Efficacy of berberine in patients with type 2 diabetes mellitus

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Abstract

Berberine has been shown to regulate glucose and lipid metabolism in vitro and in vivo. This pilot study was to determine the efficacy and safety of berberine in the treatment of type 2 diabetes mellitus patients. In study A, 36 adults with newly diagnosed type 2 diabetes mellitus were randomly assigned to treatment with berberine or metformin (0.5 g 3 times a day) in a 3-month trial. The hypoglycemic effect of berberine was similar to that of metformin. Significant decreases in hemoglobin A_{1c} (from 9.5% ± 0.5% to 7.5% ± 0.4%, $P < .01$), fasting blood glucose (from 10.6 ± 0.9 mmol/L to 6.9 ± 0.5 mmol/L, $P < .01$), postprandial blood glucose (from 19.8 ± 1.7 to 11.1 ± 0.9 mmol/L, $P < .01$), and plasma triglycerides (from 1.13 ± 0.13 to 0.89 ± 0.03 mmol/L, $P < .05$) were observed in the berberine group. In study B, 48 adults with poorly controlled type 2 diabetes mellitus were treated supplemented with berberine in a 3-month trial. Berberine acted by lowering fasting blood glucose and postprandial blood glucose from 1 week to the end of the trial. Hemoglobin A_{1c} decreased from 8.1% ± 0.2% to 7.3% ± 0.3% ($P < .001$). Fasting plasma insulin and homeostasis model assessment of insulin resistance index were reduced by 28.1% and 44.7% ($P < .001$), respectively. Total cholesterol and low-density lipoprotein cholesterol were decreased significantly as well. During the trial, 20 (34.5%) patients experienced transient gastrointestinal adverse effects. Functional liver or kidney damages were not observed for all patients. In conclusion, this pilot study indicates that berberine is a potent oral hypoglycemic agent with beneficial effects on lipid metabolism.

1. Introduction

Type 2 diabetes mellitus is a worldwide health threat, and treatment of this disease is limited by availability of effective medications. All of the existing oral hypoglycemic agents have subsequent failure after long-term administration. Thus, new oral medications are needed for long-term control of blood glucose in patients with type 2 diabetes mellitus. Certain botanical products from generally regarded as safe (GRAS) plants have been widely used in diabetes care because of their antioxidation, anti-inflammation, antiobesity, and antihyperglycemia properties [1,2]. However, the drawback of using GRAS plants is the difficulty in controlling their quality, as most of these botanical products are mixtures of multiple compounds. Compared with other products from GRAS plants, berberine is a single purified compound and has glucose-lowering effect in vitro and in vivo [3-6].

Berberine (molecular formula, $C_{20}H_{19}NO_5$; molecular weight, 353.36) is the main active component of an ancient Chinese herb *Coptis chinensis French*, which has been used to treat diabetes for thousands of years. Berberine is an over-the-counter drug that is used to treat gastrointestinal tract infections in China. Berberine hydrochloride (B·HCl·nH2O), the most popular form of berberine, is used in this pilot study. The chemical structure of berberine and related isoquinoline alkaloids is quite different from other commonly used hypoglycemic agents, such as sulfonylureas, biguanides, thiazolidinediones, or acarbose. Hence, if the efficacy and safety of berberine are confirmed, it can serve as a new class of antidiabetic medication.

This pilot study was to assess the efficacy of berberine in human subjects with type 2 diabetes mellitus. Berberine was given to both newly diagnosed diabetic patients and poorly controlled diabetic patients alone or in combination with

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other hypoglycemic agents for 3 months. Hemoglobin A_{1c} (HbA$_{1c}$), blood glucose, and homeostasis model assessment (HOMA) index were used to determine the efficacy of berberine.

