is given by the

Ethics Committee of Tianjin University of Traditional Chinese Medicine with the following reference number :TJUTCM-EC20170007.

China clinical trial quality management norm/Helsinki declaration

The study will guarantee to abide Chinese clinical trial quality control standard and Helsinki declaration.

Participants will receive a complete description of the study and written informed consent will be obtained.

Ethics committee

Before the beginning of the study,the organier should provide related data about the qualification of the main researchers and laboratory conditions in order to get the permission of ethics committee.

Inform consent form

ICF shoule be approved and reviewed by ethics committee before the beginning of the study.Researchers should let participants know the relevent information in words and writing by understanding language.Before signing the ICF,participants and their representatives should have enough time to read it.ICF should be signed by the partcipants or their representatives with data.As well the signed ICF should be preserved properly by researchers and participants independently.

Security

Researchers should keep related information of participants strictly in the study.

Abbreviations

CRF:Case Report Form;ICF:Inform Consent Form;SAE:Serious Adverse Event;TC:Total Cholestero;HDL -C:High density lipoprotein cholestero;LDL-C:low densitylipoprotein cholestero;TG:Triglyceride;ECG:Electrocardiogralph;ALT:Alanine transaminase;AST:Aspartateaminotransferase;BUN:Ureanitrogen;Cr:Creatinine;RCT: Randomized controlled clinical;TCM:Traditional Chinese Medicine..

Acknowledgement

The funding support of Science and Technology Planning project of Tianjin province,the National Key Research Program of China,Innovation Team Program and State Administration of Traditional Chinese Medicine of People's Republic of China

are gratefully acknowledged.We especially wish to acknowledge the members of the Trial.

Funding

The trial is sponsored by Science and Technology Planning project of Tianjin province(No.15ZXLCSY00020),the National Key Research Program of China(No.2018YFC1707403),State Administration of Traditional Chinese Medicine of People's Republic of China (No.201107006).

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Author's contributions

LPG,MR designed and finalised the protocol;MR,XS were in charge of the trial management.JBZ were in charge of estimate of sample size.SFH,YL,NMW were in charge of monitoring.MDL and ZJH will asist with recuitment of participants.All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

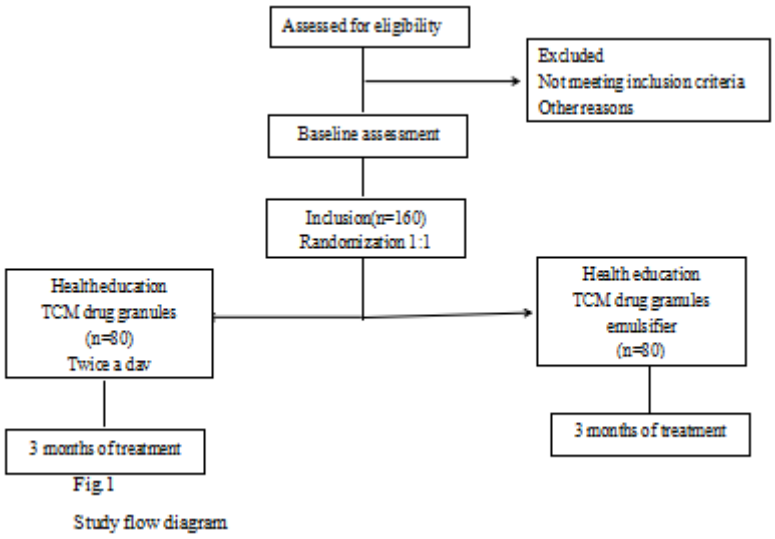

Figure 1

Study flow diagram

	Study Period				
	Phase 1	Phase 2	Phase 3		
	Screening	Inclusion	Post-allocation		
Timepoint(month)	Month -1	Month 0	Month 1	Month 2	Month 3
ENROLLMENT Presentation of study Informed consent Randomized allocation (Group 1 or 2)	X	 X X			
INTERVENTION Health Education TCM drug granules TCM drug granules emulsifier			Group 1+2 Group 1 Group 2	Group 1+2 Group 1 Group 2	Group 1+2 Group 1 Group 2
ASSESSMENTS Primary outcome the score of FS-14		Baseline measures	X	X	X
Secondary outcomes Height,weight,BMI FBG,2hPG TC/TG/LDL/HDL		Baseline measures	 X X	X X	X X X

Figure 2

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.pdf