Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine

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Context: Berberine, a natural plant alkaloid, is usually used as an antibiotic drug. The potential glucose-lowering effect of berberine was noted when it was used for diarrhea in diabetic patients. *In vitro* and *in vivo* studies have then showed its effects on hyperglycemia and dyslipidemia.

Objective: The objective of the study was to evaluate the efficacy and safety of berberine in the treatment of type 2 diabetic patients with dyslipidemia.

Design: One hundred sixteen patients with type 2 diabetes and dyslipidemia were randomly allocated to receive berberine (1.0 g daily) and the placebo for 3 months. The primary outcomes were changes in plasma glucose and serum lipid concentrations. Glucose disposal rate (GDR) was measured using a hyperinsulinemic euglycemic clamp to assess insulin sensitivity.

Results: In the berberine group, fasting and postload plasma glucose decreased from 7.0 $\pm$ 0.8 to 5.6 $\pm$ 0.9 and from 12.0 $\pm$ 2.7 to 8.9 $\pm$ 2.8 mM/liter, HbA1c from 7.5 $\pm$ 1.0% to 6.6 $\pm$ 0.7%, triglyceride from 2.51 $\pm$ 2.04 to 1.61 $\pm$ 1.10 mM/liter, total cholesterol from 5.31 $\pm$ 0.98 to 4.35 $\pm$ 0.96 mM/liter, and low-density lipoprotein-cholesterol from 3.23 $\pm$ 0.81 to 2.55 $\pm$ 0.77 mM/liter, with all parameters differing from placebo significantly ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P = 0.001$, $P < 0.0001$, and $P < 0.0001$, respectively). The glucose disposal rate was increased after berberine treatment ($P = 0.037$), although no significant change was found between berberine and placebo groups ($P = 0.063$). Mild to moderate constipation was observed in five participants in the berberine group.

Conclusions: Berberine is effective and safe in the treatment of type 2 diabetes and dyslipidemia. (***J Clin Endocrinol Metab* 93: 2559–2565, 2008**)

The prevalence of diabetes is dramatically increasing throughout the world as well as in China with a 4.3% prevalence among 20- to 79-yr-old persons in 2007, estimated to increase to 5.6% in 2025 (1). Hyperglycemia and dyslipidemia are two major components of the metabolic dysregulation of type 2 diabetes and are crucial risk factors for cardiovascular diseases (2, 3).

Berberine, a natural plant alkaloid (Fig. 1) isolated from the Chinese herb, *Coptis chinensis* (Huanglian), is commonly used for diarrhea, and a potential glucose-lowering effect has been noted (4). *In vitro* and *in vivo* studies subsequently showed that berberine has potentially beneficial effects in the treatment of diabetes and obesity. Berberine can reduce body weight and cause a significant improvement in glucose tolerance in db/db mice and high-fat-fed Wistar rats (5). Berberine may increase glucose-stimulated insulin secretion and proliferation in Min6 cells (6) and inhibit α-glucosidase activities and reduce glucose

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Abbreviations: ANCOVA, Analysis of covariance; BMI, body mass index; c, cholesterol; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.

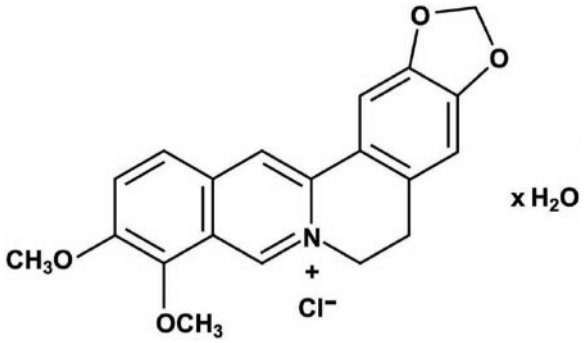

FIG. 1. Chemical structure of berberine.

absorption in Caco-2 cell (7). Berberine promoted glucose uptake in HepG2 and 3T3-L1 cells independent of insulin action (8, 9) and improved glucose metabolism via glycolysis (10). Berberine also facilitated insulin secretion in HIT-T15 cells and murine pancreatic islets *in vitro* and in BALB/C mice (11).

Several clinical investigations of berberine in the treatment of diabetes were reported in Chinese over the past 2 decades. Ni (4) reported that fasting plasma glucose concentrations in 60 patients with type 2 diabetes were reduced from 11.6 to 6.6 mmol/liter for 1–3 months when treated with berberine (0.3–0.5 g, three times daily). Xie *et al.* (12) found that when berberine (0.3–0.5 g, three times daily) was administrated to 40 type 2 diabetic patients for 2 months without change in their previous therapy, fasting and postprandial plasma glucose concentrations were reduced by 21 and 27%, respectively. Wei *et al.* (13) also reported that treatment with berberine (0.5 g, three times daily) for 2 months in 30 type 2 diabetic patients with fatty liver decreased fasting plasma glucose, triglyceride, and total cholesterol concentrations by 31, 40, and 23%, respectively, and was associated with decrease in serum alanine aminotransferase and aspartate aminotransaminase concentrations. Participants in these clinical studies tolerated berberine well, with one subject in one study having mild gastrointestinal discomfort.