2. Subjects and methods

The subjects were recruited from diabetes outpatient department of Xinhua Hospital by advertising in the clinic. Ninety-seven Chinese volunteers were screened, and 13 subjects were excluded from the study because of failure to meet the recruitment criteria. Thus, 84 subjects (49 women and 35 men) with type 2 diabetes mellitus were included in the study. All participants received written and oral information regarding the natural and potential risks of the study and gave their informed consent. The experimental protocol was approved by the ethics committee of Xinhua Hospital. The monotherapy study was designed to compare berberine with metformin (study A, n = 36). The combination therapy was aimed at evaluating additive or synergistic effects of berberine on the classic antidiabetic agents (study B, n = 48).

Major inclusion criteria were HbA$_{1c}$ >7.0% or fasting blood glucose (FBG) >7.0 mmol/L, body mass index >22 kg/m^2, age 25 to 75 years, and a negative pregnancy test result for female patients. A total of 36 patients who were newly diagnosed for type 2 diabetes mellitus were assigned to study A. After a 2-month phase during which the patients were treated with diet alone, they were randomly assigned to receive berberine or metformin. A total of 48 type 2 diabetes mellitus patients inadequately treated with diet plus sulfonylureas, metformin, acarbose, or insulin therapy alone or with a combination were assigned to study B (Table 1). The dose of the medications was stable for at least 2 months before enrollment in the study and remained unchanged throughout the study. All participants were instructed to maintain their lifestyle habits during the course of the study.

Each study involved a 13-week treatment. For study A, 18 subjects took 500 mg berberine 3 times daily at the beginning of each major meal or 500 mg metformin 3 times daily after major meals. For study B, 500 mg berberine

Table 1
Baseline characteristics of administration of hypoglycemic agents

Subjects (n)	Diet	Sulfonylureas	Metformin	Acarbose	Insulin
36	+				
7	+	+			
3	+		+		
1	+			+	
8	+				+
12	+	+	+		
9	+	+		+	
4	+		+	+	
1	+		+		+
1	+			+	+

3 times daily was added to their previous treatment of 3 months. If heavy gastrointestinal adverse effects occurred, the dose of berberine was reduced to 300 mg 3 times daily.

Patients were evaluated weekly for the first 5 weeks of treatment and then every 4 weeks until the end of study. The primary efficacy end point was glycemic control as determined by HbA$_{1c}$ levels. Secondary efficacy parameters included changes in FBG, postprandial blood glucose (PBG), plasma triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations. Adverse events were recorded throughout the study by direct questioning.

2.1. Measurements

Blood glucose was determined by a glucose oxidase method (Roche, Basel, Switzerland). Serum insulin and C-peptide were determined by radioimmunoassay (Linco Research, St Charles, MO). Hemoglobin A_{1c} was analyzed using the high-pressure liquid chromatography (BioRad, Hercules, CA). Plasma triglyceride, total cholesterol, HDL-C, LDL-C, alanine transaminase (ALT), γ-glutamyl transpeptidase (γ-GT), and creatinine concentrations were determined by enzymatic assays (Roche). The HOMA method was used to compare differences in the profiles for insulin resistance (HOMA-IR) and for β-cell dysfunction (HOMA β-cell) [7]. Ten insulin-treated subjects were excluded from the HOMA analysis.

$$HOMA{-}IR = fasting\ insulin\ (in\ microunits\ per\ milliliter)$$
$$\times\ fasting\ glucose\ (in\ millimoles\ per\ liter)/22.5$$

$$HOMA\beta{-}cell = [20 - fasting\ insulin\ (in\ microunits\ per\ milliliter)]$$
$$/[fasting\ glucose\ (in\ millimoles\ per\ liter) - 3.5]$$

2.2. Statistical analysis

Descriptive statistics and analysis were performed in SPSS 12.0 for Windows (SPSS, Chicago, IL). In study A, the significance of the differences between means of metformin and berberine groups was analyzed by Wilcoxon rank sum test. The statistical differences between baseline and end point were calculated using Wilcoxon signed rank test. In study B, the significance of the differences among different time points was analyzed by repeated-measure analysis of variance. The α level was set at .05.

