Efficacy of Chinese Herbal Medicine Compared with Metformin for Glucose Regulation and Cardiovascular Risk Factors in Patients with Type 2 Diabetes with Dyslipidaemia: A Multicenter, Randomised Clinical Trial

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Abstract

Background: Previous studies have showed that traditional Chinese medicine can regulate glycaemia, bodyweight, lipids, and blood pressure in populations with various different cardiovascular risk factors. Yet no studies have established the benefits of traditional Chinese medicine in patients with type 2 diabetes with dyslipidaemia and abdominal obesity. We aimed to assess the efficacy and safety of the Jiangtangtiaozhi decoction (known as JTTZF), a Chinese herbal medicine, on glycaemia, lipids, and weight variables, compared with metformin.

Methods: We did a randomised, multicenter, clinical trial in nine research centres in China. Adult patients (aged 18-70 years old) with type 2 diabetes and dyslipidaemia (defined as triglyceride 1.70-5.65 mmol/L^{-1}) inadequately controlled by diet and exercise were enrolled. Patients were randomly allocated (1:1) via a computer-generated randomisation sequence to receive JTTZF (30g, twice per day) or metformin (0.25 g, three times a day) for 48 consecutive weeks. Patients were treated with gliclazide sustained-release tablets once per day when their HbA1c was more than 7% after 24 weeks. If their triglyceride was more than 5.65 mmol/L^{-1}, bezafibrate was given twice a day. Patients and clinicians were masked to group assignment. The primary endpoint was change from baseline to week 48 of mean HbA1c in each treatment group. Secondary endpoints included lipid concentrations (ie, triglyceride, total cholesterol, LDL, and HDL), waist circumference, bodyweight, and BMI. Analyses were done in the per-protocol population who complied with the protocol and had no violations. Percentages of patients that reached HbA1c targets (<7·0%) and lipid targets (triglyceride <1·7 mmol/L, total cholesterol <5·7 mmol/L) were also assessed. Ethical approval was granted by the Guang'anmen Hospital Medical Ethics Commission in Beijing, China. Informed patient consent was given by all participants. This study is registered with ClinicalTrials.gov, number NCT01471275.

Results: Between Nov 25, 2011, and Jun 27, 2013, we randomly assigned 450 patients to either JTTZF (n=225) or to metformin (n=225). 378 patients were included in the per-protocol analysis (201 patients in the JTTZF group and 177 patients in the metformin group). At week 48, JTTZF reduced mean HbA1c to 7.30% (SD 1.21, -0.94% from baseline) and metformin reduced mean HbA1c to 7.23% (SD 1.15, -1.00% from baseline; p=0.55 for difference between groups). 46% of patients attained the HbA1c goal in the JTTZF group and 41% in the metformin group. Compared with metformin, JTTZF did not significantly reduce mean concentrations of triglycerides (-0.87 mmol/L, SD 2.73 in the JTTZF group vs -0.53 mmol/L, 2.33 in the metformin group; p=0.19), total cholesterol (-0.53 mmol/L, 1.36 vs -0.39 mmol/L, 1.27; p=0.324), LDL (-0.45 mmol/L, 1.00 vs -0.33 mmol/L, 0.82; p=0.204), and HDL (-0.08 mmol/L, 0.43 vs -0.06 mmol/L, 0.27; p=0.54). More patients in the JTTZF than the metformin group reached targets for triglycerides (42% vs 28%, p=0.007) and total cholesterol (78% vs 69%, p=0.047). After 48 weeks, compared with metformin, JTTZF decreased mean waist circumference (-4.15 cm, SD 5.41 vs -2.95 cm, 5.70; p=0.036), bodyweight (-2.72 kg, SD 4.29 vs -1.75 kg, 4.31; p=0.029), and BMI (-0.99 kg/m^2, SD 1.55 vs -0.62 kg/m^2, SD 1.59; p=0.021). Serious adverse events were reported in four (2%) of 225 patients in the JTTZF group and in six (3%) of 225 patients in the metformin group. No severe hypoglycaemia was reported in either group.

Conclusions: JTTZF showed improvements in several cardiovascular risk factors compared with metformin. JTTZF might be a promising alternative treatment for patients with type 2 diabetes.

Trial registration Clinicaltrials.gov Identifier: NCT01471275

Background

Type 2 diabetes is a complex metabolic disease with multiple metabolic abnormalities. These abnormalities represent major risk factors for the development of cardiovascular disease (CVD)[1–4]. Reducing these risk factors for CVD in patients with type 2 diabetes depends on effective management of not only the control of glycemia but also the modification of cardiovascular risk factors [5]. Serum lipid values are among the strongest predictors of CVD and lowering lipids has been shown to reduce cardiovascular events in patients with diabetes [6–9]. As lipids control is difficult to achieve in patients with diabetes, combination therapy is often required. However, some common antilipemic agents, such as statin, may be associated with muscle complaints, increased liver or muscle enzymes or various neurological symptoms [10]. As an independent risk factor of CVD, overweight could lead to increased risk of cardiovascular events [11, 12]. Obesity is often seen in diabetic patients [13], but sulfonylureas and insulin may increase the body weight, which limits the medication of diabetic patients with obesity. And the weight-loss drug itself has the adverse effect of anorexia, fatigue and heart valve damage etc [14]. Thus, agents that can provide glucose lowering, together with beneficial effects on lipids and other cardiovascular risk factors, are needed for the treatment of patients with type 2 diabetes.

Traditional Chinese medicine (TCM) has long history of more than two thousand years in treating diabetes mellitus [15]. Our research group has demonstrated that TCM could effectively reduce hyperglycemia in patients with type 2 diabetes [16–18]. In addition, TCM could offer particular benefits on weight loss, lipids and blood pressure lowering [19–21]. However, those studies were conducted in heterogeneous populations on different cardiovascular risk factors separately. It is important to understand the benefits of TCM with pharmacological and clinical profiles on diabetes patients accompanied by other risk factors. The purpose of this study was to evaluate the efficacy and safety of TCM on glycemic, lipids and weight parameters, compare to that of metformin. This information should be useful on TCM that have significant potential in the future management of the condition.

Methods

Study design and setting

The study was a 52-week, multicentered, randomized and positive-controlled clinical trial which included a 4-week run-in period. Between Nov 25, 2011, and Jun 27, 2013, a total of 450 subjects were enrolled from 9 clinical research sites after run-in period (Fig. 1A). Informed consent was obtained from every study subject. The research protocol was approved by the Guang'anmen Hospital Medical Ethics Commission in Beijing, China. The clinical trial registration number of this study is NCT01471275

(www.ClinicalTrials.gov). The study was conducted in accordance with the Declaration of Helsinki guidelines on good clinical practices [22].