All these clinical studies were open and nonplacebo-controlled. Insulin sensitivity changes have still not been carefully investigated. Therefore, in the present study, we performed a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of diabetes and dyslipidemia.

Patients and Methods

Study design

The study was a randomized, double-blind, placebo-controlled and multiple-center trial consisting of a screening visit, a 2-wk run-in, and a 3-month treatment period. The study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine, and written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. The registration number is NCT00462046 (clinicaltrials.gov).

We recruited study participants between May 2005 and May 2006 from the Rui-Jin Hospital, Ren-Ji Hospital, and Min-Hang Hospital of Shanghai Jiao-Tong University School of Medicine and the Changhai Hospital of the Second Military Medical University in Shanghai. Initial screening included a medical history, physical examination, renal and hepatic function, serum lipid concentrations, serum electrolytes, blood counts and urinary analysis, and a 75-g oral glucose tolerance test (OGTT). During the 2-wk run-in period, 152 recently diagnosed type 2 diabetic patients who had not received previous pharmacological treatment were instructed in diet and exercise. Thirty-six patients were excluded because of plasma glucose concentrations 8 mmol/liter or greater and/or a 2-h OGTT plasma glucose concentration $\geq$17 mmol/liter. The remaining 116 patients were randomly assigned to receive double-blind berberine or placebo (Fig. 2). Randomization was performed centrally and was concealed and stratified in blocks of four. In 116 patients, six were lost after randomization without any visits and four dropped out with one or two visits, including one patient completing the first visit from placebo and two and one completing the second visits from the placebo and berberine groups, respectively. A total of 110 patients (94.8%), including those four who dropped out were analyzed for the intention-to-treat efficacy.

Patients

Eligibility criteria were: 1) age of 25–70 yr; 2) newly diagnosed type 2 diabetes according to the 1999 World Health Organization criteria: fasting plasma glucose 7 mmol/liter or greater and/or 2-h OGTT 11.1 mmol/liter or greater (14) and fasting plasma glucose less than 8 mmol/liter; 3) dyslipidemia with triglycerides greater than 150 mg/dl (1.70 mmol/liter), total cholesterol greater than 200 mg/dl (5.16 mmol/liter), and/or low-density lipoprotein (LDL)-cholesterol (c) greater than 100 mg/dl (2.58 mmol/liter) according to the National Cholesterol Education Program's Adult Treatment Panel III (15) without previous treatment; and 4) body mass index (BMI) 19–40 kg/m^2. The exclusion criteria were: 1) moderate or severe liver dysfunction, including serum alanine aminotransferase greater than 120 IU/liter, aspartate aminotransaminase greater than 80 IU/liter, and abnormal renal function (serum creatinine greater than 115 μmol/liter); 2) severe dysfunction of the heart, New York Heart Association class phase III or greater; 3) histories of acute diabetic complications including diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic coma; 4) psychiatric disease or severe infection; 5) pregnancy or planned pregnancy; 6) present or previous use of drugs for treatment of diabetes or dyslipidemia; and 7) fasting plasma glucose 8 mmol/liter or greater and/or postload plasma glucose concentration 17 mmol/liter or greater after a 2-wk run-in.

Treatment

Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets. A dose reduction to 0.25 g twice daily was suggested whenever the constipation occurred and lasted more than 2 wk. The berberine and placebo tablets were provided by Huashi Pharmaceutical Inc. (Shanghai, China). The berberine is extracted from rhizomes of Coptis chinensis Franch with acidic water (0.3% H_2SO_4) soaking and chromatographic purification and had a purity 97% or greater.

Clinical and biochemical measurements

Patients visits were studied between 0700 to 0800 h after an overnight fast of 10–12 h. Date of birth, smoking, alcohol consumption, and past medical history were assessed. Height and weight (light clothes and without shoes), waist and hip circumference, and seated blood pressure (measured on the patient's nondominant arm supported at heart level) were determined by a senior physician (16). Biochemical measurements of serum lipids, glycated hemoglobin (HbA1c), and insulin were performed in a central laboratory (Shanghai Institute of Endocrinology and Metabolism, Shanghai, China). All patients were required to refrain from alcohol, cigarettes, and heavy physical exercise for at least 1 wk before obtaining blood samples for biochemical measurement and performing the 75-g OGTT. Women were studied in the follicular phase of the menstrual cycle. Glucose was measured immediately using an enzymatic method (CX-7 biochemical autoanalyzer; Beckman Brea, CA). Serum insulin was measured using a double-antibody RIA (Diagnostic Systems Laboratories, Webster, TX). Serum total cholesterol and triglycerides

