

Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control

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Background: Suboptimal glycemic control is a common situation in diabetes, regardless of the wide range of drugs available to reach glycemic targets. Basic research in diabetes is endeavoring to identify new actives working as insulin savers, use of which could delay the introduction of injectable insulin or reduce the insulin dose needed. Commonly available as a nutraceutical, berberine is a potential candidate.

Methods and results: Because its low oral bioavailability can be overcome by P-glycoprotein inhibitors like herbal polyphenols, we have tested the nutraceutical combination of *Berberis aristata* extract and *Silybum marianum* extract (Berberol[®]) in type 2 diabetes in terms of its additive effect when combined with a conventional oral regimen for patients with suboptimal glycemic control. After 90 days of treatment, the nutraceutical association had a positive effect on glycemic and lipid parameters, significantly reducing glycosylated hemoglobin, basal insulin, homeostatic model assessment of insulin resistance, total and low-density lipoprotein cholesterol, and triglycerides. A relevant effect was also observed in terms of liver function by measuring aspartate transaminase and alanine transaminase. The product had a good safety profile, with distinctive gastrointestinal side effects likely due to its acarbose-like action.

Conclusion: Although further studies should be carried out to confirm our data, Berberol could be considered a good candidate as an adjunctive treatment option in diabetes, especially in patients with suboptimal glycemic control.

Keywords: berberine, silymarin, glycosylated hemoglobin, diabetes

Introduction

Diabetes mellitus is recognized as a group of heterogeneous disorders, with common elements of hyperglycemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both. The prevalence of type 2 diabetes increases with age, is increasing worldwide, and its economic impact currently accounts for a significant portion of health care expenditure.¹ Injection of long-acting insulin is a common therapeutic approach for patients with type 2 diabetes that is poorly controlled with multiple oral regimens.² Unfortunately, although insulin use as the mainstay of treatment for diabetes has resulted in favorable treatment outcomes, poor adherence/compliance continues to be a problem because of fear of insulin or fear of injection, and this can be associated with poor glycemic control, clinical complications, psychological comorbidity, poor general well being and health status, and increased mortality risk in patients with diabetes.³ Last but not least, use of insulin is very often considered to be the “point of no return” in medical intervention for diabetes. These observations

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suggest a need for implementation of new therapeutic strategies to delay the need for insulin as far as possible.

Berberine, an isoquinoline alkaloid of the protoberberine type and found in an array of plants, has been used in Indian and Chinese medicine for many decades. It is present in *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (the Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric). Berberine and extracts of berberine have demonstrated significant antimicrobial activity against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. The predominant clinical uses of berberine, at least in the recent past, have included bacterial diarrhea and intestinal parasite infections.⁴

More recently, clinical research on berberine has revealed novel pharmacological properties and multiple therapeutic applications, mainly concerning hypercholesterolemia and diabetes.⁵ With regard to the lipid profile, berberine upregulates low-density lipoprotein receptor expression independent of sterol regulatory element-binding proteins, but dependent on extracellular signal-regulated kinases and c-Jun N-terminal kinase activation, leading to reductions in total cholesterol and low-density lipoprotein cholesterol of about 30% and 25%, respectively. This upmodulation occurs via a post-transcriptional mechanism that stabilizes mRNA and enables berberine to act as a cholesterol-lowering drug via a mechanism of action different from that of the statins.⁶ In addition to its cholesterol-lowering properties, berberine reduces triglycerides by about 35%. These effects on the lipid profile have been observed in both animals and humans.^{6,7}

Berberine also has an important additive effect in the presence of statins.⁸ This is likely due to the ability of berberine to downmodulate proprotein convertase subtilisin/kexin type 9, a protein which reduces the cholesterol-lowering properties of statins.⁹ This effect of berberine could be relevant when treating patients with suboptimal control of hypercholesterolemia despite receiving high doses of statins. Due to this additive effect, it is quite common to find nutritional supplements containing berberine¹⁰ along with a natural source of lovastatin (ie, *Monascus purpureus*).¹¹ However, these products do not take into consideration the poor standardization of the raw materials¹² and the risk to consumers due to the possible presence of mycotoxic contaminants like citrinin.¹³

Berberine has also been shown to be effective in the treatment of diabetes, in which it significantly decreases glycosylated hemoglobin (HbA_{1c}), fasting blood glucose, and postprandial blood glucose. In this respect, berberine has an

effect similar to that of metformin,¹⁴ even if it likely acts via a mechanism different from that of metformin.¹⁵

Berberine regulates glucose metabolism via multiple mechanisms of action. It enhances glucose uptake by upmodulation of glucose transporter type 4, activates 5'-AMP-activated protein kinase as a consequence of inhibition of mitochondrial function, suppresses adipogenesis by inhibition of peroxisome proliferator-activated receptor gamma and C-enhancer-binding protein alpha function, and decreases intestinal glucose absorption by inhibition of alpha-glucosidase.¹⁶ However, despite these functions, berberine has poor oral bioavailability.¹⁷ In humans, this appears to be due to a P-glycoprotein-mediated gut extrusion process¹⁸ and substantial excretion in bile.¹⁹ P-glycoprotein seems to decrease the amount of berberine able to cross enterocytes by about 90%,²⁰ suggesting that inhibition of P-glycoprotein could potentially improve its oral poor bioavailability. Among the potential P-glycoprotein inhibitors, silymarin from *Silybum marianum* could be a good candidate due to its very poor oral bioavailability and its good safety profile.²¹

Therefore, we investigated the activity of a combination of berberine and silymarin when added to oral hypoglycemic regimens for patients with suboptimal glycemic control. Our aim was to evaluate the impact of this approach on body mass index, hyperglycemia, hypercholesterolemia, triglyceride levels, and liver enzymes in patients with type 2 diabetes.

