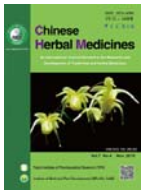

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Original article

Efficacy and Safety of Berberine in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

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ABSTRACT

Objective To assess the efficacy and safety of berberine (BBR) in patients with type 2 diabetes mellitus (T2DM) by performing a systematic review. **Methods** PubMed, Cochrane Library, Embase, CNKI, and CBM were searched until May 2014. The randomized controlled trials (RCTs) of the effects of BBR on blood glucose in patients with T2DM were included. The quality of RCTs was assessed by the Jadad scale, and the Review Manager 5.1 software was used for data syntheses and analyses. **Results** Seventeen RCTs involving 1198 patients were included. The methodological quality of these RCTs was generally low. Compared with the control groups (placebo or no intervention with medicine), BBR suggested the statistically significant benefits in improving fasting blood glucose (FBG), postprandial blood glucose (PBG), glycosylated hemoglobin, and homeostasis model assessment of insulin resistance. Subgroups analysis of BBR compared with metformin (MET) showed that 1.5g/d MET was significantly better than BBR (0.9–1.5 g/d) in lowering FBG and PBG. However, there was no significant difference between 1.5g/d BBR and 0.75g/d MET groups in blood glucose profiles. In comparison with rosiglitazone, BBR suggested the statistically significant benefits in lowering FBG. And there was no significant difference between BBR and glipizide groups in blood glucose profiles. In addition, the combination therapy of BBR and oral hypoglycemic agents had the advantages over oral hypoglycemic agents alone. No serious adverse effects of BBR have been reported. **Conclusion** BBR may have the beneficial effects in the control of blood glucose levels, though the efficacy of BBR is not superior to MET. BBR appeares to have advantages over rosiglitazone in improving FBG levels. In addition, the combination therapy of BBR and oral hypoglycemic agents may be a new attempt. However, the efficacy of BBR in patients with T2DM should be further evaluated by more RCTs in a larger population of patients.

Key words

berberine; efficacy; hypoglycemic agents; Meta-analysis; type 2 diabetes mellitus

1. Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases, which is the result of interaction between hereditary and environmental factors. More than 90% of diabetes is type 2 diabetes mellitus (T2DM, non-insulin dependent). Its incidence rate increases steadily together with the improvement of living level and population aging. The prevalence of DM was dramatically increasing throughout the world as well as in China with a prevalence of 4.3% among

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20- to 79-year-old people in 2007, estimated to increase to 5.6% in 2025 (Zhang et al, 2008). T2DM was recognized as Xiaokezheng (disease with symptomatic polydipsia) or Xiaodanzheng (disease with symptomatic polydipsia and polyphagia), and traditional Chinese medicine (TCM) has a long history in the treatment of Xiaokezheng (Ning et al, 2009).

Berberine (BBR, molecular formula $C_{20}H_{19}NO_5$ and molecular weight of 353.36), a natural plant alkaloid isolated from the Chinese herb, *Coptis chinensis* Franch. (Huanglian), is commonly used for the treatment of diarrhea, and its potential glucose-lowering effect has been noted (Ni, 1988). *In vitro* and *in vivo* studies subsequently showed that BBR has potentially beneficial effects in the treatment of diabetes (Lee et al, 2006; Zhang et al, 2008; Ding, et al, 2013). A number of reports on clinical trials have also been published on this subject in medical journals over the past 20 years. However, most of these trials are small sample size that may impact the reliability of the results. In addition, there are few multicenter, large sample clinical trials to confirm the hypoglycemic action. Therefore, we performed a Meta-analysis of randomized and controlled trials (RCTs) to systematically review the potential roles and effects of BBR in the regulation of blood glucose in order to provide the scientific evidence-based medicine basis for its clinical applications in the treatment of T2DM.

2. Materials and methods

2.1 Literature search

A systematic literature search was performed using the following electronic databases (until May 2014): PubMed, Embase, Cochrane Central Registry of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Weipu Database. The searched literature included the following terms and/or combinations in their titles, abstracts, or keyword lists: randomized controlled trials, BBR, and diabetes. No date or language limits were applied. References of included studies and previous relevant reviews were scanned for potentially relevant studies that had been missed in literature searching.

2.2 Study selection

RCTs were included, irrespective of blinding, publication status, or language. The inclusion criteria were as follows: 1) The subjects consumed a single chemical entity of BBR alone or with other hypoglycemic agents in the treatment of T2DM for at least two weeks; 2) The study was an RCT with either a parallel or a crossover design; 3) The effects of BBR on blood glucose profiles (including FBG, PBG, and HbA1c), and HOMA-IR could be extracted from the report.

Data expressed as medians were not included in this Meta-analysis, and the duplicates, case series, and case reports were also excluded.

2.3 Data extraction

Two authors (Xiao-chen Wei and Li-qin Zhu) independently extracted the data (patient characteristics, treatment details, and clinical outcomes) and assessed the methodological quality of included trials. Disagreements on study inclusion or data extraction were resolved by consensus of all coauthors. The outcomes included FBG, PBG, HbA1c, and HOMA-IR.

