The Effects of Berberine vs. Metformin for Decreasing Waist Circumference and Serum Lipid Levels in Women with Polycystic Ovarian Syndrome

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The Effects of Berberine vs. Metformin for Decreasing Waist Circumference and Serum Lipid Levels in Women with Polycystic Ovarian Syndrome

Abstract
Background: Polycystic ovarian syndrome (PCOS) is a highly prevalent disease that affects both metabolic and reproductive systems in women. PCOS is associated with a high incidence of obesity, insulin resistance, hyperandrogenism, hyperlipidemia, menstrual cycle dysfunction, and infertility. Diagnosis is made using the Rotterdam Criteria, and current accepted medical management of PCOS includes lifestyle changes such as diet and exercise, oral contraceptive pills (OCP), metformin (MET), and bariatric surgery. The aim of this systematic review is to assess the effect of berberine on waist circumference and cholesterol levels.

Methods: A comprehensive literature search was done using Medline, Web of Science, and Clinical key using keywords PCOS or polycystic ovarian syndrome and berberine. Relevant studies were critically assessed using GRADE.

Results: Two studies were chosen for this systematic review, one randomized control trial, and one case control study, that adequately assessed the effects of berberine compared to metformin as well as alone for the treatment of PCOS. The RCT showed that BBR appears to have greater effect than metformin on decreasing waist circumference and waist-to-hip ratio, total cholesterol, triglycerides, and low-density lipoprotein after 3 months of treatment. The case control study showed that BBR therapy caused a statistically significant decrease in waist circumference, LDL levels, and triglycerides in women with PCOS after 6 months of treatment. These studies resulted in a low quality of evidence overall.

Conclusion: BBR caused a greater decrease in waist circumference and lipid profile than MET. This effect is additive when combined with lifestyle changes such as diet and exercise. More studies are needed to evaluate the long-term efficacy of BBR on weight loss and BMI. Overall as a weak recommendation, berberine can be considered as a suitable alternative to metformin for the treatment of polycystic ovarian disease.

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waist circumference and waist-to-hip ratio, total cholesterol, triglycerides, and low-density lipoprotein

Subject Categories
Medicine and Health Sciences

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The Effects of Berberine vs. Metformin for Decreasing Waist Circumference and Serum Lipid Levels in Women with Polycystic Ovarian Syndrome

Megan Pattee

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 9th, 2019

Faculty Advisor: Saje Davis Risen

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Abstract

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Conclusion: BBR caused a greater decrease in waist circumference and lipid profile than MET. This effect is additive when combined with lifestyle changes such as diet and exercise. More studies are needed to evaluate the long-term efficacy of BBR on weight loss and BMI. Overall as weak recommendation, BBR can be considered as a suitable alternative to metformin for the treatment of polycystic ovarian disease.

Keywords: Polycystic Ovarian syndrome, Berberine
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<tr>
<td>AMPK</td>
<td>5' adenosine monophosphate-activated protein kinase</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BBR</td>
<td>Berberine</td>
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<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin Resistance</td>
</tr>
<tr>
<td>LDLC</td>
<td>Low Density Lipoprotein Cholesterol</td>
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<tr>
<td>LH</td>
<td>Luteinizing Hormone</td>
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<td>MET</td>
<td>Metformin</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic Ovarian Syndrome</td>
</tr>
<tr>
<td>TC</td>
<td>Total Cholesterol</td>
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<td>TG</td>
<td>Triglycerides</td>
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<tr>
<td>WC</td>
<td>Waist Circumference</td>
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<td>WHR</td>
<td>Waist to Hip Ratio</td>
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The Effects of Berberine vs. Metformin for decreasing Waist Circumference and Serum Lipid Levels in Women with Polycystic Ovarian Syndrome

BACKGROUND

Polycystic ovarian syndrome (PCOS) is a complex, highly prevalent disease that effects both metabolic and reproductive systems in women.¹ This diagnosis should be considered in any reproductive age female presenting with acne, hirsutism, menstrual irregularities, or elevated BMI. PCOS encompasses a high incidence of obesity, insulin resistance, hyperandrogenism, hyperlipidemia, amenorrhea, and infertility. Alterations in menstrual cycling and fertility in women with PCOS are caused by altered levels of circulating luteinizing hormone, follicular stimulating hormone, androgens such a total testosterone (TT), obesity, and insulin resistance (IR).