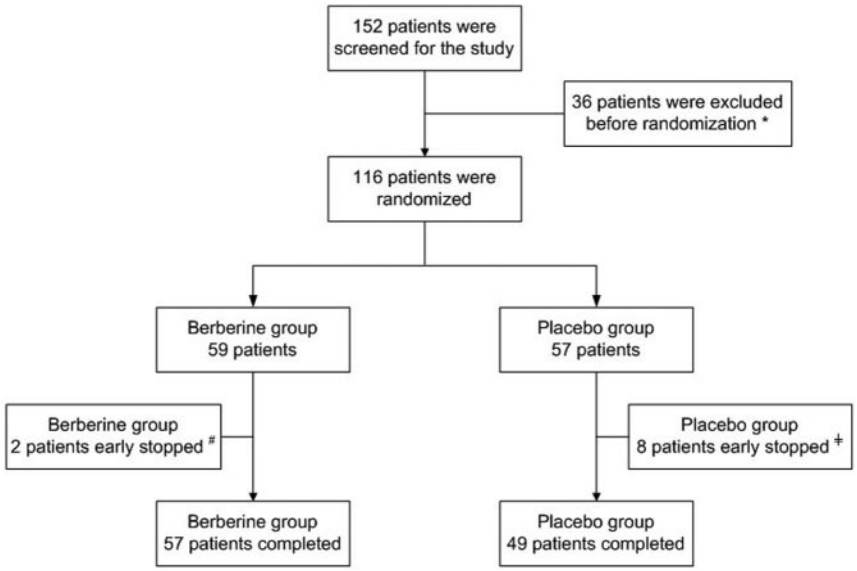

FIG. 2. Patients who were screened and randomized in the study. *, Thirty-six patients were excluded because of plasma glucose concentrations 8 mmol/liter or greater and/or 2-h OGTT plasma glucose concentrations17 mmol/liter or greater; #, reasons for early stop in berberine group: two moved during the follow-up; ‡, reasons for early stop in placebo group: one had higher fasting plasma glucose concentrations (14.5 mmol/liter), two moved during the follow-up, and five had personal conflicts.

were measured by enzymatic methods (Beckman Coulter Inc., Fullerton, CA). High-density lipoprotein (HDL)-c and LDL-c were determined by immunoinhibition methods (HDL-c, LDL-c Direct; Wake Pure Chemical Industries Ltd. GmbH, Neuss, Germany). HbA1c was measured by HPLC using a variant hemoglobin HbA1c assay (Bio-Rad Laboratories, Hercules, CA). Serum IL-6 was measured using ELISA kits (R&D Systems, Minneapolis, MN) and high-sensitivity C-reactive protein (CRP) using ELISA kits (Biocheck Inc., Foster, CA).

Hyperinsulinemic euglycemic clamp

The hyperinsulinemic euglycemic clamp studies were performed in one center (Rui-Jin Hospital), and the participants randomly selected from four centers were all invited to receive clamp examination in Rui-Jin Hospital. A total of 54 patients were randomly selected for clamp assessment of insulin sensitivity, performed 6–8 d after OGTT as described previously (17–19). A small polyethylene catheter was placed in an antecubital vein for blood sampling. A second catheter was placed in a vein in the contralateral forearm for infusion of insulin and 20% dextrose solution. After a 30- to 45-min stabilization period, a 10-min priming insulin infusion was administered, followed by a constant infusion of 60 mU/m^2 surface area per minute over 140 min. Twenty percent glucose was infused at a variable rate beginning 4 min after initiation of the insulin infusion to maintain blood glucose concentrations at 5.0–5.5 mmol/liter. During the clamp, blood glucose levels were repeatedly measured with a glucose analyzer (Biosen 5130; Neckar Healthcare Co. Ltd., Magdeburg, Germany). Blood samples for insulin measurement were collected at 10-min intervals. The glucose disposal rate (GDR; milligrams per kilogram per minute), defined as the amount of glucose required to maintain stable blood glucose concentrations during the last 30 min of the clamping, was used to evaluate insulin resistance.

Evaluation and outcomes

Study assessments were performed at 0, 1, 2, and 3 months. Fasting plasma glucose was checked at each visit and serum total cholesterol, triglycerides, HDL-c, and LDL-c were checked at 0, 1, and 3 months. OGTT, HbA1c measurement, and hyperinsulinemic euglycemic clamp were performed at 0 and 3 months.

The primary efficacy outcome was the change in fasting glucose and 2-h OGTT plasma glucose, total cholesterol, triglycerides, HDL-c LDL-c, HbA1c levels, and GDR. Secondary efficacy outcome was the change in BMI and blood pressures.

