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ORIGINAL ARTICLE

Effect of Berberine Administration on Metabolic Syndrome, Insulin Sensitivity, and Insulin Secretion

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Abstract

Background: The aim of this study was to evaluate the effect of berberine administration on metabolic syndrome, insulin sensitivity, and insulin secretion.
Methods: A randomized, double-blind, placebo-controlled clinical trial was carried out in 24 patients with a diagnosis of metabolic syndrome. Glucose and insulin levels after a dextrose load were measured. Triglycerides and high-density lipoprotein cholesterol concentrations at baseline were also measured. Twelve patients received berberine hydrochloride (500 mg) three times daily before meals for 3 months. The remaining 12 patients received placebo. Area under the curve (AUC) of glucose and insulin, total insulin secretion, first-phase of insulin secretion, and insulin sensitivity were assessed.
Results: After berberine administration, patients had a remission of 36% ($P = 0.037$) in the presence of metabolic syndrome and a significant decrease in waist circumference in females (106 ± 4 vs. 103 ± 3 cm, $P < 0.05$), systolic blood pressure (SBP) (123 ± 7 vs. 115 ± 9 mmHg, $P < 0.01$), triglycerides (2.4 ± 0.7 vs. 1.4 ± 0.5 mmol/L, $P < 0.01$), area under the curve (AUC) of glucose (1182.1 ± 253.6 vs. 1069.5 ± 172.4 mmol/l, $P < 0.05$), AUC of insulin ($92{,}056 \pm 72{,}148$ vs. $67{,}407 \pm 46{,}441$ pmol/L, $P < 0.01$), and insulinogenic index (0.78 ± 0.69 vs. 0.62 ± 0.46, $P < 0.05$), as well as an increase in the Matsuda index (2.1 ± 1.0 vs. 3.1 ± 1.6, $P < 0.01$).
Conclusions: Administration of berberine leads to remission of metabolic syndrome and decreases in waist circumference, SBP, triglycerides, and total insulin secretion, with an increase in insulin sensitivity.

Introduction

Metabolic syndrome is a cluster of endocrine disturbances including obesity, dysglycemia, dyslipidemia, and hypertension, predisposing individuals to increased risk for atherosclerosis, cardiovascular events, and eventually type 2 diabetes mellitus (T2DM).[1] Metabolic syndrome is strongly related to insulin resistance with the consequent compensatory hyperinsulinemia and visceral obesity and is associated with increased cardiovascular morbidity and mortality as well as an augmented risk for the development of T2DM.[2] In addition, visceral adiposity is a significant independent predictor of insulin resistance, hyperinsulinemia, and metabolic syndrome.[3] Furthermore, intra-abdominal fat is metabolically active as a source of free fatty acids and adipokines.[4] Thus, a role of intra-abdominal fat in metabolic syndrome is biologically plausible, and any effort to decrease adiposity, insulin resistance, and hyperinsulinemia in patients with metabolic syndrome should be considered.

Berberine is an isoquinoline derivative alkaloid isolated from medicinal herbs. It is safe and inexpensive and has been proven to have many pharmacological effects, including lowering of blood glucose, increasing insulin sensitivity, correcting lipid metabolism disorders, and reducing cardiovascular risk factors along with the probability of weight reduction, among others.[5] Some findings indicate that adipose tissue is the main target of berberine, inhibiting differentiation of mouse 3T3-L1 preadipocytes into fat cells, reducing leptin and resistin secretion, increasing mRNA expression of adiponectin, and moderating glucose and lipid metabolism through a multipathway mechanism that includes the adenosine monophosphate (AMP)-activated protein kinase (AMPK)-p38 MAPK-GLUT4, JNK pathway, and peroxisome proliferator-activated receptor-α (PPARα).[6]

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The above-mentioned findings show that berberine has excellent potential for the prevention and treatment of metabolic syndrome; however, clinical studies performed in such populations are scarce. The aim of this study was to evaluate the effect of berberine administration on metabolic syndrome, insulin sensitivity, and insulin secretion.

Materials and Methods

A randomized, double-blind, placebo-controlled clinical trial was carried out in 24 patients without diabetes (30–40 years of age) with newly diagnosed metabolic syndrome in accordance with the International Diabetes Federation (IDF) criteria[7] and without pharmacological treatment. Subjects were selected from the same residential area and socioeconomic status. No participant was excessively sedentary or participated in heavy physical activity. All individuals were nonsmokers and had stable body weight for at least 3 months prior to the study. There was no personal history of hepatic, renal, or coronary artery disease. Subjects had not consumed any medications known to affect carbohydrate or lipid metabolism during the previous 6 months. Exclusion criteria were pregnancy, breastfeeding, and allergy to berberine. All subjects consumed an isocaloric diet containing >250 grams of carbohydrate/day for 3 days before the tests, as confirmed by dietary history. Women were in the first phase of their menstrual cycle (3–8 days). Patients were evaluated before and after the 3-month study period. All patients received general recommendations about their medical nutritional therapy and were instructed to not modify their usual exercise routine. Tests were performed at 8:00 a.m. after a 10- to 12-hr overnight fast.