Patients

Inclusion criteria. The early type 2 diabetic status of these patients was confirmed according to the diagnosis standard [23]. Subjects, 18-70 years old, had a waistline male ≥ 90cm, female ≥ 80cm. After the initial screening, subjects entered a 4-week run-in period with diet control and programmed daily exercise. Then, those subjects with sustained HbA1c≥7.0% and FPG level between 7.0 and 13.9 mmol/L, or 2-h postprandial plasma glucose (2-h PG) ≥11.1 mmol/L, triglyceride (TG) between 1.7 and 5.65 mmol/L were enrolled. A consent form was signed by all subjects prior to enrollment.

Exclusion criteria. Any patient with the following conditions were excluded from participation of the trial: those who had used insulin therapy; had been treated for diabetes for over 3 months by conventional medications, physical therapy, psychological therapy, herbal medicines or dietary supplements; had been treated with antidiabetic and lipid-lowering drugs 1 month prior to screening; had complications of diabetes; had serious heart, lung, liver, kidney, brain related primary diseases or complications; had uncontrolled hypertension (SBP ≥ 160 mmHg and/or DBP ≥100 mmHg); had diabetic ketoacidosis or serious infections within 1 month; had mental disorders; pregnant females, or those planning to be pregnant; breast feeding; allergic to Chinese herbal medicines; participating in other clinical trials within 1 month prior to screening; alcoholism, taking antipsychotic agents or substance abuse or dependence; had factors that may affect trial execution based on investigators' judgment, such as changeable working and living environments that may lead to withdrawal from the trial; had unstable antihypertension effects during drug administration; or taking weight-loss medicines; had hepatic and renal dysfunctions [aspartate aminotransferase (AST), alanine aminotransferase (ALT) more than two times higher than the normal upper limit and serum creatinine above normal upper limit]; insensitive to hypoglycemia.

Withdrawal criteria. Patients who met the following criteria were asked to withdraw from the trial: those who experienced serious diabetic complications (such as diabetic ketoacidosis, hyperosmolar nonketotic syndrome, lactic acidosis, hypoglycemic coma); had poor compliance, with test medication use less than 80% of or more than 120% of the prescribed dose; had violated protocol, such as taking another oral hypoglycemic agent.

Intervention

Study Medication. JTTZF (manufactured by Tianjiang Pharmaceutical, Jiangyin, China) and metformin (by the Lilinghengtai Pharmaceutical, Beijing, China; batch number: 110508) were used. The JTTZF, prepared in formula granules, consists of eight Chinese medicinal herbs, including rhizoma anemarrhenae (batch number: 1110318), monascus (batch number: 1209335), aloe (batch number: 1110316), coptis chinensis (batch number: 1110317), balsam pear (batch number: 1110322), salvia miltiorrhiza (batch number: 1110323), schisandra chinensis (batch number: 1110320) and rhizoma

zingiberis (batch number: 1110319). The manufacturer was not involved in the design and analysis of this study.

The subjects were randomly allocated to receive either JTTZF or metformin for 48 consecutive weeks. For JTTZF group, each subject ingested 30 g with warm water, two times daily with meals. For metformin group, subjects ingested 0.25 g with warm water, three times daily after each meal.

Chemical Analysis of JTTZF. The formulation of JTTZF was prepared according to the 2005 Edition of Chinese Pharmacopoeia. The chemical composition of JTTZF was measured by using an ultra-performance liquid chromatography/mass (UPLC/MS) method. An example chromatographic fingerprint is shown in Figure 2. Chemical structures of eight major compounds (mangiferin, coptisine chloride, jatrorrhizine, lithospermic acid B, aloin, berberine, palmatine, lovastatin) in the finished dosage are also shown. These compounds were also used as the quality control markers in the JTTZF formulation.

Adjustments of Drugs and Dosages. The medication remained stable during the first 24-week trial period for all the subjects. If HbA1c was over 7% at 24-week, subjects should add gliclazide sustained-release tablets once per day; additionally, if their TG was over 5.65 mmol/L, add bezafibrate twice per day.

Co-administration with Other Drugs. Subjects were not allowed to take weight-loss medicines and other antidiabetic drugs throughout the study. For those subjects who had to take other drugs related to other diseases during the trial period, the dosage of these medications should be recorded in combination therapy table.

Test Medication Delivery. There were thirteen visits during the trial period in every 4weeks. During each visit, physical and biochemical tests were performed based on the trial design. Each patient was given a 4-week drug supply. Unused testing medications for the period before each visit were re-collected and counted for compliance check.

Randomization

A stratified, block randomization method was conducted by the study center. Study drugs were packed and numbered according to the random coding form and randomly allocated to each research site using concealed opaque envelopes. These envelopes and case report forms were not collected until the end of the trial. Study drugs were provided based on the assigned numbers, which were determined according to the visit sequence and study drug number sequence, and remained unchanged throughout the trial. The only basis of drug distribution was the unique drug number. Independent statisticians performed the data analysis.

2.5 Endpoints and assessment

During this 48-week period, subjects were assessed at each 4weeks. In each session, subjects were asked if there were any adverse events. All subjects received a symptom assessment, physical examination, and the compliance of the test drug administration. FPG, waist circumstance, body weight and BMI were

monitored. The HbA1c, 2-h postprandial PG (2-h PG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), fasting insulin were measured at week 0, 12, 24, 36 and 48.

Primary Endpoints. The primary endpoints were change in HbA1c from baseline to 48 weeks and proportion of patients achieving HbA1c□7.0, □6.5, and □6.0 at week 48. The HbA1c level was measured in a central laboratory (Guang'anmen Hospital, China Academy of Chinese Medical Sciences) using an ADAMSPMALCHA-8160 automated HbA1c analyzer (Japan).

Secondary Endpoints. The secondary endpoints were changes in the FPG, 2hPG, fasting insulin, lipids, waist circumstance and the body weight between the two groups. Fingertip blood was collected at each visit and FPG was measured using a blood glucose analyzer (ACCU-CHEK Active meter, Roche Diagnostics, Indianapolis, USA). The 2hPG level was measured at each 12 weeks (Olympus AU2700 Analyzer, Olympus Life and Material Science, Europa GmbH, Hamburg, Germany). An immunonephelometry method was used to measure lipids (COBAS Integra 400 Plus System, Roche Diagnostics Ltd. Basel, Switzerland). Immunoreactive insulin was measured by electrochemiluminescence immuno assay (Roche Diagnostics Ltd, Basel, Switzerland), and the homeostatic model assessment (HOMA) was performed to quantify insulin resistance (HOMA-IR) and β-cell function (HOMA-β). Percentages of patients achieving TG <1·7 mmol/L, TC <5·7 mmol/L, and body mass index (BMI) were also evaluated.