Statistical analysis

This study was designed in accordance with a predetermined statistical analysis plan. A sample size of 60 patients in each of the two study groups, with a dropout rate up to 10%, was planned to provide a 90% power to detect a 20% or greater (with 95% confidence intervals, $\alpha = 0.05$, $\beta = 0.1$) reduction in fasting plasma glucose concentrations (the primary end point variable) in the berberine group, compared with the placebo group after 3 months at the end of the study.

Statistical analysis was performed using the SPSS 10.0 system (SPSS Inc., Chicago, IL), and data are presented as mean ± SD. Logarithmic transformation was used for IL-6 and CRP because of the high degree of skewing. Within-group comparisons were performed with paired-sample *t* tests to evaluate differences from baseline in each group. Independent-sample *t* test and the analysis of covariance (ANCOVA) analysis with a model that included the baseline value of the dependent variable as a covariate were also used for comparison between groups.

Results

Baseline characteristics

Patients were middle-aged Chinese living in the Shanghai region. Of 116 randomized patients, 106 completed the study, four dropped out with one or two visits, and six were lost without any visits. The data of 110 participants including those four who dropped out were analyzed as shown in Table 1. The baseline variables are not significantly different between the berberine and placebo groups.

The primary outcomes

As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose and 2-h OGTT plasma glucose, HbA1c, triglyceride, total cholesterol, and LDL-c. Fasting plasma glucose decreased from 7.0 ± 0.8 to 5.6 ± 0.9 mM/liter with berberine and decreased from 6.8 ± 0.9 to 6.4 ± 1.6 mM/liter with placebo (Fig. 3B), with corresponding falls in 2-h glucose from 12.0 ± 2.7 to 8.9 ± 2.8 *vs.* 12.2 ± 2.4 to 11.0 ± 2.8 and in HbA1c from 7.5 ± 1.0 to 6.6 ± 0.7% *vs.* from 7.6 ± 1.2 to 7.3 ± 1.1%, with all parameters differing significantly (Table 1).

Triglyceride decreased from 2.51 ± 2.04 to 1.61 ± 1.10 mM/liter with berberine and increased from 1.97 ± 0.94 to 2.05 ± 1.26 mM/liter, total cholesterol decreased from 5.31 ± 0.98 to 4.35 ± 0.96 mM/liter *vs.* 5.38 ± 0.93 to 5.28 ± 0.77 mM/liter, and LDL-c decreased from 3.23 ± 0.81 to 2.55 ± 0.77 mM/liter *vs.* 3.37 ± 0.73 to 3.24 ± 0.74 mM/liter (Table 1).

The ANCOVA analysis showed that serum total cholesterol, triglycerides, and LDL-c concentrations in berberine group were significantly reduced as compared with the changes in placebo group ($P < 0.0001$, $P = 0.001$, $P < 0.0001$, respectively). Serum

TABLE 1. Baseline and 3-month clinical characteristics of berberine and placebo groups

	Berberine			Placebo[a]			
	Before	After	*P* value[b]	Before	After	*P* value[b]	*P* value[a]
No. (male/female)		58 (30/28)			52 (31/21)		
Age (yr)	51 ± 9	51 ± 10					
Current smokers		14			20		
Alcohol use		4			15		
Body weight (kg)	68.7 ± 11.3	66.4 ± 11.8	0.000	71.8 ± 11.2	70.5 ± 11.0	0.000	0.034
BMI (kg/m^2)	25.2 ± 3.1	24.3 ± 3.2	0.000	25.9 ± 3.8	25.4 ± 3.6	0.000	0.021
Waist to hip ratio	0.91 ± 0.06	0.89 ± 0.06	0.023	0.91 ± 0.05	0.90 ± 0.05	0.014	0.340
Systolic blood pressure (mm Hg)	124 ± 14	117 ± 15	0.001	126 ± 15	123 ± 14	0.094	0.038
Diastolic blood pressure (mm Hg)	81 ± 9	77 ± 11	0.005	83 ± 8	80 ± 9	0.047	0.108
Fasting plasma glucose (mmol/liter)	7.0 ± 0.8	5.6 ± 0.9	0.000	6.8 ± 0.9	6.4 ± 1.6	0.091	0.000
Postload plasma glucose (mmol/liter)	12.0 ± 2.7	8.9 ± 2.8	0.000	12.2 ± 2.4	11.0 ± 2.8	0.010	0.000
HbA1c (%)	7.5 ± 1.0	6.6 ± 0.7	0.000	7.6 ± 1.2	7.3 ± 1.1	0.129	0.000
Triglycerides (mmol/liter)	2.51 ± 2.04	1.61 ± 1.10	0.000	1.97 ± 0.94	2.05 ± 1.26	0.543	0.001
Total cholesterol (mmol/liter)	5.31 ± 0.98	4.35 ± 0.96	0.000	5.38 ± 0.93	5.28 ± 0.77	0.248	0.000
HDL-c (mmol/liter)	1.31 ± 0.47	1.37 ± 0.79	0.564	1.30 ± 0.27	1.28 ± 0.24	0.474	0.415
LDL-c (mmol/liter)	3.23 ± 0.81	2.55 ± 0.77	0.000	3.37 ± 0.73	3.24 ± 0.74	0.138	0.000
Fasting serum insulin (μIU/ml)	12.4 ± 10.1	9.8 ± 5.7	0.128	11.7 ± 7.2	11.1 ± 7.7	0.586	0.174
Postload serum insulin (μIU/ml)	81.3 ± 78.2	57.7 ± 46.8	0.217	72.4 ± 61.7	68.8 ± 40.8	0.588	0.171
HOMA-IR (μIU/mol·liter^2)	3.90 ± 3.20	2.44 ± 1.67	0.010	3.40 ± 2.39	3.29 ± 2.88	0.947	0.057
IL-6 (pg/ml)	2.95 ± 3.46	1.49 ± 2.19	0.030	4.36 ± 5.33	3.30 ± 3.96	0.140	0.010
CRP (mg/liter)	5.56 ± 4.44	4.74 ± 5.21	0.257	7.19 ± 6.00	7.51 ± 6.49	0.552	0.256