2.4 Assessment of trial quality

Methodology of trials included into the review was assessed with the Jadad scale (Jadad et al, 1996). Description of randomization procedure (0−2 points), description of a blinding method (0−2 points), and description of patients withdrawn from the trial (0 or 1 point) were taken into account. Studies with a Jadad score of 3 or above were regarded as high quality.

2.5 Data synthesis

All statistical analyses were performed using Review Manager 5.1 software. Two-sided *P* values less than 0.05 were considered statistically significant. For binary outcomes, the relative risk (RR) was used as a summary statistic. For continuous outcomes, so the relevant effects were differences between the means, summarized as weighted mean differences (MD) or where different scales were used to measure the same general attribute, standardized mean differences (SMD). All summary effects are presented with a 95% confidence interval (CI). Heterogeneity was specifically examined using I^2, where I^2 values of 50% and more indicated a substantial level of heterogeneity (Higgins et al, 2003). A random effects model was preferred where there was marked heterogeneity ($I^2 > 50\%$) and a fixed effects model in other circumstances. Further sensitivity analyses were performed by repeating the analysis based on different statistical models. Subgroup analyses according to the differences of agents and doses used in the control groups were performed as well.

3. Results

3.1 Study characteristics and quality

A total of 17 of 1948 screened studies were finally included (Zhang et al, 2008; Liu, 2004; Li and Liu, 2007; Cao, 2007; Yin et al, 2008; Li et al, 2008; Xu et al, 2008; Li, 2008; Wang, 2009; Sheng and Xie, 2010; Zhang et al, 2010; Yin et al, 2011; Zhang et al, 2011; Wang et al, 2012; Cao et al, 2012; Liu, 2012; Zhang and Yuan, 2012) with a total of 1198 patients. The main reasons for RCT exclusion were inclusion of duplicates, missing data, and unfulfilling the inclusion criteria. The included studies were published as full text between 2004 and 2013. All RCTs originated from China. Three studies were published in English (Zhang et al, 2008; Yin et al, 2008; Zhang et al, 2010), and the remaining studies

were published in Chinese. All studies were parallel designs. Four studies had three arms (Li and Liu, 2007; Cao, 2007; Li 2008; Zhang et al, 2010). Details of included studies are presented in Table 1. According to the Jadad scale, most of the included trials in this Meta-analysis were of poor quality (Jadad score < 3), suggesting a high risk of bias. Only two studies (Zhang et al, 2008; Li et al, 2008) were of high quality (4 and 3 points respectively).

3.2 Outcomes

3.2.1 BBR vs control (placebo or no intervention with medicine)

As shown in Figure 1, a total of 231 patients with T2DM were randomized in three trials to BBR *vs* control (Zhang et al, 2008; Cao, 2007; Wang, 2009). Meta-analysis showed BBR suggested the statistically significant benefits in improving FBG (MD −0.86, 95% CI −1.19, −0.53), PBG (MD −1.67, 95% CI −2.28, −1.05), HbA1c (MD −0.48, 95% CI −0.74, −0.21) and HOMA-IR (MD −1.62, 95% CI −2.42, −0.83). The results of the meta-analysis are summarized in Table 2.

3.2.2 BBR vs oral hypoglycemic agents

1) BBR (0.9−1.5g/d) vs metformin (1.5g/d)

As shown in Figure 2, a total of 243 patients were randomized in five trials to BBR *vs* metformin (MET) (Cao, 2007; Yin et al, 2008; Li, 2008; Zhang et al, 2010; Wang et al, 2012). Meta-analysis showed MET was significantly better than BBR in lowering FBG (MD 0.93, 95% CI 0.44, 1.43) and PBG (MD 1.57, 95% CI 0.81, 2.34). There was no significant difference between groups in HbA1c (MD 0.33, 95% CI −0.09, 0.75). The results of the Meta-analysis are summarized in Table 3.