Safety Evaluation. Vital signs were collected, hepatic functions (ALT and AST) and renal function (serum creatinine and BUN) were measured at each 4 weeks. Routine blood tests, urine tests, stool tests (including occult blood test) and ECG were determined at week 0, 12, 24, 36 and 48. Adverse events were recorded immediately after reporting.

Statistical Analysis

Data entry was completed twice by two staff members using Epidata software. Numerical variables were summarized as means and standard deviations (SD), mean differences and proportions of change between baseline and the 48-week follow-ups. For between-group comparison, *t*-test or Wilcoxon rank sum test was performed. When examining the central effects and covariates, the analysis of covariance was used. χ2 test or Fisher's exact test were used to compare the incidence of adverse events between the two groups. The level of statistical significance was set at $P < 0.05$.

Results

Patient characteristics

A total of 450 patients were randomized to JTTZF and metformin. Demographic and baseline characteristics were balanced between treatment groups (Table 1). At entry into the study, the median age of participants was 52.1 years, the mean HbA1c was 8.26%, the mean TG was 3.28mmol/L, and the

mean waist circumstance was 97.28 cm. A total of 45 (10%) patients discontinued the study. Disposition throughout the 48-week study period is shown in Fig. 1B.

Table 1
Baseline characteristics and demographics of randomized patients

	JTTZ Group (n = 225)	Metformin Group (n = 225)	P values
Demographics			
Age (years)	51.98 ± 9.03	52.22 ± 8.56	0.235
Sex (male/female)	108/117	105/120	0.584
PMH (no/yes)	81/144	94/131	0.515
Current medications (no/yes)	133/92	146/79	0.414
Physical examinations			
Systolic BP (mmHg)	129.26 ± 12.59	130.97 ± 11.78	0.486
Diastolic BP (mmHg)	82.81 ± 8.01	82.71 ± 8.03	0.658
Heart rate (beat/min)	74.64 ± 8.39	73.39 ± 7.78	0.899
Height (cm)	165.62 ± 8.29	165.11 ± 8.59	0.995
Weight (kg)	77.58 ± 12.07	76.42 ± 12.23	0.775
BMI (kg/m^2)	28.22 ± 3.32	27.95 ± 3.31	0.701
Waist circumference (cm)	97.19 ± 8.06	97.37 ± 9.16	0.646
Hip circumference (cm)	104.98 ± 7.17	105.14 ± 7.39	0.556
Laboratory data			
HbA1c (%)	8.24 ± 1.33	8.27 ± 1.35	0.813
FPG (mmol/L)	9.59 ± 2.59	9.65 ± 2.47	0.127
2-h PG (mmol/L)	16.80 ± 4.92	17.16 ± 4.83	0.425
Fasting insulin (pmol/L)	105.11 ± 99.20	101.83 ± 126.00	0.663
TG (mmol/l)	3.40 ± 2.77	3.18 ± 2.08	0.595
TC (mmol/l)	5.46 ± 1.23	5.53 ± 1.37	0.186
HDL-C (mmol/l)	1.25 ± 0.38	1.22 ± 0.28	0.639
LDL-C (mmol/l)	3.22 ± 0.96	3.26 ± 0.94	0.766
Data presented as mean ± S.D or n(%)			

Efficacy

JTTZF and metformin both lowered HbA1c levels from baseline (P<0.01, both comparisons). The reduction in HbA1c was similar in both groups (P = 0.643, Fig. 3A). Figure 3B shows HbA1c values at baseline and over time up to 48 weeks. At week 48, mean HbA1c levels were 7.30% (-0.94% from baseline) with JTTZF and 7.23% with metformin (-1.00% from baseline; P = 0.545, JTTZF vs. metformin). At 48 weeks, the percentage of patients attaining the HbA1c goal of <7.0% was 45.77% treated with JTTZF and 41.24% with metformin, respectively (difference 4.53%, 95% CI -5.47 to 14.53). At the same time point, 23.27%/7.92% and 24.02%/10.61% of patients receiving JTTZF and metformin achieved HbA1c target of <6.5%/6.0% (P = 0.479/P = 0.232; Fig. 3C).

Both JTTZF and metformin lowered FPG and 2-h PG levels from baseline (P<0.01, both comparisons). At week 48, the mean FPG changes from baseline were − 1.23 ± 2.78 mmol/L for JTTZF, and − 1.32 ± 2.30 mmol/L for metformin (P = 0.719; Fig. 3D). Progressive decreases in FPG were observed in both groups from baseline through week 20 and remained generally stable thereafter. The mean 2-h PG changes from baseline to 48 weeks were − 3.05 ± 5.00 mmol/L for JTTZF, and − 3.78 ± 4.60 mmol/L for metformin (P = 0.167; Fig. 3E).

The mean change in FINS from baseline to 48 weeks was − 1.11 ± 8.21 pmol/L for JTTZF, and 16.38 ± 13.57 pmol/L for metformin (P = 0.281; Fig. 3F). The mean change in HOMA-β from baseline to 48 weeks was 0.35 ± 0.82 for JTTZF, and 0.47 ± 0.96 for metformin (P = 0.215; Fig. 3G). The mean change in HOMA-IR from baseline to 48 weeks was-0.06 ± 0.93 for JTTZF, and 0.04 ± 0.95 for metformin (P = 0.333; Fig. 3H). Both groups showed increases from baseline in the pancreatic β-cell function(P<0.01, both comparisons). Compared with metformin, JTTZF significantly increased HOMA-β after 24 weeks' intervention (3.92 ± 0.83 vs. 3.72 ± 0.87; P = 0.026).