3. Results

In study A, 36 patients were included and randomly assigned to metformin or berberine treatment. Three patients of the berberine group and 2 patients of the metformin group withdrew from the study because of treatment failure. In study B, 48 patients were included; and 5 subjects were excluded from the study before week 13. Among the 5 subjects, 3 failed to complete the study in lack of efficacy,

one failed in lack of participation time, and one was excluded because of lack of compliance (pill count <80%). Thus, 74 participants were eligible for the final analysis.

3.1. Berberine vs metformin (study A)

In newly diagnosed diabetic patients, berberine reduced blood glucose and lipids (Table 2). There were significant decreases in HbA_{1c} (by 2%, $P < .01$), FBG (by 3.8 mmol/L, $P < .01$), and PBG (by 8.8 mmol/L, $P < .01$) in the berberine group. The FBG (or PBG) declined progressively during the berberine treatment, reaching a nadir that was 3.7 mmol/L (or 8.7 mmol/L) below baseline by week 5, and remained at this level until the end of the study (Fig. 1A). Triglycerides and total cholesterol decreased by 0.24 mmol/L ($P < .05$) and 0.57 mmol/L ($P < .05$) with berberine treatment. It seemed that there was a declining trend of HDL-C and LDL-C; however, no significant differences between week 1 and week 13 were observed in the berberine group. Compared with metformin, berberine exhibited an identical effect in the regulation of glucose metabolism, such as HbA_{1c}, FBG, PBG, fasting insulin, and postprandial insulin. In the regulation of lipid metabolism, berberine activity is better than metformin. By week 13, triglycerides and total cholesterol in the berberine group had decreased and were significantly lower than those in the metformin group ($P < .05$).

3.2. Combination therapy of berberine (study B)

In the first 7 days of treatment, berberine led to a reduction in FBG from 9.6 ± 2.7 to 7.8 ± 1.8 mmol/L ($P < .001$, Fig. 1C) and in PBG from 14.8 ± 4.1 to 11.7 ± 3.6 mmol/L ($P < .001$). During the second week, FBG and PBG declined further; reached a nadir that was 2.1 mmol/L (7.5 ± 2.1 mmol/L) and 3.3 mmol/L (10.5 ± 2.5 mmol/L) below the baseline, respectively; and remained at this level thereafter.

In the combination therapy for 5 weeks, berberine led to a reduction in HbA_{1c} from 8.1% to 7.3% ($P < .001$, Table 3). Fasting blood glucose and PBG declined remarkably, too ($P < .001$). Fasting insulin and HOMA-IR

were reduced by 29.0% ($P < .01$) and 46.7% ($P < .001$), respectively. Blood lipids including triglyceride, total cholesterol, and LDL-C decreased and were significantly lower than baseline. In the absence of weight change, waist and waist-hip ratio of the patients declined significantly. No significant changes in the criteria were observed between week 5 and week 13 except the increment of fasting C-peptide ($P < .05$) and postprandial C-peptide ($P < .01$). During the study, fasting C-peptide of the patients with insulin treatment went down then up; and postprandial C-peptide increased by 70.5% ($P < .01$) at 13 weeks.

3.3. Safety results

Incidence of gastrointestinal adverse events was 34.5% during the 13 weeks of berberine treatment including monotherapy and combination therapy. These events included diarrhea (n = 6; percentage, 10.3%), constipation (4; 6.9%), flatulence (11; 19.0%), and abdominal pain (2; 3.4%). The adverse effects were observed only in the first 4 weeks in most patients. In 14 (24.1%) patients, berberine dosage decreased from 0.5 g 3 times a day [TID] to 0.3 g TID as a consequence of gastrointestinal adverse events. Of the 14 patients, 10 were treated with metformin or acarbose in combination with berberine. The rest were treated with insulin combined with berberine. None of the patients experienced severe gastrointestinal adverse events when berberine was used alone. In combination therapy, the adverse events disappeared in 1 week after reduction in berberine dosage. The data suggest that berberine at dosage of 0.3 g TID is well tolerated in combination therapy.

