Traditional Chinese Medicine Based on Zheng Differentiation versus Angiotensin Receptor Blocker/Angiotensin-converting Enzyme Antagonist in Efficacy of Treating Diabetic Kidney Disease: A Meta-analysis of Randomized Clinical Trials

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Abstract

Objective: To compare the efficacy of traditional Chinese medicine (TCM) based on Zheng differentiation with angiotensin receptor blocker/angiotensin-converting enzyme inhibitor (ARB/ACEI) in treating diabetic kidney disease (DKD) from the aspects of decreasing urinary microalbumin, declining 24-h urinary protein, reducing endpoint events, and renal function protection. Methods: The Chinese Biomedical Literature Database (CBM), the Chinese Academy of Sciences database (CNKI), the VIP Chinese journal database, Wanfang DATA, Medline database, Cochran library, excerpt medical database (Embase), and Web of science were used for literature searching. The reviewer manager 5.3 software was utilized to analyze the data. Results: Twenty-four studies including 1956 participants were involved in this review. Results showed that TCM had a better effect (mean difference [MD], −23.20, 95% confidence interval [CI], −30.60 to −15.79, P < 0.00001) than ARB/ACEI on lowering urinary albumin excretion rate (UAER) and urine albumin-to-creatinine ratio (MD −4.56 mg/mmol, 95% CI, −5.76 to −3.36, P < 0.00001). Moreover, the advantage of decreasing UAER was greater as the follow-up period become longer (P = 0.04). TCM also had a better effect in 24-h urinary protein, decreasing 0.36 g/24 h (95% CI, −0.45 to −0.27, P < 0.00001) more than the control in shorter follow-up period (ranged from 12 to 24 weeks) subgroup but only 0.08 g/24 h (95% CI, −0.13 to −0.03, P = 0.0006) in the longer follow-up period (>24 weeks) subgroup. TCM worked as well as ACEI/ARB in reducing endpoint events (relative risk, 0.67, 95% CI, 0.20–2.224, P = 0.51) and decreasing urinary albumin concentration (UAC) (MD, −16.50, 95% CI, −46.28–13.28, P = 0.28). As for protecting renal function, TCM had an equal effect to ACEI/ARB in improving creatinine clearance rate (MD, −3.30, 95% CI, −6.66–0.03, P = 0.05) or estimated glomerular filtration rate (MD, 1.00, 95% CI, −0.59–2.58, P = 0.22). However, TCM had a better effect in releasing the glomerular hyperfiltration state (MD, −9.64, 95% CI, −14.45 to −4.84, P < 0.0001). Conclusions: TCM based on Zheng differentiation can work as well as ACEI/ARB in treating DKD and even better in decreasing urinary microalbumin and releasing glomerular hyperfiltration. It is a good alternative treatment of DKD.

Keywords: Angiotensin receptor antagonists, angiotensin-converting enzyme inhibitors, diabetic kidney disease, meta-analysis, traditional Chinese medicine

INTRODUCTION

Diabetic kidney disease (DKD) is a common microvascular complication of diabetes, which has been the main cause of end-stage renal disease (ESRD).[1] DKD is characterized by the rapid progress. The progressing speed is almost 14 times to other kidney diseases when mass proteinuria appears.[2] Angiotensin-converting enzyme inhibitors and angiotensin II Type 1 receptor blockers (ACEI and ARB) are the only
two proved effective treatments for DKD up to now. The Reduction of Endpoints in NIDDM with the Angiotsensin II Antagonist Losartan study has proved that losartan could reduce the incidence of a doubling of the serum creatinine concentration (risk reduction, 25%; \( P = 0.006 \)) and ESRD (risk reduction, 28%; \( P = 0.002 \)), but had no effect on the rate of death.\(^3\) The IDNT study showed that irbesartan safely and significantly slowed the rate of \( \Delta \text{estimated glomerular filtration rate} \) (\( \Delta \text{eGFR} \)) from baseline) decline in patients with established type 2 diabetic nephropathy and CKD Stages 1–5, compared to amlopidine and placebo.\(^4\)

Similar to ARB and ACEI drugs, traditional Chinese medicine (TCM) also has been demonstrated to have positive effect in treating DKD. Our studies showed that TCM therapies have a better effect of protecting the kidney function, delaying the progression of DKD, and reducing the proteinuria.\(^5,7\) However, some studies failed to prove that TCM had a better effect.\(^8\) To assess whether TCM has a better effect than ACEI/ARB in treating DKD or not, we performed this meta-analysis. Anti-proteinuria and renoprotective effect were the main points for analyzing. Only randomized clinical trials fulfilling the inclusion criteria were included for analysis.