Table 1 Characteristics of included trials

Study	No. of patients		Course of disease /y		Intervention		Duration/d	Outcomes
	Treatment	Control	Treatment	Control	Treatment	Control		
Zhang et al, 2008	58	52	NS		BBR, 0.5 g, bid	PL	90	FBG, PBG, HbA1c, HOMA-IR
Liu, 2004	35	33	NS		BBR, 0.5 g, tid + MET, 0.25−0.5 g, tid	MET, 0.25−0.5 g, tid	14	FBG, PBG
Li and Liu, 2007	51	50	0.5−4		BBR, 0.3 g, tid	GLIP, 15 mg, qd		FBG, PBG, HbA1c
	51				BBR, 0.3 g, tid + GLIP, 15 mg, qd		60	
Cao, 2007	30	30	9.6 ± 3.4	9.9 ± 3.3	BBR, 0.5 g, tid	No	90	FBG, PBG, HbA1c, HOMA-IR
		30		9.7 ± 3.6		MET, 0.5 g, tid		
Yin et al, 2008	15	16	newly-diagnosed		BBR, 0.5 g, tid	MET, 0.5g, tid	91	FBG, PBG, HbA1c
Li et al, 2008	33	32	9.01 ± 1.99	8.11 ± 2.24	BBR, 0.5 g, tid	MET, 0.25 g, tid	90	FBG, PBG, HbA1c
Xu et al, 2008	32	32	0−2		BBR, 0.3 g, tid + PIO, 30 mg,qd	PIO, 30 mg, qd	84	FBG, PBG
Li, 2008	17	17	NS		BBR, 0.3 g, tid	MET, 0.5 g, tid	84	FBG, PBG
	18				BBR, 0.3 g, tid + MET, 0.5 g, tid			
Wang, 2009	31	30	newly-diagnosed		BBR, 0.3 g, tid	No	84	FBG, PBG, HbA1c
Sheng and Xie, 2010	30	30	5 ± 3		BBR, 0.5 g, tid + MET, 0.5 g, tid + GLIP, 5 mg, bid	MET, 0.5 g, tid + GLIP, 5 mg, bid	90	FBG
Zhang et al, 2010	50	26	NS		BBR, 0.5 g, bid	MET, 0.75 g, bid	60	FBG, HbA1c
		21				RGZ, 4 mg, qd		
Yin et al, 2011	30	30	newly-diagnosed		BBR, 0.3 g, tid + MET, 0.5 g, tid	MET, 0.5 g, tid	180	FBG, PBG, HbA1c
Zhang et al, 2011	30	30	5.1 ± 1.3	6.1 ± 1.2	BBR, 0.02 g·kg^{-1}·d^{-1}	RGZ, 4 mg, qd	90	FBG, HbA1c, HOMA-IR
Wang et al, 2012	22	20	newly-diagnosed		BBR,0.3g,tid	MET, 0.5 g, tid	180	FBG, PBG, HbA1c
Cao et al, 2012	38	40	newly-diagnosed		BBR, 0.5 g, tid + MET, 0.5 g, tid	MET, 0.5 g, tid	112	FBG, PBG, HbA1c，HOMA-IR
Liu, 2012	16	16	5.5 ± 3.5	5.5 ± 4.5	BBR, 0.5 g, tid	GLIP, 10−30 mg, bid or tid	90	FBG
Zhang and Yuan, 2012	38	38	NS		BBR, 0.5 g−0.8 g, tid + MET, 0.5 g, tid	MET, 0.5 g, tid	90	FBG, PBG, HbA1c

NS: not specified; BBR: berberine; MET: metformin; GLIP: glipizide; PIO: pioglitazone; RGZ: rosiglitazone

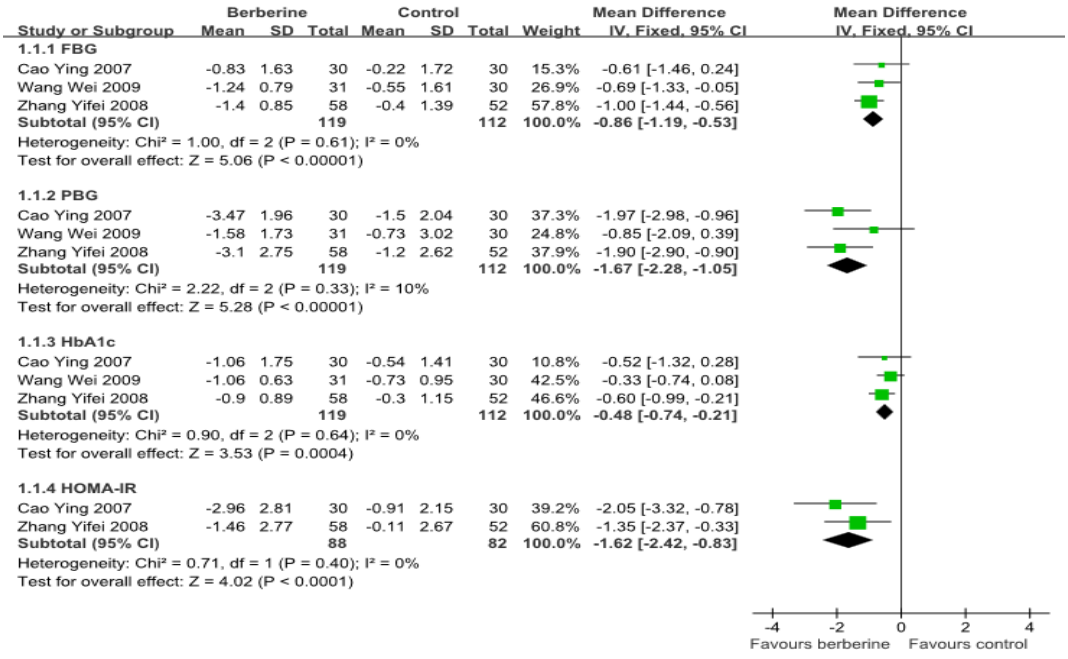

Figure 1 Forest plot of BBR *vs* control

Table 2 Outcomes of Meta-analysis of BBR *vs* control

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity / %	*P*
FBG	3	231	Fixed, MD = −0.86 [−1.19, −0.53]	I^2 = 0, *P* = 0.61	< 0.00001
P2hBG	3	231	Fixed, MD = −1.67 [−2.28, −1.05]	I^2 = 10, *P* = 0.33	< 0.00001
HbA1c	3	231	Fixed, MD = −0.48 [−0.74, −0.21]	I^2 = 0, *P* = 0.64	0.0004
HOMA-IR	2	170	Fixed, MD = −1.62 [−2.42, −0.83]	I^2 = 0, *P* = 0.40	< 0.0001