Materials and methods

The study was performed in routine clinical practice in accordance with international guidelines and in line with the principles outlined in the Declaration of Helsinki, so approval from the local ethics board was not required. This study was carried out in a single center in Italy where it is not mandatory to obtain ethical approval when performing experiments involving nutraceutical products. Twenty-six patients diagnosed with type 2 diabetes were enrolled. The patient demographics are shown in Table 1. Twenty-two of the 26 patients completed the study, with four dropouts as a result of gastrointestinal discomfort and/or other side effects.

Table 1 Demographic characteristics of the 22 patients who completed the study

	Gender	
	Males n = 17	Females n = 5
Age (years)	61.3 ± 8.6	58.7 ± 7.1
Weight (kg)	104.5 ± 23.4	90.1 ± 22.8

Note: All values for ages and weight are expressed as the median ± standard deviation.

The main inclusion criteria were stable (for at least 6 months) but suboptimal glycemic control (HbA_{1c} 7.5%–9.5%), body mass index > 22 kg/m², age 25–75 years, and a negative pregnancy test for female patients. All patients had suboptimal glycemic control despite use of the following drugs, unchanged at least in the last 3 months: metformin (n=20), incretins (n=4), sulfonylureas (n = 14), glitazones (n = 3), and insulin (n = 5). Twenty patients were also receiving antihypertensive drugs, and 13 were receiving anticoagulant therapy. As regards the lipid profile, 12 patients were receiving statins, 1 was receiving a fibrate whereas 5, previously under treatment with statins, had interrupted the therapy due to unwanted effects, mainly myalgia.

Exclusion criteria were moderate to severe liver dysfunction (serum alanine aminotransferase > 120 IU/L and aspartate aminotransferase > 80 IU/L), abnormal renal function (serum creatinine > 115 μ mol/L), severe heart failure (New York Heart Association Class III or greater), history of acute diabetic complications, including diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic coma, psychiatric disease, severe infection, pregnancy or planning for pregnancy, and fasting plasma glucose ≥ 200 mg/dL.

All patients received add-on nutraceutical therapy, ie, Berberol® (PharmExtracta, Pontenure, Italy), an oral tablet containing 588 mg of *B. aristata* extract titrated as 85% berberine and 105 mg of *S. marianum* extract titrated as $>60\%$ flavonolignans. The product, in agreement with the Italian legislation (law number 169/2004) had been notified to the Minister of Health in 2010 (E10 40753Y) and registered as a food supplement, with both its actives (standardized extracts of *B. aristata* and *S. marianum*) belonging to the list of botanicals approved as nutraceuticals and its excipients all being food grade. The patients took two tablets per day on an empty stomach in the late evening for the 90-day duration of the study. Berberol was manufactured by SIIT (Trezza S/N, Milan, Italy). The two actives, ie, *B. aristata* extract and *S. marianum* extract, were provided, respectively, by SIIT and Indena, both located in Milano, Italy.

Statistical analysis

The statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). Statistical differences between baseline and different time points were analyzed using the nonparametric paired *t*-test. The α level was set at 0.05.

Results

Berberol containing extracts of *B. aristata* and *S. marianum* extract, dosed at two tablets daily for 90 days, was

demonstrated to be a valid add-on treatment option for patients with type 2 diabetes and suboptimal glycemic control. As shown in Table 2, a significant reduction was observed in HbA_{1c} , basal insulin, total cholesterol, low-density lipoprotein cholesterol, triglycerides, HOMA-R (homeostatic model assessment for insulin resistance, calculated as glucose \times insulin/405, where glucose is expressed as mg/dL and insulin as μ U/mL), and alanine transaminase. Aspartate transaminase also showed a downwards trend. There were no significant changes in high-density lipoprotein cholesterol, fasting glucose, body mass index, weight, or waist circumference.