**Methods**

The prospective protocol was registered on the international prospective register of systematic reviews PROSPERO (CRD42017058101). The Preferred Reporting Items for Systematic Review and Meta-Analysis statement was followed when we reported this study.

**Literature search**

Four Chinese databases were used to retrieve articles, including the Chinese Biomedical Literature Database (CBM), the Chinese Academy of Sciences database (CNKI), the VIP Chinese journal database, and Wanfang DATA. Meanwhile, articles published in English were retrieved in the Medline database, Cochrane library, excerpt medical database (Embase), and Web of science. The keywords including “Diabetic Nephropathy,” “Chinese Herbal Drugs,” “Traditional Chinese Medicine,” “Angiotsensin-Converting Enzyme Inhibitors,” “Angiotsensin II Type I Receptor Blockers,” and “Randomized Controlled Trial.” Their related free words were also used to retrieve articles. Publication date had no limitation. The search strategy of Medline database is presented as follows:


The eligibility criteria are as follows: (1) The diagnostic criteria of the type 2 diabetes are from the World Health Organization and the participants of DKD were diagnosed with stage III or stage IV according to Mogensen (1984) staging. (2) Research style is randomized clinical study. (3) The intervention is Chinese herbal medicine and the positive...
control is ACEI/ARB. (4) The sample size should be no <30. (5) The outcomes should include urinary albumin or urine albumin-to-creatinine ratio (UACR) or 24-h urine albumin or 24-h urine protein or endogenous creatinine clearance ratio (Ccr) or eGFR. However, the exclusion criteria are as follows: (1) Ingredients of Chinese herbal drugs (CHD) are not clear. (2) The research has no syndrome diagnostic criteria. (3) Length of follow-up is <12 weeks.

Data extraction
The data were first extracted by one researcher and then were double-checked by the second researcher. If there was inconformity, the decision would be made after negotiating with the third researcher. We developed a data extraction form based on the Cochrane consumers and communication review group’s data extraction template. Data of study ID (made up with the name of first author and year of publication), stage of DKD, age of participants, intervention, control, ingredients of CHD, sample, length of follow-up period, and outcomes were extracted from the reports.

Quality assessment and publication bias
Biases of included literature were evaluated according to the Cochrane Collaboration Network Standard. Biases were assessed via the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Bias evaluation was mainly completed by two researchers, while the ultimate decision was made after consulting the third researcher if dissension existed. The assessment of quality and bias was completed with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK).

Statistical analysis
Both event (dichotomous) data and continuous data were included in this analysis. Dichotomous data were expressed as relative risk (RRs) with 95% confidence interval (CI). Continuous data were expressed as weighted mean differences (WMD) with 95% CI and an overall WMD was calculated. A fixed-effect model was utilized for meta-analysis when there was no statistically significant heterogeneity between groups (P > 0.05). Otherwise, a random effect model was utilized for the analysis. Subgroup analysis by follow-up period was performed. The Review Manager 5.3 Software was utilized to analyze the data.

Results
Search results and study characteristic
Flow diagram of articles filtration is shown in Figure 1. Two thousand and thirty-six records were identified after database searching. After duplicate screening, 993 records left to the next screening. With the eligibility and exclusion criteria, 969 records had been removed and 24 studies were left in the end. The 24 studies included nine academic dissertations and 15 journal articles. All the studies were published in Chinese and were carried out in China. Among these studies, TCM interventions included ancient classic prescription, experiential prescription, and Chinese patent medicine. One thousand nine hundred and fifty-six participants were involved in this review. Fifteen studies enrolled stage III DKD patients. Three studies enrolled stage IV DKD patients and the other six studies enrolled both stage III and IV DKD patients. All studies were randomized controlled trials. Characteristics of each article are shown in Table 1.

Bias risk of included records
All these studies were grouped randomly. However, only 10 records[12-17,23,26,29,31] had clearly stated the method of randomization. The random sequence was generated by statistic software in two studies[12,31] and by random number table in the other eight studies.[14-17,23,26,29,30] In case of allocation concealment, only one record[31] showed the specific method and allocation concealment method of the other 23 studies were unclear. As for the blinding, only three studies[12,17,31] were conducted under blinding. Among the three records, two records[12,31] clearly described the blinding process and the other one record[17] only stated that single blinding had been used. Besides, two records[8,19] had not reported the incomplete outcome data. Selective reporting was not seen in the 24 records. The risk of bias for each study is summarized in Figure 2.