[a] *P* value refers to comparison between berberine and placebo groups after treatment using the ANCOVA analysis.

[b] *P* value refers to comparison between before *vs.* after treatment within each group.

total cholesterol, triglycerides, and LDL-c concentrations were reduced from 1 month ($P < 0.0001$) as compared with the baseline, whereas no change was found in placebo group at 1 and 3 months (Fig. 3, C–E).

Fifty-four patients, of whom 28 were from the berberine group and 26 from the placebo group, received hyperinsulinemic euglycemic clamp tests at baseline. Forty-eight patients were available for repeat clamp tests at 3 months, of whom 27 (15 males, 12 females) were from the berberine group and 21 (11 males, 10 females) from the placebo group. Serum insulin levels during the fasting condition and hyperinsulinemic phase (120–150 min) of the clamp tests were 7.93 ± 6.57 and 113.38 ± 55.15 μIU/ml, respectively, at baseline and 9.08 ± 5.95 and 103.32 ± 52.77 μIU/ml, respectively, at the end of the study in the berberine group and 10.52 ± 7.41 and 107.90 ± 43.92 μIU/ml, respectively, at baseline and 10.55 ± 5.66 and 108.85 ± 47.01 μIU/ml, respectively, at the end of the study in the placebo group. No significant difference was found between these two groups. After treatment, the GDR was significantly increased in the berberine group (6.56 ± 2.42 *vs.* 7.42 ± 2.37 mg/kg·min, $P = 0.037$), whereas no change was found in the placebo group (5.98 ± 2.46 *vs.* 6.06 ± 2.21 mg/kg·min, $P = 0.86$) (Fig. 4). Similar changes were found in the homeostasis model assessment for insulin resistance (HOMA-IR) values (Table 1). With adjustment of body weight change by ANCOVA analysis, HOMA-IR was still reduced in the berberine-treated group ($P = 0.025$), whereas no significant change was found in the placebo group ($P = 0.936$), which implied that the change of HOMA-IR values in the berberine group were not caused by the change of body weight. However, ANCOVA analysis showed that the GDR at 3 months was not significantly different between the berberine and placebo groups ($P = 0.063$).

The secondary outcomes

Body weight decreased from 68.7 ± 11.3 to 66.4 ± 11.8 kg with berberine, a significantly greater fall than that from 71.8 ± 11.2 to 70.5 ± 11.0 kg in the placebo group (Fig. 3A). A greater reduction of BMI was also found at 3 months in the berberine group than in the placebo group ($P = 0.021$) (Table 1).

Systolic and diastolic blood pressure decreased from 124 ± 14 to 117 ± 15 and from 81 ± 9 to 77 ± 11 mm Hg in those treated with berberine, exceeding the fall from 126 ± 15 to 123 ± 14 and from 83 ± 8 to 80 ± 9 mm Hg with placebo (Table 1).