Both of the groups lowered lipid levels from baseline (P<0.01, both comparisons). The mean change in TG from baseline to 48 weeks was − 0.87 ± 2.73 mmol/L for JTTZF, and − 0.53 ± 2.33 mmol/L for metformin (P = 0.191; Fig. 4A). The mean change in TC from baseline to 48 weeks was − 0.53 ± 1.36 mmol/L for JTTZF, and-0.39 ± 1.27 mmol/L for metformin (P = 0.324; Fig. 4B). The mean change in LDL from baseline to 48 weeks was-0.45 ± 1.00 mmol/L for JTTZF, and − 0.33 ± 0.82 mmol/L for metformin (P = 0.204; Fig. 4C). The mean change in HDL from baseline to 48 weeks was − 0.08 ± 0.43 mmol/L for JTTZF, and − 0.06 ± 0.27 mmol/L for metformin (P = 0.541; Fig. 4D). Compared with metformin, JTTZF significantly lowered TC after 36 week's intervention (4.99 ± 1.11 vs. 5.25 ± 1.00 mmol/L; P = 0.020), LDL (2.82 ± 0.76 vs. 3.02 ± 0.75 mmol/L; P = 0.012) and lowered LDL after 48 weeks' intervention (2.78 ± 0.83 vs. 2.97 ± 0.74 mmol/L; P = 0.024). The proportions of patients achieving TG (TG<1.7mmol/L; 41.79 vs 28.25%; difference13.54%, 95% CI 4.03 to 23.05) and TC (TC<5.7mmol/L; 78.11 vs 68.93%; difference 9.18%, 95% CI 0.29 to 18.08) target in JTTZF were higher in metformin. Progressive decreases in TG, TC and LDL were seen with JTTZF from baseline through week 48. No notable changes in HDL were observed in both groups. Compared with baseline, SBP decreased − 4.30 ± 0.85 mmol/L and − 3.80 ± 1.06 mmol/L in JTTZF group and metformin respectively after 48 weeks' intervention (P = 0.994; Fig. 4F), DBP decreased − 2.72 ± 0.57 mmol/L and − 1.60 ± 0.64 mmol/L in JTTZF group and metformin group (P = 0.935; Fig. 4G). During the follow-up, the blood pressure continuously decreased in both groups.

Compared with metformin, JTTZF more effectively decreased SBP (-1.36 ± 0.30 vs. -0.04 ± 0.20; P = 0.047) and DBP (-0.88 ± 0.56 vs. 2.19 ± 0.63; P = 0.000) after 12 week's follow-up, and decreased SBP (-3.22 ± 0.50 vs. -2.21 ± 0.40; P = 0.035) after 36 weeks' follow-up.

JTTZF and metformin both lowered waist circumstance, body weight and BMI from baseline (P<0.01, all comparisons). The mean change in body weight from baseline to 48 weeks was − 2.72 ± 4.29 kg for JTTZF, and − 1.75 ± 4.31 kg for metformin (P = 0.029, Fig. 5A). The mean change in BMI from baseline to 48 weeks was − 0.99 ± 1.55 kg/m^2 for JTTZF, and − 0.62 ± 1.59 kg/m^2 for metformin (P = 0.021, Fig. 5B). The mean change in waist circumstance from baseline to 48 weeks was − 4.15 ± 5.41 cm for JTTZF, and − 2.95 ± 5.70 cm for metformin (P = 0.036, Fig. 5C). Body weight and BMI decreased with both groups from baseline through week 24 and remained generally stable thereafter. Progressive decreases in waist circumstance were observed with JTTZF from baseline through week 48, while progressive decreases were observed with metformin from baseline through week 36, followed by a small increase thereafter.

Safety

The overall incidence of adverse events during the study was similar in the JTTZF and metformin groups (Table 2). Serious adverse events were reported for 1.8% (n = 4) of patients in the JTTZF group and 2.7% (n = 6) of patients in the metformin group. Adverse events observed in ≥ 5% of patients in the JTTZF and metformin groups were nasopharyngitis (15.1 vs. 12.0%) and urinary tract infection (9.3% vs. 6.7%). The majority of the adverse events were mild to moderate in severity. Adverse events resulted in study discontinuation in 1.3% (n = 3) and 1.3% (n = 3) patients treated with JTTZF and with metformin, respectively. A total of 8 patients (JTTZF, 2.2%; metformin, 1.3%) experienced hypoglycemia. During the follow-up, 5 patients experienced 8 times hypoglycemia. (2.2% in JTTZF, 1.3% in metformin). In the first 24 weeks' follow-up, 1 and 2 patients experienced hypoglycemia in JTTZF and metformin group respectively. After 24 weeks' follow-up, each group has 1 hypoglycemia event. 1 patient in JTTZF group experienced 4 times hypoglycemia, all of which happened after 24 weeks' follow-up and added Gliclazide in medication. The mean 1-year adjusted rates of total hypoglycemia were 1.10 and 0.44 events/patient year for JTTZF and metformin. There were no events of severe hypoglycemia in both groups and no patients discontinued due to hypoglycemia. Increases in glutamate pyruvate transaminase were similar for both groups (JTTZF, 2.2%; metformin, 3.56%). Increases in urine protein were observed with two patients and one patient had positive urine ketone in metformin group. No differences were observed for change in heart rate in both groups.

Table 2—Summary of AEs		
	JTTZ Group	Metformin Group
	(*n* = 225)	(*n* = 225)
AEs(patients with ≥1 event)	147(32)	122(26)
Drug-related[#] AEs(patients with ≥1 event)	24(4)	17(1)
Serious AEs, n(%)	4(1.8)	6(2.7)
Discontinuation due to AE, n(%)	3(1)	3(1)
Deaths	0	0
AEs with frequency of ≥5% in any group		
Infections		
Nasopharyngitis, n(%)	34(15.1)	27(12.0)
UTI, n(%)	21(9.3)	15(6.7)
Confirmed hypoglycemia, n(%)*	5(2.2)	3(1.3)
Events requiring assistance	0	0
Safety parameters		
SBP(mmHg)	-4.40 ± 0.89	-3.53 ± 0.94
DBP(mmHg)	-2.70 ± 0.64	-1.76 ± 0.68
Heart rate (beats/min)	-0.50 ± 0.74	1.02 ± 0.71
Data are n(%) and mean ± SE.[#]As assessed by the investigator. *Plasma glucose≤70mg/dl. UTI, urinary tract infection.		

Discussion

The current study is the first and the longest to compare the effect of TCM on glycemic control and lipid abnormalities in individuals with newly diagnosed type 2 diabetes. Results of this 48-week, randomized trial showed that JTTZF significantly lowered HbA1c levels similar to metformin therapy (P = 0.695), and improved the CVD risk factors (Blood lipid, body weight, waist circumference and blood pressure). A sustained decrease in HbA1c was observed during 48 weeks with both groups, and this pattern suggests that durable glycemic improvements on disease occurred. Similar proportion of patients achieving target HbA1c levels was observed with JTTZF compared with metformin (at week 48) for each of the HbA1c goals evaluated (<7.0,<6.5, and <6.0%; P ≥ 0.05 vs. metformin). The reduction in blood glucose levels with JTTZF was generally consistent with that observed in previous studies [10, 11], which provides additional support for diabetes treated by TCM. In addition to improvements in glycemic parameters, significant

improvement in HOMA-β at 24-week and reduction in level of HOMA-IR at 48-week were observed in the JTTZF group compared with metformin, suggesting ameliorated insulin resistance and improved insulin processing efficiency with interventions.