A complex interplay between insulin resistance and altered metabolic functioning makes it challenging for those with PCOS to lose weight, and predisposes them to central obesity. When insulin levels are high, the body converts to a fat-storage mode, which promotes weight gain.⁵ Hyperinsulinemia and hyperandrogenemia cause adipocytes to release free fatty acids into the circulation, which stimulates the liver to secrete more VLDL. This leads to elevated triglycerides, LDL particles, and fewer protective HDL cholesterol circulating in the body.¹⁰ However, although IR is a common finding in PCOS, not all patients exhibit this phenotypic feature.⁵

Patients with PCOS have a higher risk of developing other serious comorbidities such as metabolic syndrome, type 2 diabetes, and cardiovascular disease. Hyperlipidemia,
obesity, and insulin resistance directly correlate to these comorbidities; thus, the aim of
treatment is to abate these factors.\textsuperscript{1}

Currently, 4 recognized phenotypic presentations of PCOS exist\textsuperscript{1}, thus the
multifaceted nature of this disease makes it challenging to treat. PCOS is diagnosed using
the Rotterdam Criteria.\textsuperscript{2} Patients must exhibit 2 out of the 3 of the following to yield the
diagnosis: oligomenorrhea or anovulation, clinical or biochemical signs of
hyperandrogenism, and polycystic ovaries.

Current established medical management of PCOS includes lifestyle changes such as
diet and exercise, oral contraceptive pills (OCP), metformin (MET), and bariatric
surgery.\textsuperscript{1} Metformin improves insulin resistance by decreasing hepatic glucose
production. Metformin also lowers serum lipid levels by activating AMPK in the liver.
Unfortunately, MET causes significant gastro-intestinal distress, and is not well tolerated
in >10\% of patients. Additionally, according to Up-To-Date, MET is no longer
recommended as a front-line agent in the treatment of PCOS.\textsuperscript{6}

Berberine, a Chinese medicinal herb from China, may have similar metabolic
effects when compared to metformin for the treatment of obesity and dyslipidemia
in PCOS patients. BBR is an isoquinoline alkaloid derived from Rhizoma Coptidis
(RC). In China, berberine is an over the counter medication that has been used to
treat diabetes, cardiovascular disease, hyperlipidemia, insulin resistance, and even
bacterial and viral infections in the gut.\textsuperscript{12,13} BBR is believed to lower cholesterol by
increasing transcriptional activity of LDL receptors, as well increasing activity of PPAP-
alpha, a protein found in the liver and skeletal muscle that regulates fatty acid beta-
oxidation and energy homeostasis, which reduces plasma triglycerides.\textsuperscript{11} Berberine is
currently being studied further for the treatment of type 2 diabetes, cardiovascular disease, hyperlipidemia, weight loss, insulin sensitivity, hormonal imbalances, and infertility. The aim of this systematic review is to assess the effect of berberine compared to metformin on waist circumference and cholesterol levels in patients with PCOS.

METHODS

A comprehensive literature search using MEDLINE, Web of Science, and Clinical key using key-words PCOS or polycystic ovarian syndrome and berberine was done for this systematic review. Studies were included if they involved adult women with PCOS, the use of MET and BBR in PCOS, or the effect of BBR alone on clinical characteristics of PCOS. Studies in the English language or use of human subjects was also part of the inclusion criteria. Excluded studies where those with insufficient data regarding patient’s outcomes and response to treatment, or studies involving women with other causes of hyperandrogenism or hyperlipidemia, such as cushing’s disease, congenital adrenal hyperplasia, or type 2 diabetes. Finally, studies were excluded if PCOS subjects had normal BMIs.

RESULTS

The initial search yielded 51 articles regarding use of BBR and 43 after removing duplicates (see Figure 1). Two articles addressed the aim of this review. Various others studies were considered; however, they either did not provide statistical evidence comparing outcomes, or were evaluating a different end point such as the effect of BBR in type 2 diabetes. The articles used for this systematic review was one randomized control trial and one case control study. See Table 1.
Wei et al

The aim of this RCT was to compare the efficacy of berberine to metformin in 100 Chinese women with PCOS and insulin resistance. The researchers evaluated 3 treatment groups: one group received BBR, the second group received MET, and the third group served as the placebo group. All subjects received lifestyle modification and a cyproterone acetate (CPA) ethinyl estradiol combined pill for the duration of the 3 months. They measured the short-term effects of BBR and metformin compared to the placebo group in addition to lifestyle changes and CPA on the endocrine-metabolic profile of each participant.