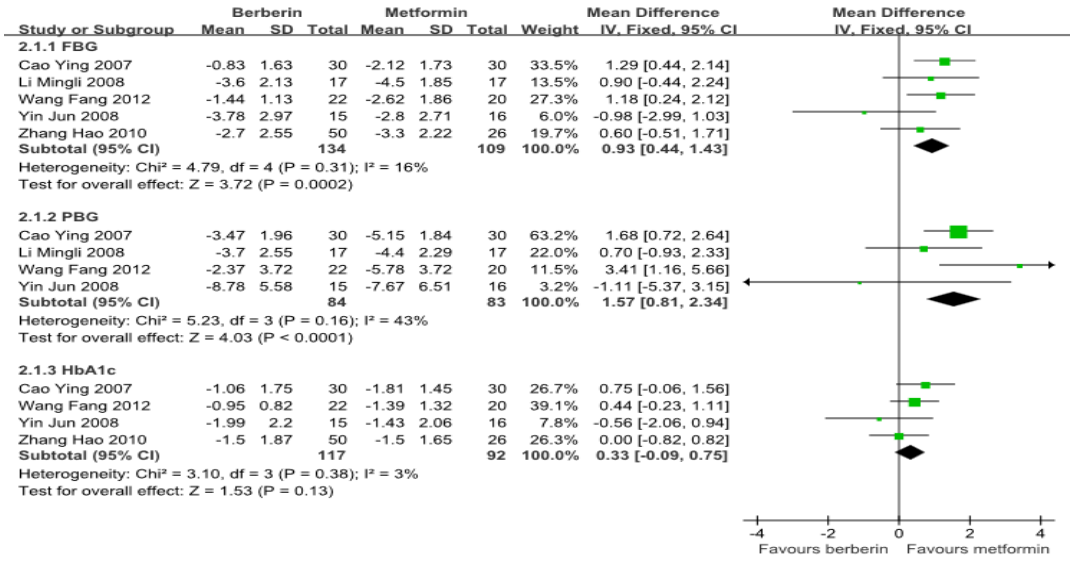

Figure 2 Forest plot of BBR (0.9−1.5 g/d) *vs* MET (1.5 g/d)

Table 3 Outcomes of Meta-analysis of BBR (0.9−1.5 g/d) *vs* MET (1.5 g/d)

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity/%	*P*
FBG	5	243	Fixed, MD = 0.93 [0.44, 1.43]	I^2 = 16, *P* = 0.31	0.0002
PBG	4	167	Fixed, MD = 1.57 [0.81, 2.34]	I^2 = 43, *P* = 0.16	< 0.0001
HbA1c	4	209	Fixed, MD = 0.33 [-0.09, 0.75]	I^2 = 3, *P* = 0.38	0.13

2) 1.5 g/d BBR vs 0.75 g/d MET

As shown in Figure 3, the only trial made this comparison (Li et al, 2008). There was no significant difference between groups in FBG (MD −0.19, 95% CI −1.41, 1.03), PBG (MD −0.48, 95% CI −2.35, 1.39) and HbA1c (MD 0.78, 95% CI −0.82, 2.38). The results of the Meta-analysis were summarized in Table 4.

3) BBR vs rosiglitazone

As shown in Figure 4, a total of 131 patients were randomized in two trials to BBR *vs* rosiglitazone (RGZ) (Zhang et al, 2010; 2011). Meta-analysis showed BBR was significantly better than RGZ in lowering FBG (MD −0.77, 95% CI −1.44, −0.11) and there was no significant difference between groups in HbA1c (MD −0.34, 95% CI −0.83, 0.15) or HOMA-IR (MD −0.20, 95% CI −0.52, 0.12). The results of the meta-analysis are summarized in Table 5.

4) BBR vs glipizide

As shown in Figure 5, a total of 133 patients were randomized in two trials to BBR *vs* glipizide (GLIP) (Li and Liu, 2007; Liu, 2012). The statistical heterogeneity among studies was found to be significant with respect to the result for FBG (I^2 = 73%). Meta-analysis showed there was no significant difference between groups in FBG (MD −0.59, 95% CI −3.54, 2.37), PBG (MD −0.20, 95% CI −1.28, 0.88) or HbA1c (MD 0.10, 95% CI −0.47, 0.67). The results of the Meta-analysis are summarized in Table 6.

