Effect of berberine on cardiovascular disease risk factors: abridged secondary publication

J Zhao *, DKM Ip, JYY Leung, D Vackova, X He, CM Schooling

KEY MESSAGES

1. In Chinese men, berberine lowers total cholesterol and probably lowers low-density lipoprotein cholesterol, with good safety and tolerability.
2. Berberine does not lower testosterone in men, which is in contrast to previous evidence on testosterone in women. This suggests a sex-specific effect of berberine on sex hormones.
3. Exploring other pathways and sex disparity is worthwhile and has relevance to public health and healthcare.

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[1] J Zhao, [1] DKM Ip, [1] JYY Leung, [1] D Vackova, [2] X He, [1] CM Schooling

[1] *School of Public Health, The University of Hong Kong, Hong Kong SAR, China*
[2] *Pok Oi Hospital, Hong Kong SAR, China*

* Principal applicant and corresponding author: janezhao@hku.hk

Introduction

In Hong Kong, cardiovascular disease (CVD) is a major disease burden and its rate is higher in men than in women. Berberine is a traditional Chinese medicine; it is an isoquinoline plant alkaloid, belonging to the class of protoberberines. Berberine tablets are extracted from *Coptis chinensis* (Huanglian) and *Phellodendron chinense* (Huangbai) and used in clinical practice for digestive diseases.[1] Berberine has beneficial effects on lowering lipids and fasting glucose in patients with hyperlipidaemia and/or diabetes.[2] Potential benefits of berberine for blood pressure control and adiposity have also been reported in a systematic review,[1] although there is high heterogeneity among studies in terms of study quality and design.[2,3] No serious adverse event has been reported,[1] which suggests good tolerability of berberine supplementation.

Nonetheless, the mechanism by which berberine exerts a protective role in atherosclerosis is unclear. Protoberberines have been identified as a new inhibitor of aldo-keto reductase family 1 member C3 (AKR1C3), an enzyme responsible for regulation of steroid hormone action, such as estrone to 17β-estradiol and androstendione to testosterone, which raises the possibility of action via sex hormones. Accumulating evidence suggests androgens might be a modifiable causal factor underlying men's cardiovascular disadvantage.[4] Berberine also lowers total testosterone in women,[5] although its effect on testosterone in men has not been examined. We hypothesised that berberine might exert its beneficial effects on CVD risk factors by lowering testosterone. We examined the effects of berberine on CVD risk factors, specifically lipids, systolic and diastolic blood pressure, thromboxane A2, and adiposity, as well as the potential mediation via testosterone in Chinese men with hyperlipidaemia.

Methods

A volunteer sample of 84 Chinese men aged 20 to 65 years with hyperlipidaemia was recruited from staff and/or their families of The University of Hong Kong and from an outpatient clinic in Department of Medicine, Queen Mary Hospital. Hyperlipidaemia was defined as triglycerides >150 mg/dL (1.70 mmol/L), total cholesterol >200 mg/dL (5.16 mmol/L), and/or low-density lipoprotein cholesterol (LDL-c) >100 mg/dL (2.58 mmol/L) according to the National Cholesterol Education Program Adult Treatment Panel II. The volunteers were not receiving hormone replacement therapy such as testosterone replacement therapy in the past 12 months or taking berberine or nutraceuticals that contain berberine. The volunteers were free of any congenital diseases (eg, familial hypercholesterolemia) or any infectious diseases (eg, seasonal influenza) and had no history of any chronic diseases (ischaemic heart disease, myocardial infarction, stroke, diabetes, cancer, and liver/renal dysfunction).

Participants were equally randomised to receive either purified berberine tablets (500 mg) orally twice a day or placebo for 12 weeks. Primary outcomes included lipids (total cholesterol, LDL-c, triglycerides, high-density lipoprotein cholesterol), systolic and diastolic blood pressure, thromboxane A2, and serum testosterone from fasting blood samples. Secondary outcomes included body mass index and waist-hip ratio. Participants were assessed at baseline and at 8 weeks and 12 weeks.