Dyslipidemia is a common comorbidity in patients with type 2 diabetes and increases the risk of cardiovascular complication [24, 25]. Compared with metformin, JTTZF resulted in a statistically significant improvement in the proportions of patients achieving target TG and TC levels, and a statistically larger reduction in LDL level at week 48 ($P<0.05$). A sustained decrease in TG, TC and LDL was observed during 48 weeks with both groups, and JTTZF could provide a greater reduction than metformin in progression. It should be noted that the maximal reduction in lipids of JTTZF is at week 48. These findings suggest that JTTZF may be an option for longer term treatment of patients with type 2 diabetes. Both groups reduced SBP and DBP over 48 weeks, with no notable changes in heart rate. Although no significant differences were observed in BP between the two groups, changes from baseline in the mean of values were greater with JTTZF relative to metformin. Decreases in lipids and BP were associated with lowered the risk of cardiovascular disease [26–28], suggesting that the risk of cardiovascular complications in the JTTZF group may be low. Abdominal obesity is associated with increased insulin resistance, incidence of fatty liver and β-cell failure [29–30], as well as a strong CVD risk factor [31]. It has been widely observed in patients with type 2 diabetes [32–33]. In our study, JTTZF resulted in statistically significant reductions of waist circumstance compared to metformin, suggesting that JTTZF may play a role in protection of metabolic abnormalities associated with abdominal obesity.

Previous researches focused on glucose lowering may accompanied certain degrees of body-weight gain [34–35], lipid [36–37] and blood pressure [38–39] increasing. Compared to these conventional interventions, this research proved that TCM could comprehensively manage the glucose control in T2DM with abnormal metabolism, and improve the CVD risk factors. The long-term efficacy of JTTZF needs further observation. JTTZF mainly consists of rhizoma anemarrhenae, monascus, aloe, coptis chinensis, balsam pear, and salvia miltiorrhiza, schisandra chinensis and rhizoma zingiberis, and the HPLC analysis has detected a number of compounds shown in Fig. 2. Previous studies have demonstrated that coptis chinensis balsam pear and rhizoma anemarrhenae can effectively control diabetes by lowering the blood glucose level, reducing lipids, body weight and BMI, and increasing β-cell function [40–42]. Similarly, monascus has been used to regulate serum lipids in dyslipidemia patients[43–45]. Emodin, one of the components in the weight loss dietary supplements, has been shown to lead to weight reduction in study subjects.

JTTZF was generally well tolerated over 48 weeks, with better compliance and lower frequencies of ineffective therapies led to discontinuation than metformin treatment. Overall incidences of AEs were similar for both groups, these were generally assessed by the investigators as mild to moderate in intensity, and led to few discontinuations. Hypoglycemia is associated with increased morbidity and mortality, reduced quality of life, and poor glycemic control in patients with diabetes [46–47], thus the risk of hypoglycemia is an important consideration for the choice. Both groups are associated with a low risk of hypoglycemia. During follow-up, 2 patients experienced 5 times hypoglycemia in JTTZF group, and 3

patients experienced 3 times hypoglycemia in metformin group. 1 patient in JTTZF group experienced 4 times hypoglycemia, all of which happened after 24 weeks' follow-up and added Gliclazide in medication. These indicated that compared with metformin, JTTZF did not increase the risk of hypoglycemia. No hypoglycemic events required medical assistance in both groups. A similar proportion of patients experienced documented hypoglycemia episodes in both groups.

Limitations

Although results of present study showed that JTTZF improved HbA1c values and lipid parameters, we must consider its limitations. It is not a double-blind study because of different treatments, however, this is unlikely to have impacted the main trial conclusions, which are mostly based on fairly objective outcome measure and investigator sites were blinded to the efficacy variable data. The excess abdominal adiposity seems to be a key determinant linking to obesity and its associated complications [48], however, little is known about the regulation on abdominal adiposity by TCM. It is valuable to understand the effects changed by TCM in the future study. The conduct of analyses at 48 weeks provides estimates of medium-term effects, the long-term impact remains to be established. The completeness of follow-up for the main efficacy outcomes would be meaningful, and the long-term trials should provide more insight into the potential benefits of TCM on cardiovascular outcomes. The mechanisms of therapeutic components in JTTZF may be further explored in the future researches.

Conclusions

In summary, treatment with JTTZF provided durable decreases in blood glucose and sustained lipids reduction on diabetes patients with dyslipidemia. Compared with metformin, JTTZF resulted in a better regulation in lipids level, and a greater decrease in body weight and waist circumstance. Besides, JTTZF could improve insulin resistance more significantly compared with metformin. The use of TCM supports the potential clinical benefits and may be particularly useful for long-term treatment of type 2 diabetes patients accompanied with metabolic disorders, in which to decrease the risk of future cardiovascular events.

Abbreviations

CVD (cardiovascular disease)

TCM (Traditional Chinese medicine)

AST (aspartate aminotransferase)

ALT (alanine aminotransferase)

JTTZF (Jiangtangtiaozhi decoction)

2-h PG (2-h postprandial PG)

TG (triglycerides)

TC (total cholesterol)

HDL (high-density lipoprotein)

LDL (low-density lipoprotein)

UPLC/MS (ultra-performance liquid chromatography/mass)

SD (standard deviations)

Declarations

Ethics approval and consent to participate

The study will be carried out under the Declaration of Helsinki and related clinical trial regulations in China. All aspects of the study should be approved by the ethic committee before conduction of the study. A thorough introduction of the study including purpose, procedure and possible risks ought to inform every patient. Informed consent will be written prior to initiation and preserved in the study record.

Consent for publication

All authors have intellectual property over the data and the submitted manuscript and read and approved the submitted version.

Availability of data and materials

All data analyzed during this study are included in this published article or as supplementary information files.

Competing interests

The authors declare no competing interests.

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Authors' contributions

FL and XT designed, coordinated, and supervised the study. FL, JT, DJ, CP, HG, JZ, LL, SW, MG, YH, WP, XY, LX, SW, and XT did the study. SL processed the data and did the statistical analyses. All authors approved the final version of the manuscript.