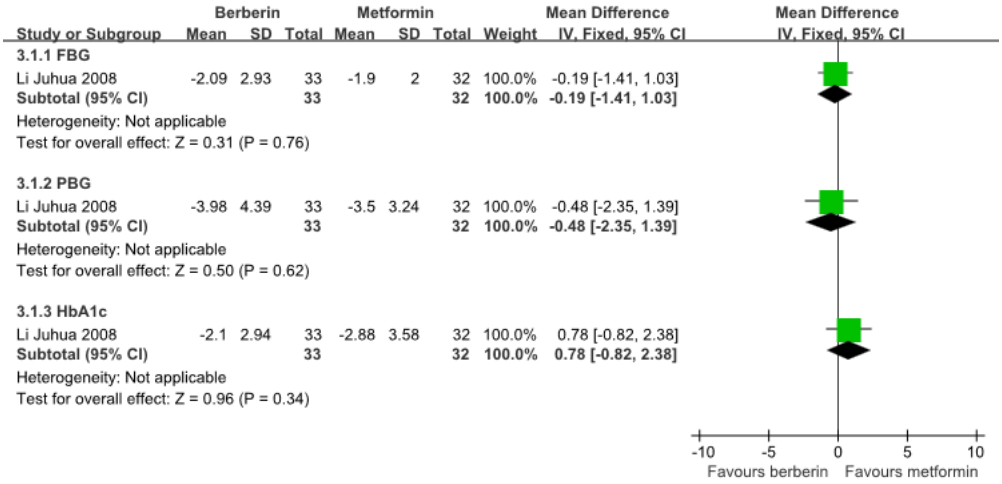

Figure 3 Forest plot of BBR (1.5 g/d) *vs* MET (0.75 g/d)

Table 4 Outcomes of Meta-analysis of BBR (1.5 g/d) *vs* MET (0.75 g/d)

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity	*P*
FBG	1	65	Fixed, MD = −0.19 [−1.41, 1.03]	Not applicable	0.76
PBG	1	65	Fixed, MD = −0.48 [−2.35, 1.39]	Not applicable	0.62
HbA1c	1	65	Fixed, MD = 0.78 [−0.82, 2.38]	Not applicable	0.34

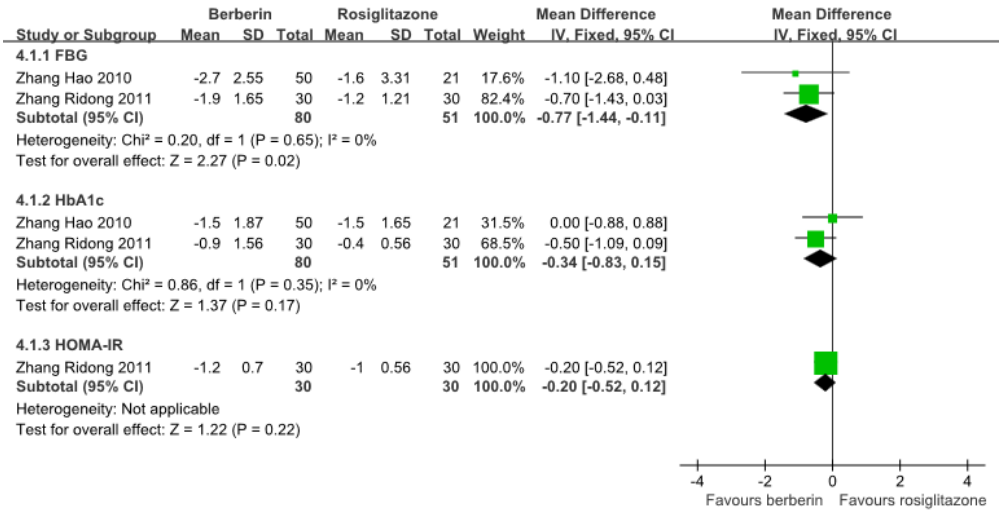

Figure 4 Forest plot of 1 g/d or (0.02 g·/kg·d) BBR *vs* RGZ (4 mg/d)

Table 5 Outcomes of Meta-analysis of BBR (1 g/d or 0.02 g·kg^{-1}·d^{-1}) *vs* RGZ (4 mg/d)

Outcomes	No. of studies	No. of patients	Effect estimate / 95% CI	Heterogeneity / %	*P*
FBG	2	131	Fixed, MD = −0.77 [−1.44, −0.11]	I^2 = 0, *P* = 0.65	0.02
HbA1c	2	131	Fixed, MD = −0.34 [−0.83, 0.15]	I^2 = 0, *P* = 0.35	0.17
HOMA-IR	1	60	Fixed, MD = −0.20 [−0.52, 0.12]	Not applicable	0.22

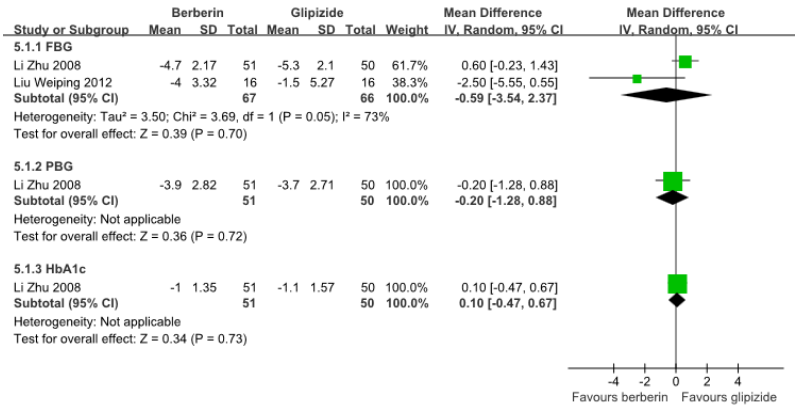

Figure 5 Forest plot of BBR (0.9−1.5 g/d) *vs* GLIP (10−30 mg/d)

Table 6 Outcomes of Meta-analysis of BBR (0.9−1.5 g/d) *vs* GLIP (10−30 mg/d)

