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SYSTEMATIC REVIEW

Effect of curcumin on rats/mice with diabetic nephropathy: a systematic review and Meta-analysis of randomized controlled trials

Wei Wu, Hua Geng, Zhaoru Liu, Hong Li, Zhangzhi Zhu

Wei Wu, Hua Geng, Zhaoru Liu, Hong Li, Institute of Diabetes, the First Clinical Medical College of Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China

Zhangzhi Zhu, Department of Endocrine, the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China

Correspondence to: Prof. Wei Wu, Institute of Diabetes, the First Clinical Medical College of Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China. wuwei.jiujiang@163.com

Telephone: +86-20-36587241; +86-13711280371

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Abstract

OBJECTIVE: To assess the renal protective effects of curcumin administration on diabetic rats/mice.

METHODS: Databases were searched electronically and conference papers searched manually for search terms to find relevant studies. Articles were assessed independently by two reviewers. Review Manager 5.1 was used for data analysis.

RESULTS: Fourteen randomized controlled experiments were included. Meta-analysis demonstrated that blood sugar levels and kidney weight to body weight ratios in the model group were higher than those in the normal group, and the curcumin group had significantly lower mesangial area to glomerular area ratios compared with the model group, and also lower levels of urinary protein, blood urea nitrogen and serum creatinine.

CONCLUSION: Curcumin shows protective effects on the kidneys of rats/mice with diabetes.

Key words: Curcumin; Diabetic nephropathies; Meta-analysis; Review; Randomized controlled trials

INTRODUCTION

Diabetic nephropathy (DN) is not only one of the most common complications of diabetes, but also one of the main causes of death from diabetes.[1] With the average lifespan increasing globally, DN has become a worldwide problem, and seriously threatens human health.[2,3] In developed countries in Europe and America, DN is a leading cause of end stage renal disease (ESRD).[4] In China, DN accounts for about 15% of ESRD, and DN will be a leading cause of ESRD in the 21st century.[5,6] Unfortunately, the pathogenesis of DN is not yet fully understood. Basic treatment includes controlling blood sugar and blood pressure levels, but there are no effective measures to reverse, arrest or even delay the progression of DN. Some DN patients gradually develop ESRD.[7] Traditional Chinese Medicine attempts to treat and control diabetes and its complications by preserving islet beta-cells, increasing serum insulin levels[8] and insulin sensitivity,[9] and improving insulin sensitivity.[10] Animal experiments, to some extent, may give insights into the mechanisms of DN, but a single study may not fully reveal all the details. A systematic review may provide more significant evaluation of the effects. Although many studies globally have reported that curcumin is able to lower blood glucose levels, improve blood lipid metabolism, and slow down the progression of DN in diabetic rats/mice, it is still necessary to evaluate the effects of curcumin administration with a systematic review to provide more significant information about the experimental results.

METHODS

Database search strategy

The following electronic databases were searched:

PubMed (Jan 1966 to May 2013), EMBASE (Jan 1966 to May 2013), China National Knowledge Infrastructure Database (CNKI) (Jan 1979 to May 2013), Chinese Biomedical Literature Database (CBM) (Jan 1979 to May 2012), Wanfang Database (Jan 1980 to May 2013), China Science and Technology Journal Database (VIP) (Jan 1989 to May 2013). Additionally, important conference papers were searched manually. The search terms used were: "rats", "mice", "animal models", "experiment", "diabetes" or "diabetic nephropathy" combined with "curcumin". All articles were written in either English or Chinese. The searches were carried out independently by two reviewers (Wei Wu and Hua Geng who studied the evidence-based medicine courses of Guangzhou University of Traditional Chinese Medicine and passed the test).

Exclusion criteria

Exclusion criteria were: (a) clinical trials; (b) cell experiments; (c) studies of non-diabetic models; (d) studies with incomplete data, statistical mistakes, and/or different basic treatments between groups; and (e) repeated and similar studies.