Liver and kidney functions were monitored in this study. No significant changes of plasma ALT, γ-GT, and creatinine were observed during the 13 weeks of berberine treatment (Table 3). None of the patients were observed with pronounced (>50%) elevation in liver enzymes or creatinine.

4. Discussion

The hypoglycemic effect of berberine was reported in 1988 when it was used to treat diarrhea in diabetic

Table 2
Monotherapeutic effects of metformin and berberine

	Metformin (n = 16)		Berberine (n = 15)	
	Baseline	End point	Baseline	End point
HbA_{1c} (%)	9.15 ± 0.57	7.72 ± 0.43**	9.47 ± 0.65	7.48 ± 0.40**
FBG (mmol/L)	9.96 ± 0.64	7.16 ± 0.71**	10.63 ± 0.88	6.85 ± 0.53**
PBG (mmol/L)	20.53 ± 1.87	12.86 ± 0.77**	19.83 ± 1.66	11.05 ± 0.92**
Fasting insulin (μU/mL)	27.3 ± 4.4	22.9 ± 5.2	29.1 ± 5.3	24.0 ± 5.5
Postprandial insulin (μU/mL)	125.3 ± 29.8	110.5 ± 21.4	120.4 ± 31.4	116.0 ± 26.9
Triglyceride (mmol/L)	1.19 ± 0.12	1.17 ± 0.13	1.13 ± 0.13	0.89 ± 0.03*
Total cholesterol (mmol/L)	4.31 ± 0.28	4.27 ± 0.15	4.40 ± 0.21	3.83 ± 0.09*
HDL-C (mmol/L)	1.25 ± 0.06	1.31 ± 0.08	1.33 ± 0.10	1.22 ± 0.04
LDL-C (mmol/L)	2.55 ± 0.38	2.43 ± 0.11	2.47 ± 0.13	2.36 ± 0.06

Data are means ± SEM.

Compared with baseline: *$P < .05$, **$P < .01$.