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity / %	*P*
FBG	2	133	Random, MD = −0.59 [−3.54, 2.37]	I^2 = 73, *P* = 0.05	0.70
PBG	1	101	Fixed, MD = −0.20 [−1.28, 0.88]	Not applicable	0.72
HbA1c	1	101	Fixed, MD = −0.10 [−0.47, 0.67]	Not applicable	0.73

3.2.3 Combination therapy of BBR and oral hypoglycemic agents vs same oral hypoglycemic agents alone

1) BBR + MET vs MET

As shown in Figure 6, a total of 317 patients were randomized in five trials to BBR and MET *vs* MET (Liu, 2004; Li, 2008; Yin et al, 2011; Cao et al, 2012; Zhang and Yuan, 2012). Meta-analysis showed the combination therapy of BBR and MET was significantly better than MET alone in lowering FBG (MD −0.62, 95% CI −1.00, −0.24), PBG (MD −0.62, 95% CI −1.09, −0.16) and HbA1c (MD −0.67, 95% CI −0.91, −0.42). There was no significant difference between groups in HOMA-IR (MD −1.01, 95% CI −2.25, 0.23). The results of the Meta-analysis were summarized in Table 7.

2) BBR + PIO vs PIO

As shown in Figure 7, the only trial (Xu et al, 2008), which made this comparison, revealed the combination therapy of BBR and PIO was statistically significant better than PIO alone in lowering FBG (MD −1.10, 95% CI −1.32, −0.88) and PBG (MD −0.90, 95% CI −1.12, −0.68). The results of the Meta-analysis were summarized in Table 8.

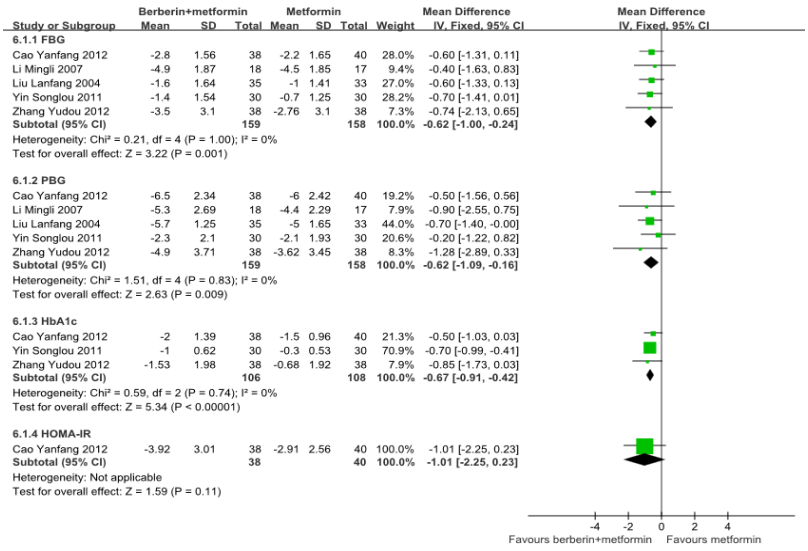

Figure 6 Forest plot of BBR+MET *vs* MET

Table 7 Outcomes of Meta-analysis of BBR + MET *vs* MET

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity/%	*P*
FBG	5	317	Fixed, MD = −0.62 [−1.00, −0.24]	I^2 = 0, *P* = 1.00	0.001
PBG	5	317	Fixed, MD = −0.62 [−1.09, −0.16]	I^2 = 0, *P* = 0.83	0.009
HbA1c	3	214	Fixed, MD = −0.67 [−0.91, −0.42]	I^2 = 0, *P* = 0.74	< 0.00001
HOMA-IR	1	78	Fixed, MD = −1.01 [−2.25, 0.23]	Not applicable	0.11

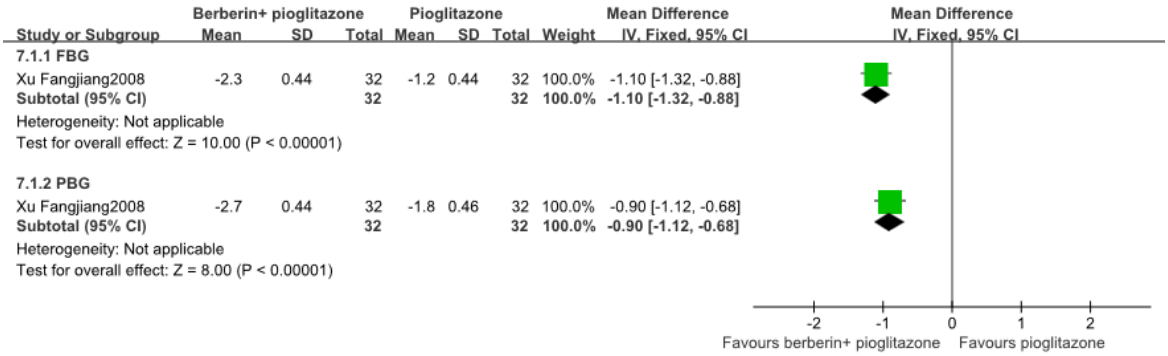

Figure 7 Forest plot of BBR + PIO *vs* PIO

Table 8 Outcomes of Meta-analysis of BBR + PIO *vs* PIO

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity	*P*
FBG	1	64	Fixed, MD = −1.10 [−1.32, −0.88]	Not applicable	< 0.00001
PBG	1	64	Fixed, MD = −0.90 [−1.12, −0.68]	Not applicable	< 0.00001

3) BBR + GLIP vs GLIP

As shown in Figure 8, the only trial (Li and Liu, 2007), which made this comparison, showed the combination therapy of BBR and GLIP was statistically significant better than glipzide alone in lowering PBG (MD −1.20, 95% CI −2.12, −0.28). There was no significant difference between groups in FBG (MD −0.20, 95% CI −0.95, 0.55) or HbA1c (MD −0.30, 95% CI −0.87, 0.27). The results of the Meta-analysis are summarized in Table 9.