IL-6 concentrations were significantly reduced at 3 months in the berberine group either as compared with baseline ($P = 0.030$) or placebo ($P = 0.010$). CRP concentrations at 3 months did not

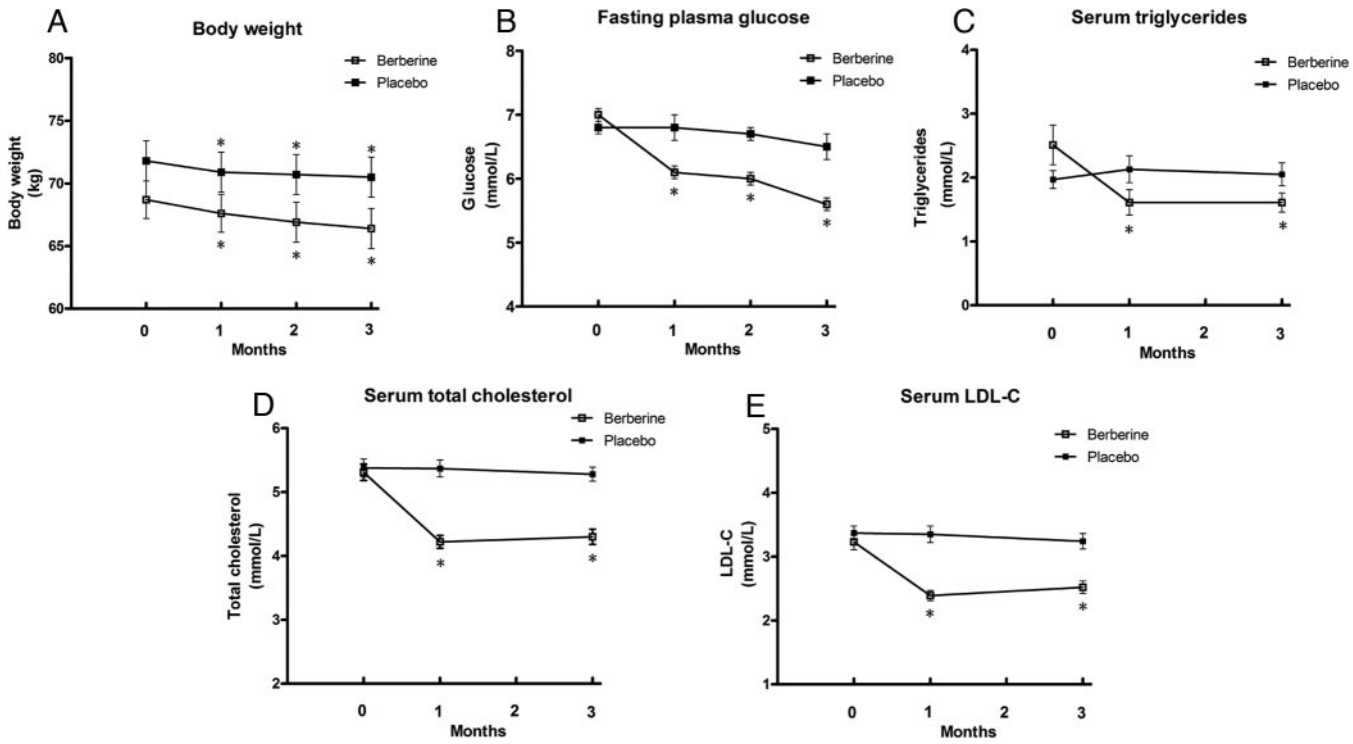

FIG. 3. Body weight (A), fasting plasma glucose concentrations (B), serum triglyceride concentrations (C), serum cholesterol concentrations (D), and serum LDL-c concentrations (E) during treatment of berberine (□) and placebo (■). Data displayed as means ± SE. *, $P < 0.0001$ after 1, 2, or 3 months treatment *vs.* before treatment within each group.

differ between the berberine and placebo groups ($P = 0.256$) (Table 1).

Safety

During the period of study, safety parameters including renal and hepatic function, serum electrolytes, blood counts, and urinary analysis were assessed. Any side effects were obtained and recorded in case report form from each patient. No serious adverse events occurred. Mild to moderate constipation occurred in five participants receiving berberine and one participant in the placebo group. However, the frequency of constipation was not significantly different between the berberine and placebo groups ($P = 0.207$). Among them, three participants in the berberine group and one in the placebo group relieved without dose reduction, and two patients with mild constipation received a reduction of dose of berberine to 0.25 g twice daily. No episode of hypoglycemia was reported.

Serum alanine aminotransferase, aspartate aminotransaminase, and γ-glutamyl transpeptidase were significantly reduced in the berberine group at 3 month as compared with baseline (30 ± 21 *vs.* 22 ± 14 IU/liter, $P = 0.001$; 26 ± 12 *vs.* 22 ± 7 IU/liter, $P = 0.006$; 34 ± 20 *vs.* 30 ± 24 IU/liter, $P = 0.053$, respectively).