Outcomes evaluated after 6 months of therapy with BBR or MET included changes in weight, waist circumference (WC), body mass index (BMI), waist-to-hip ratio (WHR), glucose tolerance, insulin resistance, cholesterol levels, sex hormone binding globulin (SHBG), and free androgen index (FAI).

Compared to metformin, the group taking BBR experienced a larger decrease in waist circumference, waist-to-hip ratio, total cholesterol, triglycerides (TGs), and LDLC after 3 months of treatment. Subjects in the BBR group averaged a 10.17% decrease in waist circumference after 3 months of treatment (89.12 cm to 80.22 cm), compared to a 4.81% decrease observed in the MET group (89.12 to 85.03 cm) and a 5.54% change in the placebo group (85.23 to 80.75 cm). Body weight and BMI decreased in all 3 treatment groups, and no significant decreases was observed in the BBR group compared to the 2 other treatment groups.

The BBR group experienced a 20% decrease in TGs (2.35 to 1.95 mmol/l) compared to an 8% decrease seen in the group treated with MET (2.26 to 2.09 mmol/l).
Similarly, a 16.6% decrease in LDLC was observed in the BBR group (4.22 to 3.62 mmol/l) compared to a 7% decrease in the MET group (4.35 to 3.95 mmol/l). BBR caused an 11% increase in plasma HDLC (1.11 to 1.24 mmol/l) compared to a 5% increase in HDLC in the MET group (1.13 to 1.39 mmol/l) \(^3\) and 1.7% increase in the placebo group (1.11 to 1.13).\(^3\)

Throughout the duration of the study, none of the subjects experienced adverse effects from taking BBR. Furthermore, this study confirmed that metformin is associated with a high incidence of gastrointestinal distress such as nausea and vomiting, but did not report how many subjects in the MET group experienced these effects\(^3\).

*Orio et al*

This study\(^4\) compared the effects of berberine in 50 oligomenorrheic PCOS women to 50 healthy controls with similar BMIs. Subjects received BBR twice a day for 6 months. No lifestyle changes were implemented as part of therapy, and subjects were encouraged to follow their normal diet and exercise routines. The study monitored changes in BMI, WC, WHR, IR, TC, LDLC, HDLC, TG, SHBG, androgen levels, and DHEA.\(^4\)

A statistically significant decrease in waist circumference (98.5 cm to 96.5 cm) occurred in women with PCOS after 6 months of treatment (p=0.04), as well as in the control group. WHR decreased from 0.90 cm to 0.88 cm in the PCOS group after 6 months of treatment, whereas WHR decreased in the control group from 0.90 cm to 0.84 cm after six months of treatment. There was no significant change in BMI with BBR in addition to changes in weight distribution during the length of this study.\(^4\)
LDL levels decreased significantly (p<0.01) by 8mg/dl (81mg/dl to 73mg/dl), however, there was no significant decrease in LDL compared to the controls. Total cholesterol decreased significantly (p<0.01) when comparing both treatment groups, respectively (2.6 to 2.2nmol/l vs 2.6 to 1.3nmol/l). In the treatment group, triglycerides decreased on average from 120 to 115 mg/dl, and in the control group TGs decreased from 120 to 64 mg/dl. BBR also showed a significant decrease in LDL (p<0.01), but did not significantly increase HDL in the PCOS group.

In addition to changes in body composition and cholesterol, this study also demonstrated that free progesterone and androgen levels improved after BBR treatment (p<0.01). BBR also improved menstruation frequency after 6 months of treatment, regulating the cycling of 22/50 (48%) of subjects with PCOS.

During the 6 months of treatment, none of the women with PCOS experienced adverse effects from the herb, and only 2 patients in the control group had mild constipation. Thus, the group that was given BBR exhibited high compliance to therapy and none of the subjects stopped treatment throughout the duration of the trial.