Berberine monotherapy

Metformin monotherapy
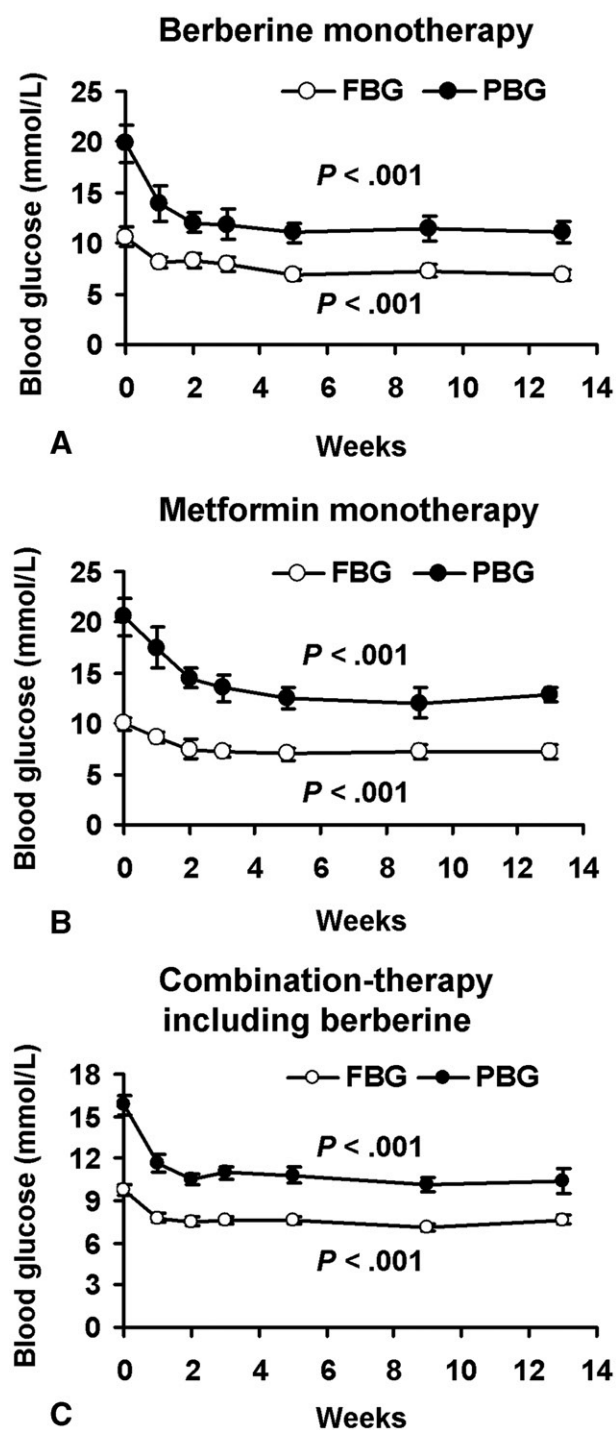

Combination-therapy including berberine

Fig. 1. Both berberine and metformin decreased FBG and PBG of type 2 diabetes mellitus patients significantly from week 1 to week 13. A, Means ± SEM of 15 patients treated with berberine alone. B, Means ± SEM of 16 patients treated with metformin alone. C, Means ± SEM of 43 patients with combination therapy including berberine.

patients in China [8]. Since then, berberine has often been used as an antihyperglycemic agent by many physicians in China. There are substantial numbers of clinical reports about the hypoglycemic action of berberine in Chinese literature. However, most of the

previous studies were not well controlled; and experiments were not well designed. In addition, none of them used HbA_{1c} as a parameter because of poor research conditions. Thus, the antidiabetic effect of berberine needs to be carefully evaluated.

In this pilot study, berberine significantly decreased HbA_{1c} levels in diabetic patients. The effect of decreasing HbA_{1c} was comparable with that of metformin, a widely used oral hypoglycemic agent [9,10]. In monotherapy, berberine and metformin all improved glycemic parameters (HbA_{1c}, FBG, and PBG). However, their effects on lipid metabolism were different. Berberine decreased serum triglyceride and total cholesterol significantly. The levels of HDL-C and LDL-C of patients treated with berberine were also reduced, but the decreases did not reach statistical significance. Whether berberine has a lowering effect on HDL-C needs further investigation. Compared with berberine, metformin had little effects on these lipid parameters.

In combination with other agents, berberine exhibited consistent activities in improvement of glycemic and lipid parameters in diabetic patients. Insulin sensitivity was

Table 3
Berberine in combination therapy

	Wk 0	Wk 5	Wk 13
BMI	26.0 ± 0.6	26.1 ± 0.8	26.0 ± 0.8
Waist (cm)	89.0 ± 1.5	86.9 ± 1.8**	87.0 ± 1.7**
Waist-hip ratio	0.89 ± 0.01	0.86 ± 0.01*	0.86 ± 0.01
HbA_{1c} (%)	8.1 ± 0.2	7.3 ± 0.2***	7.3 ± 0.3***
FBG (mmol/L)	9.6 ± 0.4	7.6 ± 0.3***	7.6 ± 0.3***
PBG (mmol/L)	14.8 ± 0.7	10.8 ± 0.6***	9.7 ± 0.9***
Fasting insulin (μU/mL)	35.2 ± 3.3	25.0 ± 2.6**	25.3 ± 5.3**
Postprandial insulin (μU/mL)	104.1 ± 9.5	88.0 ± 11.4	76.5 ± 15.6
HOMA-IR	15.2 ± 1.6	8.1 ± 1.0***	8.4 ± 1.8***
HOMA β-cell	128.6 ± 12.2	164.2 ± 27.3	151.7 ± 28.6
Fasting C-peptide (ng/mL)	0.96 ± 0.28	0.85 ± 0.24	1.12 ± 0.12*·†
Postprandial C-peptide (ng/mL)	2.27 ± 0.72	2.28 ± 0.80	3.87 ± 0.14**·‡
Triglyceride (mmol/L)	1.73 ± 0.17	1.39 ± 0.18*	1.49 ± 0.49
Total cholesterol (mmol/L)	4.97 ± 0.13	4.20 ± 0.13***	4.38 ± 0.40*
HDL-C (mmol/L)	1.37 ± 0.04	1.31 ± 0.05	1.32 ± 0.05
LDL-C (mmol/L)	3.00 ± 0.10	2.50 ± 0.10***	2.59 ± 0.27**
ALT (U/L)	31.5 ± 4.1	26.5 ± 2.6	25.2 ± 7.0
γ-GT (U/L)	41.8 ± 7.8	41.5 ± 8.4	41.4 ± 1.2
Creatinine (mmol/L)	88.5 ± 3.1	90.8 ± 3.7	90.8 ± 8.1