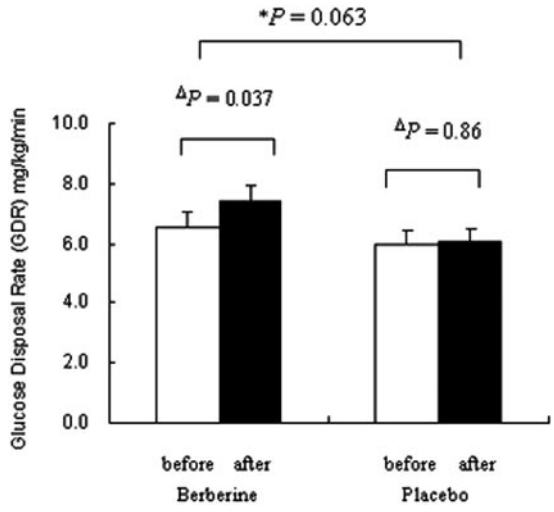

FIG. 4. GDR before and after treatment with berberine and placebo. Data displayed as means ± SE. *, *P* value refers to comparison between berberine and placebo groups after treatment using the ANCOVA analysis; Δ, *P* value refers to comparison between before *vs.* after treatment within each group.

Discussion

Berberine is usually used as an antibiotic drug for diarrhea in China. Berberine has also been used for diabetic patients in traditional Chinese medicine for hundreds of years. Recent studies have reported effects on hyperglycemia and dyslipidemia (4–13, 20).

Based on these previous *in vitro* and *in vivo* studies, we performed a randomized, double-blind, and placebo-controlled trial to investigate the efficacy and safety of berberine in treatment of persons with diabetes and dyslipidemia, major components of the metabolic syndrome. Berberine had a robust glucose-lowering effect by significantly reducing fasting and postprandial plasma glucose by 1.4 and 3.1 mmol/liter, respectively, at 3 months and HbA1c by 0.9% from the initial levels of

7.5%. The decline in HbA1c achieved with berberine is fully comparable with that with existing pharmacologic products used in treatment of type 2 diabetes (21).

However, the GDR, HOMA values, and serum fasting and postprandial insulin concentrations were not significantly different between the berberine and placebo groups at 3 months, which indicates that insulin sensitivity was only partially improved by berberine due to a trend identified ($P = 0.063$ for GDR). Furthermore, the GDR increase was observed in berberine group at 3 month as compared with baseline ($P = 0.037$).

An 18% reduction of serum cholesterol, 35.9% of triglycerides and 21% of LDL-c were achieved in type 2 diabetic patients after a 3-month treatment, which is in accordance with the report of Kong *et al.* (20) in an open clinical trial. They found berberine up-regulated LDL receptor expression independent of sterol regulatory element binding protein but dependent on ERK activation in human hepatoma cells, whereas our current findings indicate that berberine is more effective in reducing serum triglycerides than cholesterol concentrations, which is similar to fibrates (22). In addition, we also observed that systolic and diastolic blood pressures were significantly reduced with berberine by 7 and 5 mm Hg, respectively ($P = 0.001$ and $P = 0.005$, respectively). Modest weight loss was demonstrated, unlikely in itself sufficient to explain the metabolic benefits of the agent, although a clinically favorable finding.

The precise mechanism of berberine in glucose-lowering action has not been fully understood. Lee *et al.* (5) reported that berberine improved insulin resistance in db/db mice and high fat-fed rats. Berberine can activate AMP-activated protein kinase in 3T3-L1 adipocytes and L6 myotubes and facilitate GLUT4 translocation in L6 myotubes in a phosphatidylinositol 3-kinase-independent manner. Yin *et al.* (8) and Zhou *et al.* (9) reported that berberine promoted glucose uptake in HepG2 and 3T3-L1 cells independent of insulin action. In addition, berberine can effectively inhibit sucrase and maltase activities to the same extent as acarbose does in Caco-2 intestinal cells and possibly inhibit α-glucosidase activities to reduce glucose absorption (7). In the present study, we also found a significant reduction of serum IL-6 in the berberine group as compared with the control. It indicates that a reduction of inflammation could also be involved in insulin sensitivity improvement in the berberine-treated patients (2, 23, 24).

Berberine cannot provide adequate single drug therapy for all diabetic patients because the patients in the present study had relatively mild diabetes; however, it may be at least useful as an adjuvant to standard therapy.

With regard to the safety, berberine does not have any toxicity at present doses in clinical use. The major side effects can result from overdose, including mild gastrointestinal discomfort in rare cases (20). The pharmacokinetics of berberine was studied in rats (25). Berberine reached the peak concentrations at 2 h after oral administration, declined within 12 h, and then maintained at a very low concentration for 48 h. However, the area under curve and the peak concentrations of its metabolites were much higher. It suggests that blood clearance of berberine is very quick and that its biotransformation in the liver is rapid and substantial, allowing for immediate circulation of its metabolites in the body. In our present study, we found that serum berberine concentrations were 6.1 ± 4.9 ng/ml in the berberine group at the end of the study. It suggests that berberine is rapidly metabolized or/and poorly absorbed in the gastrointestinal tract. So the regulation of gut microflora could be a novel mechanism for berberine to act in antihyperglycemia and antidyslipidemia.

