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A comparison study of metformin only therapy and metformin combined with Chinese medicine jianyutangkang therapy in patients with type 2 diabetes: A randomized placebo-controlled double-blind study☆

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ABSTRACT

The aim of this 26-week, double-blind, controlled clinical trial, was to compare the efficacy of monotherapy (metformin only) with combination therapy (Chinese medicine prescription JianYuTangKang [JYTK] plus metformin) on type 2 diabetes.

All patients on metformin were randomized to receive authenticated JYTK (59 patients) or placebo JYTK (53 patients), 4.5 g daily, for 26 weeks. Patients also received information regarding diet and exercise. Fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1C}) level, and a lipid profile were measured before, during, and after the treatment.

The results of the treatment group (JYTK plus metformin) were noninferior to those of the control group (metformin plus placebo) at 8 and 18 weeks. After 26 weeks of treatment, FPG levels decreased to 6.1 ± 1.0 mmol/L in the treatment group and 7.0 ± 1.5 mmol/L in the control group ($p < 0.01$). HbA_{1C} levels after 26 weeks were also significantly decreased in the treatment group compared with the control group ($p < 0.01$). In addition, lipid profiles were also significantly different between the two groups.

Integrated traditional Chinese and Western medicine therapy (JYTK plus metformin) for patients with type 2 diabetes mellitus may not only help improve glycemia and insulin sensitivity, but also help to modify the diabetes related lipid equilibrium. And thereby provides a basis for a novel, effective, and safe approach, to treat type 2 diabetic patients.

1. Introduction

Diabetes mellitus (DM) a common endocrine disorder that affects more than 100 million people worldwide and is on a continuous rise. Its global prevalence was estimated as 285 million in 2010, and type 2 DM (T2DM) accounted for 90% of the cases.[1,2] Although hyperglycemia is the hallmark of diabetes and can increase the risk of cardiovascular, neuropathic, renal, and retinopathic complications, DM is a metabolic disorder with multiple target biomarkers such as body mass, lipid profile, blood pressure, and circulating adipokines and inflammatory cytokines.[3] The current research on the mechanisms of diabetes shows a combination of molecular events in human and mouse pancreatic β-cells, induced by elevated levels of free fatty acids or by administration of a high-fat diet with associated obesity, that comprise a pathogenic pathway to diabetes. Free fatty acids cause nuclear exclusion and reduced expression of the transcription factors forkhead box protein A2 (*FOXA2*) and hepatocyte nuclear factor 1 homeobox A (*HNF1A*) in β-cells.[4–6] Multiple anti-hyperglycemic and anti-dyslipidemic drugs with complementary mechanisms are often needed to achieve optimal glycemic control and lipid levels in T2DM.[7,8] Apart from conventional antidiabetic therapy, several studies have shown that diet, Chinese herb medicinal, complementary, and alternative medicine therapies have beneficial effects and improve glucose homeostasis and hyperlipidemia in diabetic patients[9,10] because of their anti-oxidation, anti-inflammation, anti-obesity, and anti-hyperglycemia properties.[11]

Most of these Chinese formulas are used in combination with routine compounds such as glibenclamide or metformin, and studies indicate that the combinations are more effective in lowering

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blood glucose and improving diabetic symptoms than routine drugs alone in T2DM patients.[12–16]

The Chinese traditional medicine jianyutangkang (JYTK) tablets is a preparation of PLA General Hospital containing the main components of *Acanthopanax senticosus*, *Euonymus alatus*, *Rhizoma Anemarrhenae*. The dried roots of the plant *A. senticosus* and the twigs of *E. alatus* are used in traditional oriental medicine and reportedly possess anti-inflammatory properties in vitro.[17,18] Extract of the rhizome of *Anemarrhenae asphodeloides* effectively prevented diabetic ophthalmopathy progression in streptozotocin-induced diabetic rats, and mangiferin and neomangiferin may be the main effective components.[19] Despite the many animal studies reporting the beneficial effects of JYTK for treatment of DM and its antioxidant and anti-dyslipidemia properties,[20,21] its effects in diabetes have not yet been studied in a clinical trial. Meanwhile, metformin, as a routine DM drug, is the major treatment used in our hospital. Given metformin's beneficial effects on blood sugar and JYTK's beneficial effects on fatty acids and cholesterol, combination therapy using JYTK plus metformin could be a valid choice to more effectively lower blood glucose and enhance lipid-lowering effects.

2. Materials and methods

2.1. Preparation of JYTK and placebo tablets

The placebo tablets, identical in appearance to the JYTK tablets, were prepared at the Academy of Military Medical Sciences (Beijing, China). Toast powder was chosen as the placebo and as the recipient in the JYTK preparation.