4) BBR + MET + GLIP vs MET + GLIP

As shown in Figure 9, the only trial (Sheng and Xie, 2010), which made this comparison, suggested there was a statistically significant lower FBG (MD −0.54, 95% CI −1.07, −0.01) in the BBR and MET and GLIP group. The results of the Meta-analysis are summarized in Table 10.

3.3 Adverse effects

Eleven of 17 trials reported outcomes for adverse effects (Zhang et al, 2008; Liu, 2004; Li and Liu, 2007; Cao, 2007; Yin et al, 2008; Xu et al, 2008; Wang, 2009; Yin, Li, and Liu, 2011; Wang et al, 2012; Cao et al, 2012; Zhang and Yuan, 2012). In one of these trials (Cao, 2007), no adverse effects were reported during the BBR treatment. The remaining trials mentioned in detail that adverse effects occurred in the BBR intervention group. Gastrointestinal problems, such as constipation, diarrhea, nausea, and abdominal distension were

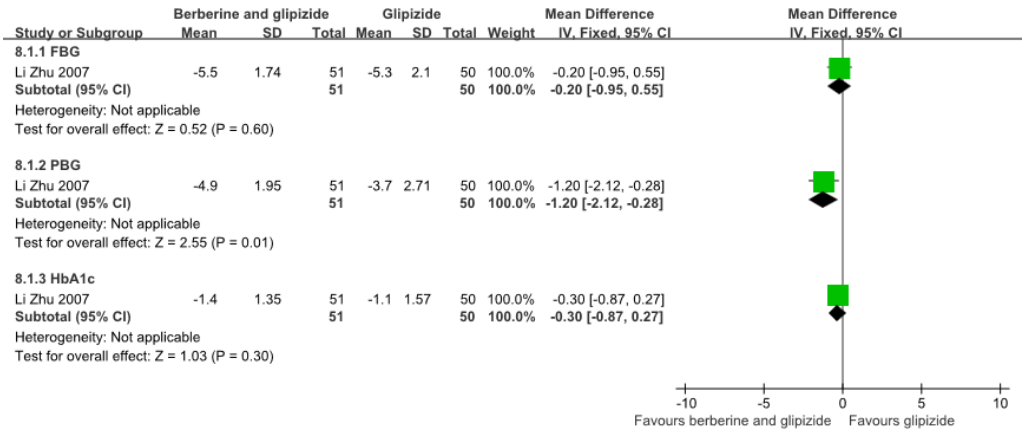

Figure 8 Forest plot of BBR+ GLIP *vs* GLIP

Table 9 Outcomes of Meta-analysis of BBR + GLIP *vs* GLIP

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity	*P*
FBG	1	101	Fixed, MD = −0.20 [−0.95, 0.55]	Not applicable	0.60
PBG	1	101	Fixed, MD = −1.20 [−2.12, −0.28]	Not applicable	0.01
HbA1c	1	101	Fixed, MD = −0.30 [−0.87, 0.27]	Not applicable	0.30

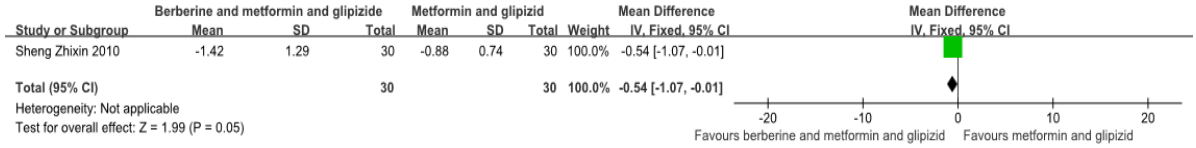

Figure 9 Forest plot of BBR + MET + GLIP *vs* MET+GLIP

Table 10 Outcomes of Meta-analysis of BBR + MET + GLIP *vs* MET+GLIP

Outcomes	No. of studies	No. of patients	Effect estimate (95% CI)	Heterogeneity	*P*
FBG	1	60	Fixed, MD = −0.54 [−1.07, −0.01]	Not applicable	0.05

the most commonly reported side effects. However, these side effects were tolerable and were relieved after reducing the dose of BBR. No severe hypoglycemia was reported in these trials.

3.4 Sensitivity analyses

No noteworthy changes in any of the study endpoints were noted after conducting sensitivity analyses.