Data extraction and quality assessment

The two reviewers independently extracted data from each article. Discrepancies were resolved by discussion or with the assistance of a third reviewer (Zhaoru Liu, studied the evidence-based medicine courses of Guangzhou University of Traditional Chinese Medicine and passed the test). The following information from each article was taken: article title, name of first author, year published and location, experimental environment, animal and model features, sample size, experimental design, drug dosage and administration, the number of animals excluded and the reasons, the number of dead animals, and outcomes (blood sugar, urinary protein, and serum creatinine levels). The quality of each study was assessed using items described in the ARRIVE guidelines (animal research: reporting *in vivo* experiments), which are recommended for quality assessment of animal experiments.[11,12] These items are based on the presence and short description of important study characteristics, such as title, abstract, background, objectives, ethical statement, study design, experimental procedures, experimental animals, housing and husbandry, sample size, allocating animals to experimental groups, experimental outcomes, statistical methods, baseline data, numbers analyzed, outcomes and estimation, adverse events, interpretation/scientific implications, generalizability/translation, and funding.

Data synthesis and analysis

We synthesized the results with Meta-analysis using Review Manager software (version 5.1;[13] Nordic Cochrane Center, Copenhagen, Denmark). Dichotomous data are presented as odds ratio (*OR*), relative risk (*RR*) or risk difference (*RD*); and continuous outcomes as weighted mean difference (*WMD*), mean differences (*MD*) or standard mean differences (*SMD*), both with 95% confidence intervals (*CI*). Heterogeneity was tested using χ^2 tests. Subgroup analysis was performed to evaluate the overall effects in possible subgroups grouped according to model type, study period, and drug dosage. A P value of <0.05 was considered statistically significant. Bias was examined using a funnel plot.

RESULTS

Characteristics of included studies

A total of 101 studies in Chinese or English were collected, and 14 articles were included in the final analysis.[14-27] Of the 14 articles, nine were from China,[14-20,23,27] three from India,[21,25,26] one from Japan,[24] and one from Thailand.[22] Of the nine studies from China, eight were published in Chinese.[14-20,27] The remaining studies were published in English.

The search steps used are shown in Figure 1. All experimental animals were purchased from one laboratory animal center, which including spontaneous diabetic rats/mice and induced diabetic rats/mice. For all but one study[27] of 10-week-old spontaneous diabetic mice, a blood glucose concentration above 16.7 mmol/L was used as the diabetic model standard in nine studies,[14-16,18-20,22-25] above 13.9 mmol/L in one study,[22] above 11.1 mmol/L in two studies,[21,26] and strong positive urine sugar in one study.[17] Intraperitoneal injection and gavage were used in the other studies. The dosage of curcumin was between 50 and 250 $mg \cdot kg^{-1} \cdot d^{-1}$ for all 14 studies. The duration of treatment ranged between 6 and 18 weeks. The characteristics of the studies are shown in Figure 1.

Quality of the included trials

All studies were randomized controlled trials. There was only one study[15] that described the specific method of randomization. In that study, animals were grouped according to blood sugar levels and weights. All studies reported the title, abstract, background, objectives, study design, experimental procedures, experimental animals, sample size, allocating animals to experimental groups, experimental outcomes, statistical methods, baseline data, numbers analyzed, outcomes and estimation, and interpretation/scientific implications. Of all included studies, 71.43% [14,17-19,21,23-27] reported housing and husbandry, and 28.57% [21,23-25] reported an ethical statement. No studies reported adverse events and generalizability/translation, and 50% [14,15,22-26] reported funding (Figure 2).

Treatment effects

Blood sugar levels: as shown in Figure 3, blood sugar levels were reported in 11 studies.[14,15,17-21,23-25,27] Subgroup analysis was carried out because different animal models were used. Blood sugar levels were significantly higher in the model group compared with the normal group [*SMD*=11.79, 95% *CI* (8.22, 15.35), P<0.01].