DISCUSSION

The current literature regarding the effects of BBR on waist circumference and serum lipid profile for the treatment of PCOS suggests that BBR may significantly improve metabolic and hormonal imbalances in women with PCOS, leading to re-distribution of adiposity and improvement of both hyperlipidemia and insulin resistant states. In the Wei et al study, BBR decreased waist circumference almost twice as much as MET after 3 months of treatment. Additionally, BBR had a larger magnitude of effect on lowering cholesterol levels, especially LDL cholesterol, compared to MET.
In the Orio et al study,\textsuperscript{4} no significant difference was noted between the BBR and MET groups in regards to improvement in insulin resistance. However, all PCOS subjects were oligomenorrheic at the beginning of the Orio et al study,\textsuperscript{4} and by the end almost half (48.3\%) of women with PCOS had regular ovulatory cycles. In addition to improved menstrual cycling, subjects receiving BBR also showed significant improvement with level of circulating androgens. Total testosterone, androstenedione, and free androgen index significantly decreased after use with berberine, suggesting that BBR also improves hyperandrogenemia associated with PCOS.\textsuperscript{4}

BBR is associated with less adverse side effects than metformin.\textsuperscript{3,4} Nine out of the thirty-one PCOS patients receiving MET experienced abdominal discomfort, while no subjects taking BBR experienced these side effects. BBR has consistently shown to be safe and well tolerated compared to MET\textsuperscript{4}.

The current evidence suggests that BBR has a greater effect when combined with lifestyle changes such as diet and exercise.\textsuperscript{8} In the Orio et al study,\textsuperscript{4} BBR caused a statistically significant decrease in waist circumference, LDL, TG, and total cholesterol, but did not cause as large of a decrease experienced by the control group. However, this is not surprising, as the women with PCOS were being compared to healthy controls without hyperinsulinemia or hyperlipidemia, and had normal metabolic functioning (hence, the decrease in the quality of evidence for this study). Furthermore, subjects who used BBR without lifestyle interventions still experienced statistically significant changes in waist circumference and with decreasing LDL after 6 months of treatment.\textsuperscript{4} Perhaps more time may be needed for the PCOS patients to catch up to the healthy controls.\textsuperscript{8}
A possible limitation to both studies\textsuperscript{3,4} is length of treatment with BBR, as 3-6 months could be too short of a time frame to evaluate a physical, metabolic, or hormonal changes. Moreover, both studies did not clearly report the outcomes in clinically applicable means. Specifically, the Wei et al study\textsuperscript{3} did not report the outcomes in a way as to clearly identify a treatment effect, but instead reported the outcomes as averages and changes from baseline (see Table 1). The Orio et al study\textsuperscript{4} conducted an intragroup comparison (comparing post treatment measurements to baseline) instead of comparing the treatment group directly with the control group. Additionally, in the Wei et al\textsuperscript{3} study, all subjects were reproductive-aged Chinese women, and although berberine had a significant effect in this population, more studies are needed to the evaluate the effect of BBR in other ethnicities. Overall, these limitations resulted in a low quality of evidence where more research with larger randomized control trials will increase the confidence of BBR usefulness in the treatment of PCOS.

\textbf{CONCLUSION}

BBR may cause a greater decrease in waist circumference and cholesterol levels compared to MET. This effect is likely additive when combined with lifestyle changes such as diet and exercise. BBR may also improve insulin resistance, menstrual irregularity, and hyperandrogenemia in patients with PCOS. Finally, BBR is a natural treatment, and is likely better tolerated than metformin.\textsuperscript{9} However, despite a low quality of evidence, a weak recommendation can be made that BBR may be a suitable alternative to metformin for the treatment of polycystic ovarian disease.
References


9. Wu, Xiao-KeHou, Li-Hui et al. Randomized controlled trial of letrozole, berberine, or a combination for infertility in the polycystic ovary syndrome. *Fertility and Sterility*, Volume 106, Issue 3, 757 - 765.e1


Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wei et al(^3)</td>
<td>RCT</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>None</td>
</tr>
<tr>
<td>Orio et al(^4)</td>
<td>Case Control</td>
<td>Serious(^b)</td>
<td>Not Serious</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

\(^a\) Failed to report outcomes where treatment effect could be clearly identified.

\(^b\) Relied on intragroup comparisons and control group where healthy and not patients with PCOS.

\(^c\) There are no confidence intervals, but they do have small standard deviations and p values that reach statistical significance.
Figure 1.