4. Discussion

With the substantial numbers of clinical reports about the antidiabetic effect of BBR, BBR had attracted more and more attention. Narenqimuge et al firstly reported a systematic review of the hypoglycemic action of BBR in patients with T2DM in January 2012 (Narenqimuge et al, 2012). There were ten RCTs involving 647 patients in their review. However, taking the differences in clinical characteristics into consideration, the authors only reported the outcomes of each trial rather than performing a Meta-analysis. Afterwards, in October 2012, Dong et al also assessed the hypoglycemic effect of BBR by performing a systematic review that included 14 RCTs with 1068 patients (Dong et al, 2012). Although the authors performed a Meta-analysis, the significant statistical heterogeneity occurred in most of outcomes. In addition, the ending values were adopted to analyze, rather than difference values before and after the trials in their review. Both of these may impact the reliability of the results. Moreover, the partial results of BBR in improving blood glucose profiles were inconsistent based on the two systematic reviews. Therefore, it was necessary to again perform a systematic review to assess the efficacy of BBR in patients with T2DM. In this systematic review, 17 RCTs involving 1198 patients were included and HOMA-IR that represented insulin resistance was firstly added to analyze in order to more comprehensively assess the efficacy of BBR in the treatment of T2DM.

This Meta-analysis revealed that BBR intake was associated with a significant decrease in FBG (0.86 mmol/L), PBG (1.67 mmol/L), HbA1c (0.48%) and HOMA-IR (1.62 μIU/mol·L^2) compared with the control group. This beneficial effect did not change when sensitivity analyses were performed. Therefore, BBR not only has benefits in lowering blood glucose, but also improving insulin resistance. The mechanism of BBR on glucose metabolism is still under investigation. Many studies attempted to elucidate its potential mechanism. Lee et al (2006) reported that BBR can activate AMP-activated protein kinase (AMPK) in 3T3-L1 adipocytes and L6 myotubes and facilitate GLUT4 translocation in L6 myotubes. Yin et al (2002) and Zhou et al (2007) reported that BBR promoted glucose uptake in HepG2 and 3T3-L1 cells independent of insulin action, Yin et al (2008) also found BBR enhanced glucose metabolism by stimulation of glycolysis. Deng et al (2005) reported that BBR improved insulin sensitivity by increasing the protein tyrosine kinase activity of membrane-bound insulin receptors from T2DM. Accordingly, BBR appeared to improve blood glucose by a variety of mechanisms.

To explore the relative efficacies of BBR, we also performed a Meta-analysis that BBR was compared with the conventional hypoglycemic agents. Because of different agents (MET, rosiglitazone, and GLIP) and doses adopted in these studies, we performed to analyze respectively. The results showed MET (1.5 g/d) intake was much better than BBR (0.9−1.5 g/d) in lowering blood glucose. However the similar glycemic control was observed when BBR (1.5 g/d) intake was compared with MET (0.75 g/d). Overall, BBR was not superior to MET in improving blood glucose. In addition, BBR (1 g/d or 0.02 g·kg^{-1}·d^{-1}) intake was better than rosiglitazone (4 mg /d) in lowering FBG. And there was no difference between groups in HbA1c and HOMA-IR. These outcomes appeared to suggest BBR had the advantages over rosiglitazone in improving FPG levels. Afterwards, compared with GLIP, BBR demonstrated the similar outcomes in improving blood glucose. However, there was a considerable heterogeneity among the studies with respect to FBG (I^2 = 73%), and only one trial included in PBG and HbA1c, so we

should cautiously interpreted. Furthermore, BBR exhibited consistent activities in improvement of glycemic parameters for patients with T2DM in combination with the anti-diabetic agents referring to MET, GLIP, and PIO. So the combination therapy of BBR, and oral hypoglycemic agents appeared to be a new attempt in the control of blood glucose levels for the patients with T2DM.

It also should be noted that the following several potential limitations of this Meta-analysis should be included. 1) All the participants were recruited from Chinese populations, indicating a risk of selection bias. This could affect the applicability of the interventions to populations from other ethnic origin. 2) Publication bias may occur, because our analyses were based entirely on published studies. 3) Most of the studies included were of poor quality. Only two RCTs (Zhang et al, 2008; Li et al, 2008) described the methods of the randomization. And only one RCT (Zhang et al, 2008) used a double blind and allocation concealment. If participants are not blinded, knowledge of group assignment may affect the responses to the intervention (Schulz and Grimes, 2002a). Moreover, inadequate allocation concealment may lead to the exaggerated estimates of treatment effect (Schulz and Grimes, 2002b). 4) Small sample size was in most studies. 5) Heterogeneity among the studies was detected in some parameters. Heterogeneity may be caused by the differences in clinical characteristics (such as course of disease, dose, and duration) and methodological characteristics. Taking this into consideration, the conclusions should be carefully interpreted because of the substantial clinical and methodological diversity of the studies.

5. Conclusion

This Meta-analysis suggests that BBR has a potential hypoglycemic effect. And it also has the benefits in improving insulin resistance. In addition, BBR is not superior to MET in improving blood glucose, while appears to have the advantages over rosiglitazone in lowering FBG levels. The combination therapy of BBR and oral hypoglycemic agents may be a new attempt in the control of blood glucose levels. However, large well-designed RCTs are needed to verify this result, if BBR is to be recommended for clinical use in the treatment of T2DM.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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