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Figures

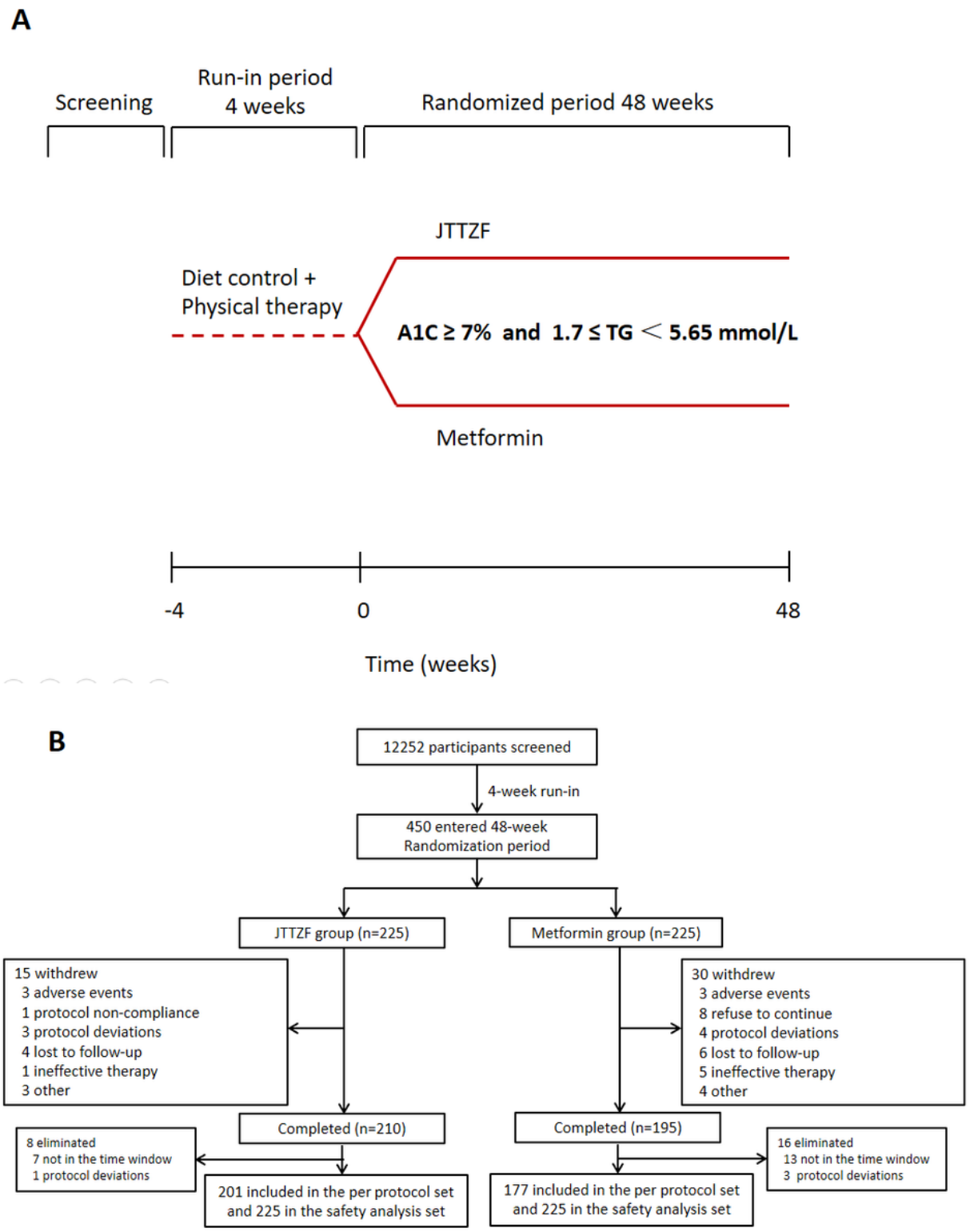

Figure 1

Study design (A) and flow diagram of participant screening and randomization (B).