An intention to treat analysis was used. Changes in CVD risk factors were compared between

TABLE 1. Baseline characteristics of the participants in berberine and placebo groups*

Characteristic	Berberine group (n=40)	Placebo group (n=40)
Place of birth		
Hong Kong	36 (90)	33 (82.5)
Macau	0	2 (5)
Mainland China	4 (10)	5 (12.5)
Education level		
Primary school	6 (15.0)	7 (17.5)
High school	25 (62.5)	20 (50)
University and above	9 (22.5)	13 (32.5)
Smoking status		
Non-smoker	24 (60)	30 (75)
Ex-smoker	12 (30)	5 (12.5)
Current smoker	4 (10)	5 (12.5)
Alcohol drinking		
Never	6 (15.0)	8 (20)
Ex-drinker	10 (25.0)	8 (20)
<1 day per week	15 (37.5)	15 (37.5)
1-2 days per week	3 (7.5)	7 (17.5)
3-7 days per week	6 (15)	2 (5)
Age, y	49.5±11.1	44.8±13.5
Time of doing physical activity per day, min		
Vigorous	85.0±43.7	71.0±60.9
Moderate	69.6±51.0	76.8±83.9
Light	67.3±61.2	60.0±59.9

* Data are presented as No. (%) of participants or mean±standard deviation

TABLE 2. Effect of berberine on cardiovascular disease risk factors and testosterone

Cardiovascular disease risk factor	Beta (95% confidence interval)	P value
Total cholesterol	-0.39 (-0.62 to -0.16)	0.001
Low-density lipoprotein cholesterol	-0.23 (-0.43 to -0.02)	0.03
Triglycerides	-0.31 (-0.67 to 0.06)	0.10
High-density lipoprotein cholesterol	-0.03 (-0.09 to 0.02)	0.26
Systolic blood pressure	-0.91 (-4.75 to 2.93)	0.64
Diastolic blood pressure	-0.31 (-3.42 to 2.80)	0.84
Body mass index	-0.39 (-0.99 to 0.21)	0.20
Waist-hip ratio	-0.006 (-0.02 to 0.01)	0.36
Thromboxane A2	8.46 (-23.0 to 39.9)	0.60
Testosterone	1.31 (0.30 to 2.33)	0.01

the berberine and placebo groups using generalised estimating equation model.

Results

A total of 84 men were randomly assigned to the berberine group (n=42) and the placebo group (n=42). Two men in each group were lost to follow-up; 40 men in each group were included for analysis (Table 1). After intervention, men taking berberine had a larger reduction in total cholesterol and LDL-c than those taking placebo (Table 2). Changes in other CVD risk factors did not differ between the two groups. Inconsistent with our hypothesis, berberine did not lower testosterone in men but may increase testosterone. Berberine was well-tolerated with no serious adverse event. Headache occurred in one participant in berberine group; diarrhoea occurred in one participant in berberine group; headache, nausea, and vomiting occurred in one participant in placebo group. All adverse events resolved after stopping taking berberine or placebo.

Discussion

Our findings are consistent with one study that shows a beneficial effect of berberine on total cholesterol and probably LDL-c,[2] but no effect on other CVD risk factors, which is not consistent with other studies,[1,3] although the directions of most effects are beneficial. Moreover, large differences between randomised controlled trials make overall estimates difficult to interpret.[2,3] For example, different trials have varying dosages (from 0.9 g daily to 1.5 g daily), intervention periods (from 1 month to 2 years), and quality.[2] The present study was conducted in men without established CVD or diabetes, in whom berberine may have more effects on CVD risk factors.

In women with polycystic ovary syndrome, supplementation with berberine (1500 mg/d for 3 months) was reported to lower testosterone,[5] although the present study suggests that berberine did not lower testosterone in men. The inconsistency might be due to the differences in dosage or polycystic ovary syndrome. In the present study, berberine tended to increase rather than decrease testosterone in men; berberine appeared to have a differential effect on testosterone by sex. Sex differences in response to drugs is increasingly recognised. Further study in women in the same setting for comparison is warranted to better understand the differential effects of berberine on endocrine factors in men and women.

Our study has several strengths. A pre-specified protocol was followed to avoid selective reporting. Our study for the first time examined the effect of berberine on testosterone and thromboxane

A2 in men. The findings may provide insight into sex-specific effects of berberine. However, there are limitations to the study. The sample size was relatively small, and the findings may not be generalised to other settings. The level of testosterone may vary at different time points of a day, although all samples for assessment were collected in the morning. Thromboxane A2 level in participants varied widely; the null effect may be due to lack of power. Our findings in Chinese men may not apply to other populations with different sex hormone profiles, but the directions of effects are not expected to differ.

Conclusion

In Chinese men, berberine lowers total cholesterol and probably lowers LDL-c, with good safety and tolerability. Berberine does not lower testosterone in men, which differs from previous evidence on testosterone in women.

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Disclosure

The results of this research have been previously published in:

1. Zhao JV, Yeung WF, Chan YH, et al. Effect of berberine on cardiovascular disease risk factors: a mechanistic randomized controlled trial. Nutrients 2021;13:2550.

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