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Clinical trials of traditional Chinese medicine in the treatment of diabetic nephropathy—A systematic review based on a subgroup analysis

Xiaoyu Liu [a,1], Ling Liu [a,1], Pinyi Chen [a], Liang Zhou [a], Yanqi Zhang [a], Yazhou Wu [a], Lei Jiang [b], Dixiang Cheng [c], Wenquan Huang [b], Dong Yi [a,*]

[a] Department of Health Statistics, College of Preventive Medicine, Third Military Medical University, Chongqing 400038, China
[b] Department of Rehabilitation and Physiotherapy, Xinqiao Hospital, Third Military Medical University, Chongqing 400038, China
[c] Soft College, Chongqing University of Posts and Telecommunications, Chongqing 400065, China

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ABSTRACT

Ethnopharmacological relevance: The purpose of this study is to systematically evaluate the efficacy of traditional Chinese medicine (TCM) decoctions with different ingredients in the treatment of diabetic nephropathy (DN).

Materials and methods: Papers obtained after the retrieval of randomized controlled clinical trials (RCTs) of TCM treatments of diabetic nephropathy through online database (e.g. Medline, CBM, CNKI, VIP, the online database of Chinese medicine, CDFD, CMFD, and CENTRAL FROM Cochrane Library, etc.) as well as research data in our library. They were published between January 2001 and December 2012. According to the categories of the main TCM ingredients, all the cases in the literature were divided into a liver–kidney YIN deficiency group, a QI-BLOOD YIN-and-YANG deficiency group, and a spleen–kidney YANG deficiency group. Stata 11.0 was applied for subgroup analysis.

Results: A total of 21 Chinese RCTs were included in this review. The Q values of the three groups were 13.18, 0.25 and 3.27, respectively, $P>0.05$, and thus, there was no clinical heterogeneity. The combined relative risk (RR) value and its 95% confidence interval were 1.48 (1.37, 1.60), 1.19 (1.06, 1.34), and 1.33 (1.19, 1.50), respectively, $P<0.05$.

Conclusions: Compared with the qi-blood yin-and-yang deficiency group and the spleen–kidney yang deficiency group, the liver–kidney yin deficiency group has better prospects in clinical application to ensure renal function during the treatment of DN, and this possibility is worthy of further study.

1. Introduction

Diabetic Nephropathy (DN) is a common microvascular complication in patients with diabetes. This condition is difficult to treat and is one of most important causes of death following cardiovascular and cerebrovascular diseases in diabetic patients (Cooper et al., 2002). With the increasing incidence of diabetes, diabetes-induced end-stage renal failure has become the leading cause of chronic renal failure in the world (Deng, 2001). If the damage to the kidney and proteinuria is irreversible it will evolve into End Stage Renal Disease (ESRD) (Zhou, 2002). Proven, effective Western medical methods for the treatment of early diabetic nephropathy include a strict control of blood glucose, blood pressure and blood lipids and thus mainly involve the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) (Mogyrosi and Sonkoch, 1999). Although their effects are positive and stable, the follow-up showing pathological changes are still in progress (China Association of Traditional Chinese Medicine, 2007). Practitioners of traditional Chinese medicine (TCM) believe that in the early stage of DN, patients mostly exhibit yin (Sekia et al., 2005) deficiency in conjunction with dryness-hest in lung and spleen. The manifested by frequent urination and easily getting thirsty, soreness and weakness of waist and knees, dizziness and tinnitus. During the course of DN, the yin deficiency spreads to the yang (Sekia et al., 2005), causing a yin-and-yang deficiency. After a protracted period of time, the illness enters the vasculature, causing blood-vessel stasis. TCM treatment of DN mainly focuses on nourishing the

Abbreviations: TCM, traditional Chinese medicine; DN, diabetic nephropathy; RCT, randomized controlled clinical trial; CBM, Chinese biomedical literature database; CNKI, Chinese academy of sciences database; CDMD, Chinese doctoral dissertation full-text database

* Corresponding author. Tel.: +86 2368752344; fax: +86 2368752344.
E-mail addresses: liuxy1105@163.com, yd_house@hotmail.com (D. Yi).
[1] Xiaoyu Liu and Ling Liu are co-first authors.

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kidney, strengthening the spleen, replenishing the qi (Sekia et al., 2005), restoring the yin, promoting the blood circulation and resolving stasis. This approach has achieved certain treatment effects in the control of blood glucose, urinary albumin, serum creatinine, and blood urea nitrogen level (Zhan and Li, 2004; Zhang, 2011a).

In recent decades, there have been increasing numbers of randomized controlled clinical trials (RCTs) that compare TCM and Western medicine in the treatment of DN, with relatively significant differences in treatment method and efficacy. Therefore, a sensible systematic review of these trials is of great significance. A TCM prescription is largely composed of one or more herbs with different properties, such as taste, function, and the primary symptoms targeted, leading to a high heterogeneity (Li et al., 2007). Whether the heterogeneity is addressed properly has a direct effect on the quality of a systematic review of TCM (Tnaia et al., 2006). In accordance with the idea of evidence-based medicine and TCM dialectics, this review divided the RCTs of TCM in the treatment of DN into subgroups according to the categories of the main TCM ingredients, thus objectively and accurately evaluating and developing an understanding of the efficacy of different categories of TCMs in DN treatment and providing guidance and a basis for clinical application.