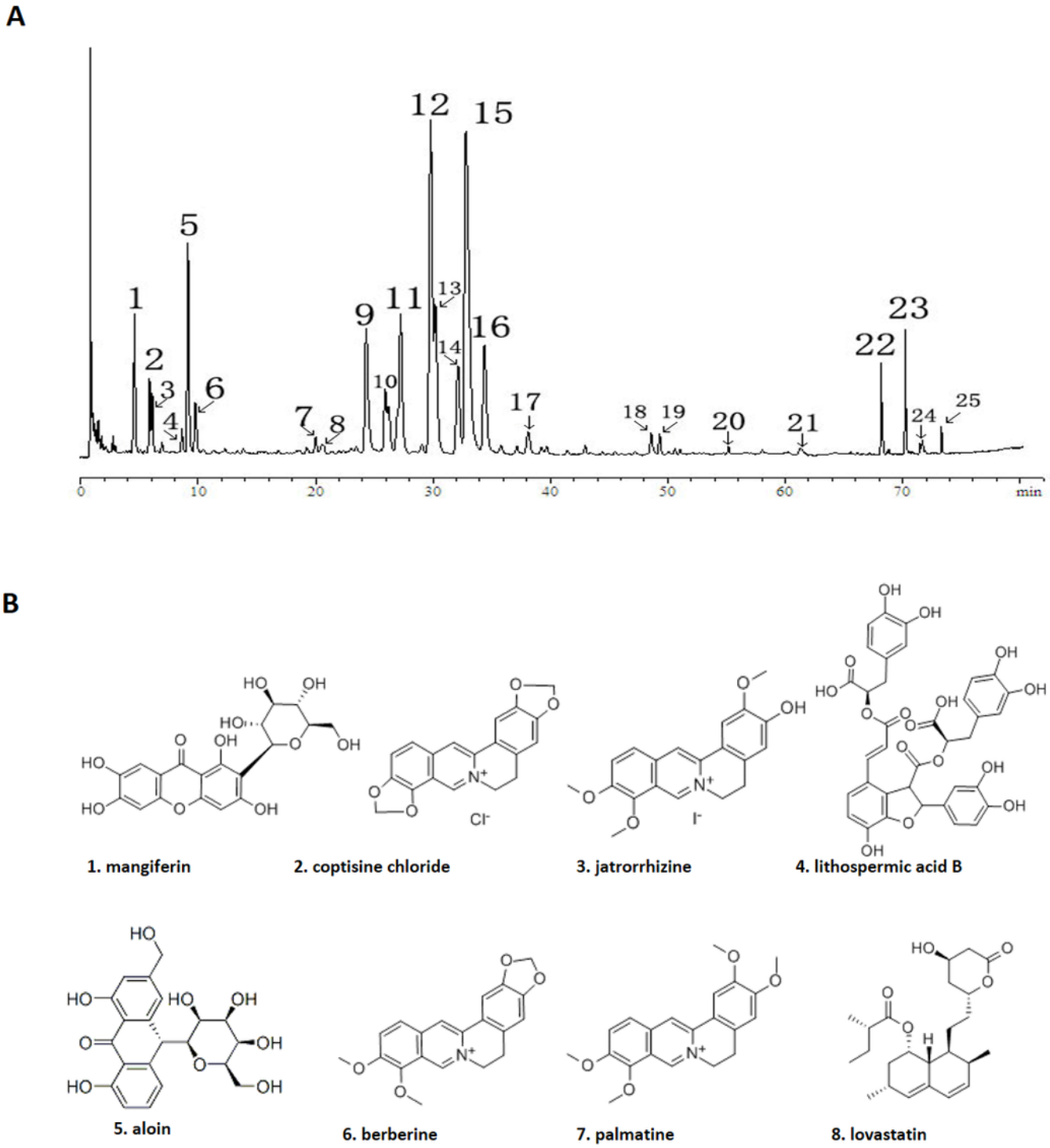

Figure 2

Representative high-performance liquid chromatography (HPLC) chromatogram of the water extract of Jiang-Tang-Tiao-Zhi-Fang (JTTZF). 8 compounds were identified from the JTTZF: mangiferin (peak 5), coptisine chloride (peak 9), jatrorrhizine (peak 11), lithospermic acid B (peak 12), aloin (peak 13), berberine (peak 15), palmatine (peak 16), and lovastatin (peak 23).

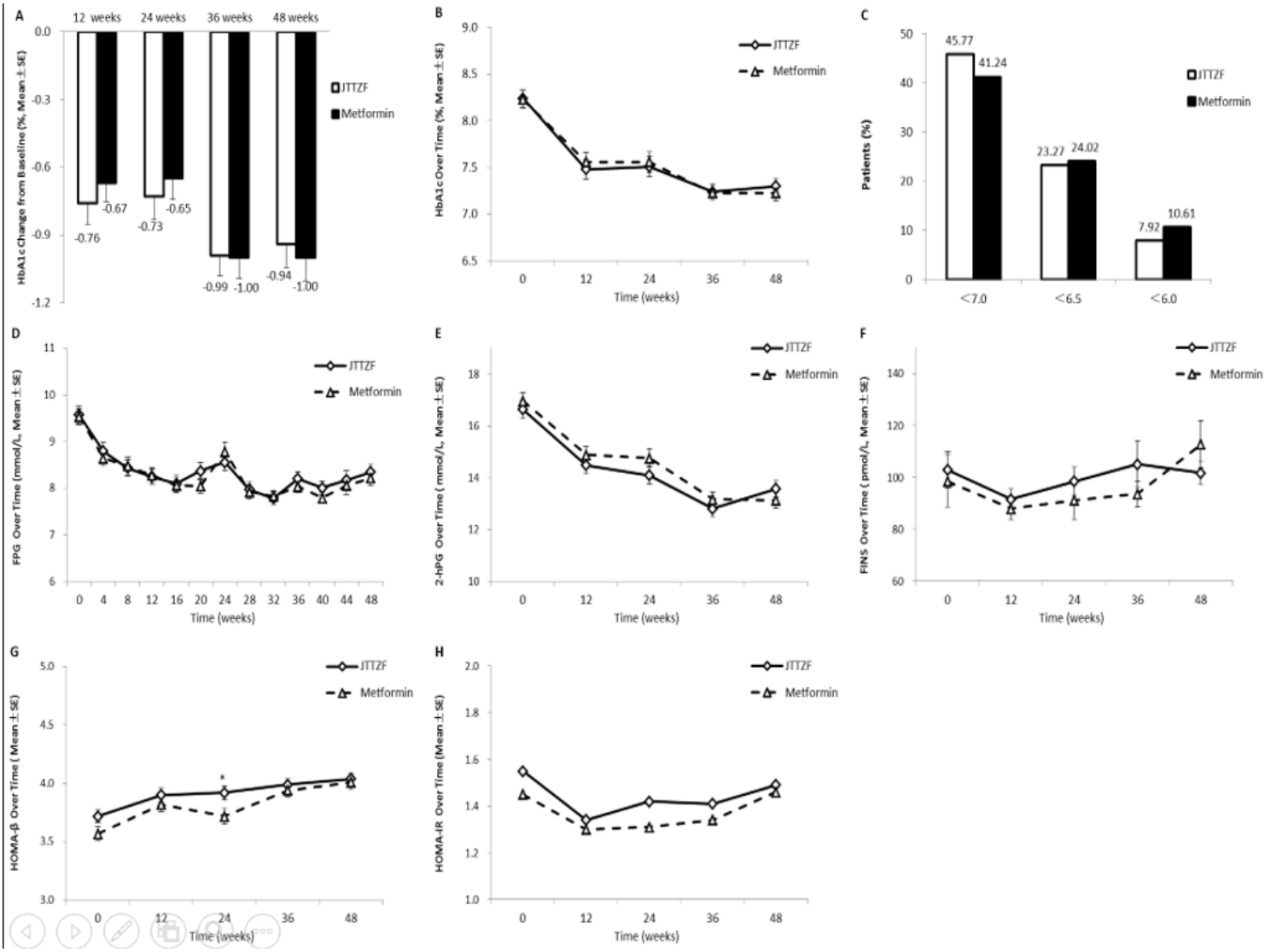

Figure 3

Changes in glucose levels in the JTTZF group and metformin group. A: Changes in HbA1c from baseline over time. B: Changes in HbA1c over time. C: Percentage of patients achieving HbA1c targets. D: Change in FPG over time. E: Change in 2-hPG over time. F: Change in FINS over time. G: Change in HOMA-β over time. H: Change in HOMA-IR over time. Data presented as mean ± S.E. *P< 0.05. **P < 0.01.