Discussion

Four of the 26 patients diagnosed with type 2 diabetes and suboptimal glycemic control who enrolled in this study dropped out, leaving data for the 22 patients who completed the study. We investigated the clinical effects of oral treatment using a nutraceutical combination of *B. aristata* extract (containing 85% berberine) and *S. marianum* extract. The latter ingredient is included with the aim of enhancing the oral bioavailability of berberine, mostly by reducing P-glycoprotein activity in the gut. To be eligible for entry into this study, patients had to have had suboptimal glycemic control (HbA_{1c} 7.5%–9.5%) unchanged for at least 3 months despite at least 6 months of treatment with a multidrug regimen. According to the international guidelines, HbA_{1c} values in this range are linked with an increased risk of developing microvascular and macrovascular complications,

Table 2 Effect of adjunctive Berberol therapy after 90 days of treatment in 22 patients with type 2 diabetes and suboptimal glycemic control

Parameter	t = 0	t = 90	$\Delta\%$	P value
HbA_{1c} (%)	8.0 \pm 0.82	7.15 \pm 1.09	-10.6	0.003
TC (mg/dL)	191 \pm 40	151 \pm 37	-21	0.002
LDL-C (mg/dL)	107.6 \pm 36	87 \pm 34	-19.2	0.013
HDL-C (mg/dL)	46.0 \pm 10.7	44.0 \pm 10.9	-4.35	ns
Triglycerides (mg/dL)	170 \pm 81	95 \pm 45	-44.1	0.012
FG (mg/dL)	149.5 \pm 21.3	122 \pm 44.02	-18.4	ns
BI (μ U/mL)	22.7 \pm 11.8	15.5 \pm 7.9	-34.4	0.04
Body mass index (kg/m ²)	34.4 \pm 6.5	34.1 \pm 9.9	-0.3	ns
Weight (kg)	101.3 \pm 23.6	100.6 \pm 24.1	-0.7	ns
Waistline (cm)	116.9 \pm 14.7	116.2 \pm 14.5	-0.4	ns
HOMA-R	6.9 \pm 3.6	5.1 \pm 3.6	-26.1	0.04

Notes: All values are expressed as the median \pm standard deviation at baseline (t = 0) and after 90 days (t = 90) of daily therapy. $\Delta\%$ corresponds to the difference (percent) between t = 0 and t = 90.

Abbreviations: BI, basal insulin; FG, fasting glucose; HOMA-R, homeostatic model assessment of insulin resistance (FG \times BI/405); LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c} , glycosylated hemoglobin; ns, not statistically significant; TC, total cholesterol.

and all possible medical effort should be made to reduce HbA_{1c} below 7%.²² Use of injectable insulin should be delayed as long as possible using oral insulin-saving drug cocktails. The basis for using such cocktails, precisely established on the basis of the metabolic features of a patient, have to be considered carefully, not only because of the very poor patient compliance with insulin injections, but also because delaying insulin therapy should spare endogenous insulin and avoid pancreatic exhaustion.²³

In patients with suboptimal glycemic control, we observed an HbA_{1c} reduction of about 0.85% after 3 months of treatment with Berberol, which was maintained after 6 months of treatment (data not shown). Such a percentage reduction is comparable with that normally obtained in patients treated with acarbose, dipeptidyl peptidase-4 inhibitors (sitagliptin, vildagliptin, saxagliptin), or glitazones, used alone or adjunctive to metformin, to achieve optimal glycemic control.

We did not modify any drug or treatment protocol established before starting treatment with Berberol in any of the 22 patients who completed the study. At the same time, no modifications in terms of food intake or lifestyle were suggested or adopted before or during the trial, and this is reflected by the minimal changes in body weight and waist circumference.

A possible mechanism of action of Berberol could be its ability to increase insulin sensitivity, as shown by the reduction in HOMA-R. Another possible mechanism of action could be linked to the acarbose-like action observed by some clinicians.²⁴ This hypothesis should explain some of the gastrointestinal side effects observed, and could explain why four patients dropped out of the trial.

We observed a relevant reduction in total cholesterol, low-density lipoprotein cholesterol, and triglycerides in our patients, all of whom had a cholesterol value within normal range or were on treatment with statins. This result, already observed by many clinicians, is likely due to the hypocholesterolemic activity of berberine and to an additive effect of berberine when combined with statin therapy.

Another effect was the reduction in alanine and aspartate transaminase levels. Similar observations have been made in animals and in humans, and berberine has been shown to reduce liver necrosis both in nonalcoholic steatosis and in steatosis due to hepatitis C infection.²⁵ However, these observations need to be confirmed by studies specifically designed to demonstrate a protective effect of berberine on the liver.

Conclusion

Berberol is a nutraceutical combination of highly standardized herbal extracts of *B. aristata* and *S. marianum* titrated, respectively, as 85% berberine and >60% flavanolignans. Berberol seems to have positive effects in patients with type 2 diabetes and suboptimal glycemic control when given orally in addition to a conventional regimen (ie, metformin, dipeptidyl peptidase-4 inhibitors, glitazones, acarbose or insulin, alone or as multidrug therapy). Berberol seems to improve the cholesterol-lowering properties of statins, and has a positive effect on liver enzymes. Treatment seems to be safe and tolerated at the doses tested, with minimal unwanted effects, which resolve on cessation of treatment without any further consequences. The results of our pilot study performed in 26 patients need confirmation by larger trials and with better definition of the diabetic patients enrolled. Allowing for these limitations, Berberol can still be considered as a potential oral nutraceutical suitable for use in addition to conventional therapy for type 2 diabetes, with the aim of ameliorating suboptimal glycemic control as a strategy for postponing the use of injectable insulin.

Disclosure

FDP developed and has patented the Berberol used in this study.

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