Height and weight were recorded with the individuals wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subjects standing. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Waist circumference was taken at the midline between the highest point of the iliac crest and the lowest rib in the mid-axillary line. Blood pressure was evaluated by the investigator after a 5-min resting period with the individual sitting in a chair and determined using a digital sphygmomanometer. SBP and diastolic blood pressure (DBP) were based on Korotkoff phases I and V, respectively. Samples of venous blood at baseline and 30, 60, 90, and 120 min after a 75-grams oral dextrose load were obtained and centrifuged. Serum was separated into two aliquots: The first was immediately used for determination of glucose and the second was frozen at −20°C for insulin measurement within the following 30 days. At time 0, triglycerides and high-density lipoprotein cholesterol (HDL-C) concentrations were also measured.

Pharmacological administration

After simple random allocation using a random number list, 12 patients received berberine hydrochloride (500 mg) (Shanghai Brightol International Co., Ltd., Shanghai, China) three times/day before meals for 3 months. The other 12 subjects received placebo in the same pharmacological presentation.

Serum glucose was determined by the glucose oxidase method. Triglycerides and HDL-C were measured enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL fractions. Determinations were performed with commercially available equipment (Vitros, Ortho-Clinical Diagnostics, Johnson & Johnson Co., Rochester, NY) with an intra- and interassay coefficient of variation of <2%. Insulin concentrations were measured with a chemiluminescent immunoassay technique (Beckman Coulter, Fullerton, CA) with an intra- and interassay coefficient of variation of 3.8 and 4.2, respectively. Area under the curve (AUC) of glucose and insulin was calculated with the polygonal formula. Total insulin secretion was evaluated with the insulinogenic index (ΔAUC insulin/ΔAUC glucose). The first phase of insulin secretion was estimated using the Stumvoll index ($1283 + 1.829 \times \text{insulin } 30' - 138.7 \times \text{glucose } 30' + 3.772 \times \text{insulin } 0'$) and insulin sensitivity with Matsuda index [$10{,}000/\sqrt{(\text{glucose } 0' \times \text{insulin } 0')}$ (mean glucose oral glucose tolerance test [OGTT] × mean insulin OGTT)].[8,9]

Statistical analyses

Sample size was calculated using a formula for clinical trials[10] with a statistical confidence of 95%, statistical power of 80%, standard deviation (SD) for a Matsuda index of 12.1, and an expected between-group difference of at least 15.5 of the Matsuda index, obtaining a total of 12 patients for each group that included 20% of expected loss. For insulin secretion and waist circumference, sample size calculation was lower. Values were converted to the International System of Units (SI) and are presented as mean ± SD. The Shapiro–Wilk test was used to evaluate normal distribution, and intra- and intergroup differences were tested using the Wilcoxon signed-rank and Mann–Whitney U-test, respectively; $P \leq 0.05$ was considered significant.

Ethical considerations

The study protocol was reviewed and approved by the local ethics committee and written informed consent was obtained from all volunteers.

Results

All patients who were eligible after enrollment completed the 3 months of the pharmacological intervention, including 7 females and 5 males in each group. There was no significant difference in age between groups (36.9 ± 3.0 vs. 38.1 ± 2.7 years, placebo, and berberine, respectively; $P = 0.145$).

There were no significant differences in clinical and laboratory tests at baseline between groups. A significant decrease in BMI, waist circumference in females, SBP, triglycerides, AUC of glucose, AUC of insulin and insulinogenic index, and increase in the Matsuda index were observed after berberine administration (Table 1). After berberine administration, patients had a remission of 36% ($P = 0.037$) in the presence of metabolic syndrome.

There were no significant adverse events with the administration of berberine.

Discussion

No single pathogenic pathway has been identified to date as a valuable therapeutic target in metabolic syndrome, and current management still addresses the various components individually with both lifestyle modifications and pharmacological therapy, often with a multidrug regimen.[11] In our