Each 500-mg JYTK tablet (Science and Technology Center, Chinese PLA General Hospital, Beijing, China) contained 129 mg of *A. senticosus*, 105 mg of *E. alatus*, and 266 mg of Rhizoma *Anemarrhenae*. Both JYTK and placebo tablets were administered three times per day (4.5 g/day). The test formulation was a hydroalcoholic extract of 10 tablets. The high-pressure liquid chromatography chemical fingerprint for the JYTK can be seen in Fig. 1B. A Diamonsil-C18 column (250×4.6 mm, 5 μm) was used for separation. The mobile phase consisted of acetonitrile/0.1% formic acid (33:67) with a flow rate of 0.8 mL/min, and the detection wavelength was set at 258 nm. The percentages of marker constituents per tablet were as follows: 0.2 mg/g kaempferol, syringin 0.46 mg/g and 1.32 g/g mangiferin.

2.2. Study design and participants

We performed a randomized (1:1), double-blind, placebo-controlled, parallel-group study in three Chinese hospitals (PLA General Hospital Outpatient Service and Chaoyang District ShiLi BaoBeiLi and BaLiTun Community Service Stations in Chaoyang District). Inclusion criteria were male and female T2DM outpatients aged 18–75 years with glycated hemoglobin (HbA_{1c}) between 6.5% and 9.0% despite taking two 500-mg metformin tablets daily. Exclusion criteria were patients taking other anti-hyperglycemic and anti-hyperlipidemic agents; patients receiving insulin therapy; patients with cardiac, renal, hepatic, or hematological diseases or hypothyroidism, tachycardia, vertigo, or seizure; patients with a history of gallstones or gallbladder surgery; patients using estrogen, steroids, β-blockers, or thiazide; and women who were pregnant, planning pregnancy, or breastfeeding.

2.3. Randomization and allocation

Patients were randomly assigned to receive study medication (combination JYTK plus metformin [treatment group] or JYTK plus placebo [control group]) by an interactive voice response system, using a randomly permuted block design with block sizes of 2 and 4. Upon production, study medications were packaged and relabeled into numbered bottles by designated pharmacists according to the randomization list prepared by the trial biostatistician. All people involved in the trial (patients, investigators, project manager, data management team, clinical research associates, and statisticians) were masked as to the group assignments.

2.4. Procedures

A total of 150 patients newly diagnosed with T2DM (short history of duration ≤5 years) according to World Health Organization criteria[24] were recruited All patients had elevated HbA_{1c} over 6.5% and were taking only metformin for regular treatment. A total of 112 patients (59 in the treatment group and 52 in the control group) completed this trial. The numbers of patients lost to follow-up because of lack of interest, lack of contact, or lack of time to return for an interview are shown in Fig. 1A, using the flow chart model of the Consolidated Standards of Reporting Randomized Clinical Trials (CONSORT) 2010.[22] Patients in both groups were reimbursed for travel costs and time. The treatment group took metformin (1500 mg/kg/day) and JYTK (4.5 g/day, 1.5 g, three times daily, for a total of 4.5 g/day), and the control group took metformin 1500 mg/kg/day with placebo. The main investigator and other investigators performing outcome analyses were blinded to the group assignments of patients by use of a coding system in which the codes were kept by an independent allocator and revealed only after treatment and analyses were completed.

All patients received lifestyle modification advice regarding diet and physical activity. Subjects were advised to eat three regular meals every day and to reduce their intake of fat in favor of carbohydrates. All subjects were given a pedometer and were encouraged to walk a minimum of 10,000 steps per day for most days of the week. They were also given homework assignments to record food intake, reason for food intake, and physical activity. These records were maintained throughout the study and were reviewed together with the research nurse at every visit. This was reinforced at each follow-up visit every 2 months.

2.5. Ethics statement

A complete list of inclusion and exclusion criteria was approved by the PLA General Hospital Ethics Committee and also registered in ClinicalTrials.gov (ID: NCT00102589). All patients provided written informed consent before enrollment. The study was conducted following the guidelines of the CONSORT statement.

2.6. Outcomes

The primary outcome measures were changes in fasting plasma glucose (FPG) and HbA_{1c} levels at screening, randomization (baseline, week 0), and weeks 8, 19, and 26 (or early discontinuation). Secondary outcome measures included blood chemistry liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), creatinine, lipid profiles, and C-reactive protein assessed at baseline and week 52 (or early discontinuation). The tests were conducted by the Clinical Laboratory in PLA General Hospital. Drug safety was assessed by the adverse events (incidence and severity), hypoglycemic episodes, body weight, laboratory analysis, and physical examination after 6 months for any side effects due to treatment.

2.7. Statistical analysis

An intent-to-treat analysis was performed for all participants, and results are expressed as means ± standard deviation. Paired