2. Materials and methods

2.1. Literature search

"Diabetic nephropathy" was used as the subject and "traditional Chinese medicine", "traditional Chinese medical practice", "Chinese herbs" or "Chinese herbal medicine" were used as keywords. Articles published from January 2001 to December 2012 that are quoted in the Medline database, the Chinese Biomedical Literature Database (CBM), the Chinese Academy of Sciences database (CNKI), the VIP Chinese journal database, the online database of Chinese medicine, a Chinese doctoral dissertation full-text database (CDFD), a full-text database of China's outstanding master's theses (CDMD), and the CENTRAL database of Cochrane Library were retrieved. In addition, the relevant research articles in our school library were manually searched.

The data of the first author, year of publication, total number of enrolled subjects in the experimental and control groups, intervention measures, and endpoint were retrieved. The data were first retrieved by one researcher, and then the articles were re-read and the data were double-checked by a second researcher. Discrepancies, if there were any, were resolved, and consensus was reached after consultation and discussion with a third researcher.

To Medline as an example, the English search strategy: #1 Diabetic nephropathy or DN #2 Traditional Chinese medicine or Chinese herbal medicine #3 #1 and #2.

2.2. Study selection

The literature inclusion criteria were as follows: (1) the diagnosis of research subjects was in line with that of the type 2 diabetes diagnostic criteria from the World Health Organization (Mogensen et al., 1983), and the subjects were diagnosed with stage III of early diabetic nephropathy according to Mogensen (1984) staging; (2) the experimental design was RCT; (3) regarding the intervention measures, generally, in addition to the routine conventional treatment, ① TCM+ACEI/ARB treatment and ACEI/ARB treatment alone were compared or ② TCM treatment alone and ACEI/ARB treatment alone were compared (Note: routine conventional treatment included diabetes education, diabetes diet, exercise, use of antihypertensive and lipid-lowering drugs, and pharmacological control of the blood glucose level); (4) there was a clear course of treatment in both the experimental and control groups; (5) The sample size in both experimental and control groups were roughly equal. (6) Unified ultimate indices (People's Republic of China, 1987, 1993): very efficacious, Clinical symptoms disappear, ALB Excretion rate becomes regular or it decreases at least1/2, blood sugar and HbAlc decrease 1/3 or they are well balanced, urinary Protein measurement and renal functional indices decease, even they are within the normal range. Efficacious, clinic symptoms are on the mend, ALB Excretion rate, blood sugar and HbAlc decrease, but less effective by comparison with previous index. And urinary protein measurement and renal functional indices are normal and they decease insignificantly. Ineffective, clinical symptoms either not improve or aggravate, as well as those clinical indices.

The literature exclusion criteria were as follows: (1) no clear diagnostic criteria for the research subjects; (2) randomization was not mentioned or the experimental design was not RCT; (3) a lack of a clear course of treatment; (4) a lack of standard indicators to evaluate efficacy; (5) clinical trials of different TCMs; (6) translated from foreign literature or duplicate publications; (7) animal studies; (8) the gap of the sample size in both experimental and control groups were no more than 50%.

2.3. Data extraction and quality assessment

The quality of the included literature was evaluated in accordance with the Cochrane Systematic Review Manual and JADAD quality scoring (Jadad et al., 1996; Rafael and Agustin, 2002) by two evaluators, Xiaoyu Liu and Pinyi Chen. Ling Liu has helped us to understand the standards of scoring while scores inconsistent. Eventually, scores were consistent, two evaluators reached a consensus., as follows: ① whether the randomization method was correct; ② whether allocation concealment was performed; ③ whether the research was blinded with an appropriate method; and ④ whether patients were lost during follow-up or dropped from the trial, and if so, whether the number of patients that were lost during follow-up and the reasons were reported. The score was on a scale of 1–7 (1–3 for low quality and 4–7 for high quality).

2.4. Basis of subgroup analysis

Diabetic nephropathy was also defined as Xiaoke by TCM. (XiaoKe, The main symptom of this disease is excessive urination leading to low body fluid levels) (Zhang 2011b). Kidneys will be impaired if XiaoKe is not cured. Traditional Chinese medical visceral dialectical theory has pointed out impaired renal function would cause diabetic nephropathy. The subgroups were categorizing by Traditional Chinese medical visceral dialectical theory. In other words, they were grouped by the principle of TCM treatment, the pharmaceutical ingredients follow a strict hierarchy with 4 levels ranked by amount of power and influence, so that we were able to deduce the type of syndrome from authors' descriptions. Diabetic nephropathy is about renal disease and it is closely related to liver. In TCM definition, renal disease is due to YIN/Yang deficiency, or it is excessive.

Given the complexity and diversity of TCM diagnosis and treatment, there is not only "the same disease with different symptoms" but also "different diseases with the same symptoms". Moreover, there are significant differences in ingredients, formulation, categories of single herb-TCM and compound TCM treatment, and Doses. All of these parameters are important factors that affect the quality of a systematic review of TCM (Kang et al., 2000; Hu et al., 2010). Therefore, the systematic review should be conducted by dividing the cases in the literature into groups according to the