Table 1. Characteristics Before and After Interventions

	Placebo		*Berberine*	
	Baseline	*3 Months*	*Baseline*	*3 Months*
BMI (kg/m^2)	34.2 ± 3.6	34.1 ± 4.0	36.1 ± 2.3	35.5 ± 2.4**
Waist circumference (cm ♀)	108 ± 9	107 ± 8	106 ± 4	103 ± 3*
Waist circumference (cm ♂)	116 ± 10	112 ± 10	121 ± 2	116 ± 1
Systolic blood pressure (mmHg)	118 ± 7	116 ± 7	123 ± 7	115 ± 9**
Diastolic blood pressure (mmHg)	77 ± 7	78 ± 8	80 ± 8	77 ± 6
Glucose (mmol/L)	5.2 ± 0.3	5.1 ± 0.5	5.6 ± 0.8	5.5 ± 0.7*
Triglycerides (mmol/L)	2.1 ± 0.7	2.0 ± 0.8	2.4 ± 0.7	1.4 ± 0.5**
HDL-C (mmol/L ♀)	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.4	1.2 ± 0.4
HDL-C (mmol/L ♂)	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.2	0.9 ± 0.2
AUC glucose (mmol/L)	989 ± 122	997 ± 200	1182 ± 253	1069 ± 172*
AUC insulin (pmol/L)	67,605 ± 18,730	86,852 ± 57,863	92,056 ± 72,148	67,407 ± 46,441**
Insulinogenic index	0.64 ± 0.23	0.81 ± 0.53	0.78 ± 0.69	0.62 ± 0.46*
Stumvoll index	1554 ± 688	1736 ± 783	1506 ± 1392	1483 ± 1207
Matsuda index	2.5 ± 0.6	2.6 ± 1.8	2.1 ± 1.0	3.1 ± 1.6**

*$p < 0.05$.
**$p < 0.01$.
BMI, body mass index; HDL, high-density lipoprotein cholesterol; AUC, area under the curve.

study, more than one-third of the patients had remission of metabolic syndrome after berberine administration as monotherapy, indicating that the multitherapeutic activity of this compound explained later could be explored in the routine treatment of this syndrome.

The effects of berberine on glucose metabolism are related to modifications of insulin secretion, glycolysis, and adipogenesis, inhibiting mitochondrial function, activating the AMPK pathway, and increasing glycokinase activity. Berberine also increases glucose transporter-4 (GLUT-4) and glucagon-like peptide-1 (GLP-1) levels. All of the above mechanisms may also be associated with the antiobesity effect of berberine.[12] Our results, as well as other reports in the medical literature (in diabetic populations), showed that berberine administration improved metabolic control, decreasing fasting and postprandial glucose concentration and glycosylated hemoglobin (HbA1c) levels.[13–15] This was certainly due to an increment in insulin sensitivity and decrease in insulin secretion.[14,15] Similar findings regarding metabolic control have recently been published with the administration of berberine alone or in combination with other nutraceutical compounds.[6,11] As expected in accordance with other studies,[6,11,14] waist circumference in females and BMI in all groups decreased significantly with the administration of berberine; however, the effect of weight loss may be an influencing factor for the beneficial metabolic results observed. This could be considered as a limitation of the study. On the other hand, it is assumed that unfavorable changes in the secretion of adipokines, considered as an early symptom of impaired adipose tissue function, are the potential link between obesity and insulin resistance, influencing the development of metabolic syndrome. Preliminary findings on the mechanisms of the effects of berberine on serum adipokines suggested that insulin sensitivity is improved by inhibiting fat stores and adjusting adipokine profile in human preadipocytes and in patients with metabolic syndrome.[6] Unfortunately, these inflammatory markers were not measured in our study; however, experiments to explore these mechanisms are necessary.

With regard to lipid metabolism, the lipid-lowering effect of berberine appears to be mainly due to stabilization of hepatic low-density lipoprotein receptor (LDL-R) by the extracellular signal-regulated kinase-dependent pathway and also by increasing transcriptional activity of the LDL-R promoter, although it was not measured in our investigation.[5] Other recently reported explanations include an increment of PPARα receptor expression.[16] Several publications[12,17,18] show the triglyceride-lowering effect of berberine, as observed in our study. When conflicting results were reported with regard to HDL level, our findings were in accordance with those that did not observe modifications.[11,13,14]

Administration of berberine in the present study showed a decrease in SBP similar to other investigations in patients with diabetes and dyslipidemia[14] and in patients with metabolic syndrome with berberine administration in combination with other nutraceutical compounds.[11] The vasodilator effect of berberine is the result of its action on both endothelium and vascular smooth muscle in addition to angiotensin-converting enzyme inhibitor effect, direct release of nitric oxide/cyclic guanosine monophosphate (NO/cGMP), and α1-adrenoreceptor antagonistic action, among other mechanisms that may explain decrease of blood pressure.[12]

The above-mentioned findings may be the basis for proposing the administration of berberine as a treatment option for patients with metabolic syndrome. Long-term studies with larger sample sizes will be necessary to confirm our results. In conclusion, berberine administration leads to remission of metabolic syndrome and a decrease in waist circumference, SBP, triglycerides, and total insulin secretion, with an increase in insulin sensitivity.

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Author Disclosure Statement

No conflict of interest is reported with regard to this manuscript. The authors declare no competing interests with the mentioned pharmaceutical company.

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