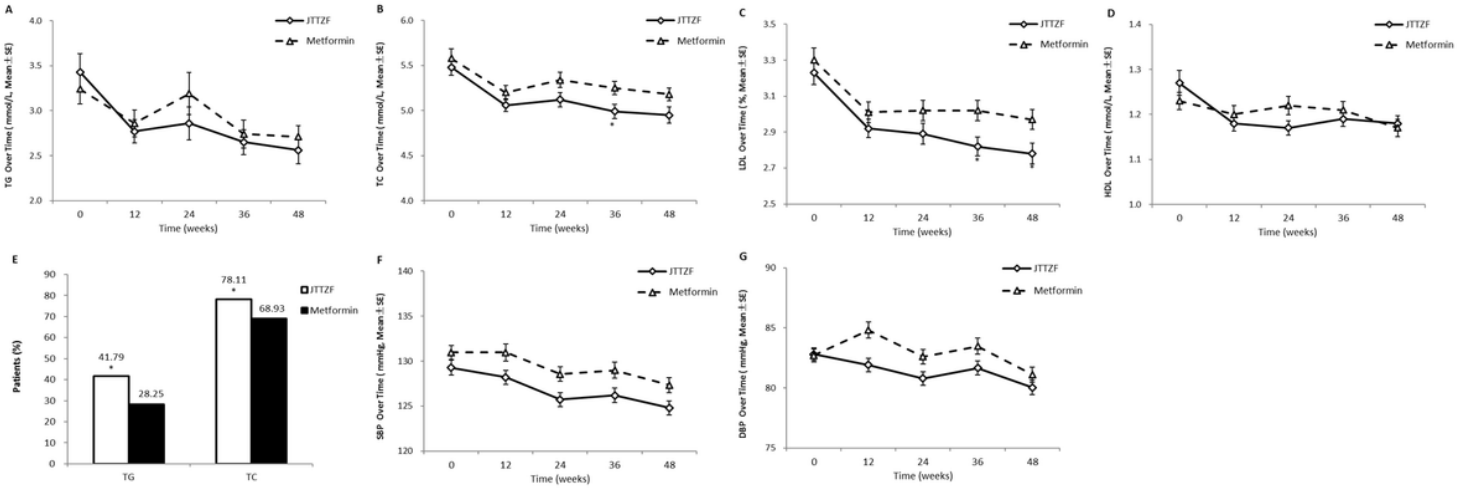

Figure 4

Changes in lipids levels in the JTTZF group and metformin group. A: Changes in TG over time. B: Changes in TC over time. C: Changes in LDL over time. D: Changes in HDL over time. E: Percentage of patients achieving TG and TC targets. F: Changes in SBP over time. G: Changes in DBP over time. Data presented as mean ± S.E. *P< 0.05.

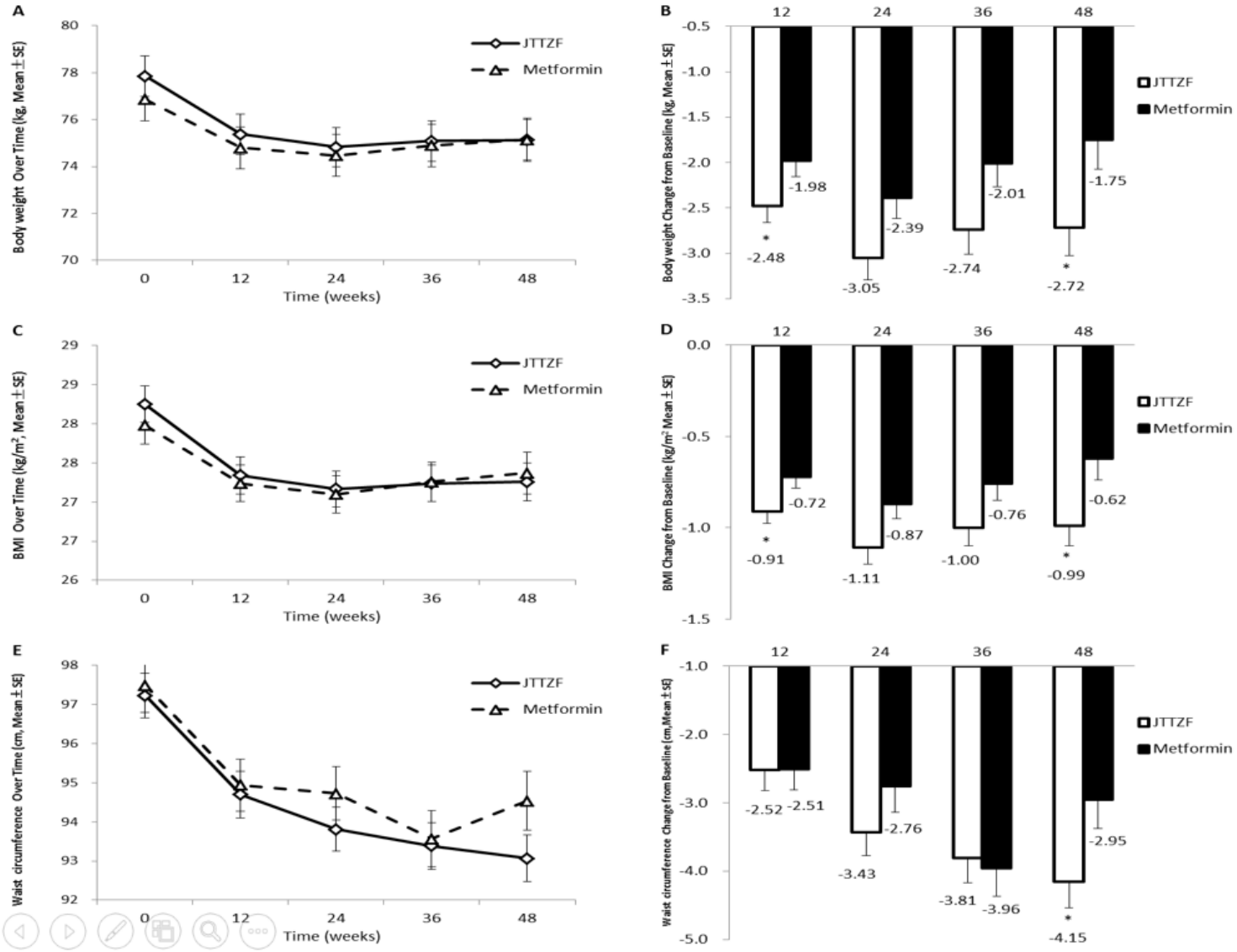

Figure 5

Changes in waist circumference, body weight and BMI in the JTTZF group and metformin group. A: Changes in body weight over time. B: Changes in body weight from baseline over time. C: Changes in BMI over time. D: Changes in BMI from baseline over time. E: Changes in waist circumference over time. F: Changes in waist circumference from baseline over time. Data presented as mean ± S.E. *P< 0.05.

Supplementary Files

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