Data are means ± SEM of the patients with combination therapy including berberine. Values of fasting insulin, postprandial insulin, HOMA-IR, and HOMA β-cell were obtained from 33 patients treated only with oral hypoglycemic agents. Values of fasting C-peptide and postprandial C-peptide were obtained from the other 10 patients treated including insulin. The rest of the parameters were obtained from all the 43 patients with combination therapy. BMI indicates body mass index.
Compared with week 0: *$P < .05$, **$P < .01$, ***$P < .001$.
Compared with week 5: †$P < .05$, ‡$P < .01$.

enhanced by berberine because the HOMA-IR value was reduced by nearly 50%. This effect may be related to fat distribution by berberine because waist and waist-hip ratio of the patients were decreased significantly in the absence of weight change. Interestingly, both fasting and postprandial C-peptides increased significantly in patients when berberine was used together with insulin, which suggests that long-term berberine treatment may improve insulin secretion of the patients with consequent failure of oral hypoglycemic agents. The effects of berberine on islet function need further studies.

The mechanism of berberine on glucose metabolism is still under investigation. We and others have demonstrated that berberine has an insulin-sensitizing effect in vivo and in vitro [3-5,11,12]. In diet-induced obese rats, berberine reduced insulin resistance, similar to metformin [13,6]. In hepatocytes, adipocytes, and myotubes, berberine increased glucose consumption and/or glucose uptake in the absence of insulin [3,6,14]. Berberine-enhancing glucose metabolism may be due to stimulation of glycolysis, which is related to inhibition of oxidation in mitochondria [6]. Berberine may also act as an α-glucosidase inhibitor. It inhibited disaccharidases activities and decreased glucose transportation across the intestinal epithelium [15,16]. This may contribute to the adverse gastrointestinal effects of berberine in some patients. This adverse effect was often observed when berberine was used in combination with metformin or acarbose. These 2 agents also have similar gastrointestinal adverse effects by themselves; thus, when combined with these 2 agents, the dosage of berberine should be reduced to 0.3 g TID to avoid severe flatulence or diarrhea.

Berberine is proposed to have potential as a therapeutic agent for lipid lowering. In this pilot study, berberine reduced serum cholesterol, triglycerides, and LDL-C. This activity is similar to that reported elsewhere in vivo [17,18]. However, further studies including outcome studies in humans are needed to confirm this activity and its benefit. The mechanism of berberine regulating lipid metabolism has been investigated by several groups. In hamsters with hyperlipidemia, berberine reduced serum cholesterol and LDL-C, and increased LDL receptor messenger RNA as well as protein in the liver [19]. These effects were partly due to stabilization of LDL receptor messenger RNA mediated by the ERK signaling pathway [20]. In addition to up-regulation of the LDL receptor, berberine was reported to inhibit lipid synthesis in human hepatocytes through activation of AMPK [21].

In summary, berberine is a potent oral hypoglycemic agent with modest effect on lipid metabolism. It is safe, and the cost of treatment by berberine is very low. It may serve as a new drug candidate in the treatment of type 2 diabetes mellitus. However, this is a pilot study. The efficacy of berberine needs to be tested in a much larger population and characterized as a function of the known duration of the diabetes. Further studies are needed to evaluate the

action of berberine on type 2 diabetes mellitus in other ethnic groups.

Acknowledgment

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