Given the benefits of berberine in lowering blood glucose, lipids, body weight, and blood pressures, we speculate that berberine may be used for patients with type 2 diabetes and metabolic syndrome. Long-term study with a larger sample size is needed to confirm these findings.

Appendix

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References

1. 2006 Diabetes atlas. 3rd ed. Brussels: International Diabetes Federation
2. **Ford ES** 2005 Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome. Diabetes Care 28:1769–1778
3. **Ravaglia G, Forti P, Maioli F, Bastagli L, Chiappelli M, Motesi F, Bolondi L, Patterson C** 2006 Metabolic syndrome: prevalence and prediction of mortality in elderly individuals. Diabetes Care 9:2471–2476
4. **Ni YX** 1988 Therapeutic effect of berberine on 60 patients with type II diabetes

mellitus and experimental research [article in Chinese]. Zhong Xi Yi Jie He Za Zhi 8:711–713
5. **Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT, Hohnen-Behrens C, Gosby A, Kraegen EW, James DE, Kim JB** 2006 Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistance states. Diabetes 55:2256–2264
6. **Ko BS, Choi SB, Park SK, Jang JS, Kim YE, Park S** 2005 Insulin sensitizing and insulinotropic action of berberine form cortidis rhizoma. Biol Pharm Bull 28: 1431–1437
7. **Pan GY, Huang ZJ, Wang GJ, Fawcett JP, Liu XD, Zhao XC, Sun JG, Xie YY** 2003 The antihyperglycaemic activity of berberine arises from a decrease of glucose absorption. Planta Med 69:632–636
8. **Yin J, Hu R, Chen M, Tang J, Li F, Yang Y, Chen J** 2002 Effects of berberine on glucose metabolism *in vitro*. Metabolism 51:1439–1443
9. **Zhou L, Yang Y, Wang X, Liu S, Shang W, Yuan G, Li F, Tang J, Chen M, Chen J** 2007 Berberine stimulates glucose transport through a mechanism distinct from insulin. Metabolism 56:405–412
10. **Yin J, Gao Z, Liu D, Liu Z, Ye J** 2008 Berberine improves glucose metabolism through induction of glycolysis. Am J Physiol Endocrinol Metab 294:E148–E156
11. **Leng SH, Lu FE, Xu LJ** 2004 Therapeutic effects of berberine in impaired glucose tolerance rats and its influence on insulin secretion. Acta Pharmacol Sin 25:496–502
12. **Xie P, Zhou H, Gao Y** 2005 The clinical efficacy of berberine in treatment of type 2 diabetes mellitus [article in Chinese]. Chin J Clin Healthcare 8:402–403
13. **Wei J, Wu J, Jiang J, Wang S, Wang Z** 2004. Clinical study on improvement of type 2 diabetes mellitus complicated with fatty liver treatment by berberine [article in Chinese]. Zhong Xi Yi Jie He Ganbing Za Zhi 14:334–336
14. **Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC** 2000 The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. Diabetes Care 23:1108–1112
15. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults** 2001 Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497
16. **Zhang YF, Hong J, Zhan WW, Li XY, Gu WQ, Yang YS, Xu M, Ning G** 2006 Hyperglycemia after glucose loading is a major predictor of preclinical atherosclerosis in nondiabetic subjects. Clin Endocrinol (Oxf) 64:153–157
17. **Zhang YF, Hong J, Zhan WW, Li XY, Gu WQ, Yang YS, Xu M, Ning G** 2006 Elevated serum level of interleukin-18 is associated with insulin resistance in women with polycystic ovary syndrome. Endocrine 29:419–423
18. **Defronzo RA, Tobin JD, Andres R** 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–E223
19. **Soonthornpun S, Setasuban W, Thamprasit A** 2003 Novel insulin sensitivity index derived from oral glucose tolerance test. J Clin Endocrinol Metab 88: 1019–1023
20. **Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S, Wu J, Li Z, Liu J, Jiang JD** 2004 Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med 10:1344–1351
21. **Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE** 2006 Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 29:2137–2139
22. **Elisaf M** 2002 Effects of fibrates on serum metabolic parameters. Curr Med Res Opin 18:269–276
23. **Morley JE, Baumgartner RN** 2004 Cytokine-related aging process. J Gerontol Med Sci 59A:924–929
24. **Kritchevsky SB, Cesari M, Pahor M** 2005 Inflammatory markers and cardiovascular health in older adults. Cardiovasc Res 66:265–275
25. **Zuo F, Nakamura N, Akao T, Hattori M** 2006 Pharmacokinetics of berberine and its main metabolites in conventional and pseudo germ-free rats determined by liquid chromatography/ion trap mass spectrometry. Drug Metab Dispos 34:2064–2072