Analysis of the outcomes
Efficacy confrontation on urinary albumin
Nineteen records[8,12-17,19-25,27,30,31] reported the effect of TCM and ACEI/ARB on urinary albumin. Among these studies, some used urinary albumin excretion rate (UAER) to estimate the effect and urinary albumin concentration (UAC) was used in the other studies. Therefore, the 19 records were divided into two groups (UAER group with 16 records[8,10,12-17,19,20,22,24,25,27,30,31] and UAC group with
Table 1: Characteristics for each record

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Age (years)</th>
<th>Sample</th>
<th>DKD phase</th>
<th>TCM group</th>
<th>Control group</th>
<th>Intervention</th>
<th>Ingredients</th>
<th>Control group</th>
<th>Follow-up period</th>
<th>Outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du et al., 2012(11)</td>
<td>53±8</td>
<td>52±9</td>
<td>IV</td>
<td>Jinlida granule combined with tongxinhuo capsule</td>
<td>Rhizoma polygonati, atractylodes, radix sophorae flavescentis, ophiopogon, rehmannia, cornus, perit, coptis chinensis, anemarrhena, salvia, puerarin, cortex lycii, poria, leech, scorpion, eupolyphaga, centipede, periostracum cicadae, red peony, sandalwood, incense, mastic</td>
<td>Irbesartan</td>
<td>12 weeks</td>
<td>24-h urinary protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2015(13)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>III</td>
<td>Sanhuangyishen granule</td>
<td>Astragalus, anemarrhena, antlers, angelica, ligusticum wallichii, turmeric, ripe rhubarb</td>
<td>Irbesartan</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate, endpoint events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gao et al., 2015(10)</td>
<td>54.3±5.02</td>
<td>55.0±4.68</td>
<td>IV</td>
<td>Decoction of tonifying kidney qi, dispersing blood stasis, dredging collaterals, clearing heat and purging turbidity</td>
<td>Astragalus, angelica, ligusticum wallichii, salvia, codonopsis, poria, atractylodes, ripe rhubarb, arctium, medlar, plantago, fried rhubarb, scutellaria, licorice</td>
<td>Irbesartan</td>
<td>24 weeks</td>
<td>Urinary albumin excretion rate, 24-h urinary protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI et al., 2011(8)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>III</td>
<td>Buyang huanwu decoction</td>
<td>Red peony, ligusticum wallichii, angelica, earthworm, astragalus, peach kernel, safflower</td>
<td>Benazepril</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI et al., 2014(13)</td>
<td>48.2±6.02</td>
<td>50.01±5.02</td>
<td>IV</td>
<td>Decoction of dispersing blood stasis, dredging collaterals, clearing heat and purging turbidity</td>
<td>Astragalus, angelica, chuanxiong, fried rhubarb, scutellaria, artem, medlar, plantago, rhizoma imperatae, licorice, rehmannia, thistle</td>
<td>Irbesartan</td>
<td>24 weeks</td>
<td>Urinary albumin excretion rate, 24-h urinary protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI 2013(14)</td>
<td>53.6±11.7</td>
<td>54.1±10.3</td>
<td>III</td>
<td>Qizhi jiangtang capsule</td>
<td>Astragalus, leeches, rehmannia, polygonatum</td>
<td>Valsartan</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
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<td>LIU et al., 2012(5)</td>
<td>51.43±11.28</td>
<td>52.4±12.32</td>
<td>III</td>
<td>Zhuang shengy lijing decoction</td>
<td>Astragalus, polygonatum, Rosa laevigata, echinacea, raspberry, sah octopus, leeches</td>
<td>Irbesartan</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
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<tr>
<td>Peng et al., 2013(9)</td>
<td>56.5±8.1</td>
<td>57.1±7.9</td>
<td>III</td>
<td>Zishen huoxue decoction</td>
<td>Astragalus, radix rehmanniae racen, yam, pulp of comus, houttuynia, salvia, rhubarb, ligusticum wallichii, leeches, ramulus euryomi, stephania tetrandra, epimedium, ligustrum lucidum, dodder, licorice</td>
<td>Benazepril</td>
<td>12 weeks</td>
<td>Urine microalbumin</td>
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<td>Shi et al., 2014(48)</td>
<td>53.13±8.78</td>
<td>52.17±7.88</td>
<td>III</td>
<td>Shenqidantang shenxiao decoction</td>
<td>American ginseng, astragalus, yam, raspberry, gorgon, salvia, cortex moutan, millettia, silkworm, periostracum cicada, achyranthes</td>
<td>Benazepril or irbesartan</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
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<td>Song et al., 2017(17)</td>
<td>55.7±8.5</td>
<td>54.2±9.9</td>
<td>III</td>
<td>Tangshen decoction</td>
<td>Aconite, cinnamon, angelica, alisma, plantago, motherwort, rhubarb, rehmannia glutinosa, astragalus, Chinese yam, comus officinalis, poria, loranthaceae, achyranthes bidentata, leeches</td>
<td>Losartan</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate, 24-h urinary protein</td>
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<tr>
<th>Study ID</th>
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<th>DKD phase</th>
<th>Intervention</th>
<th>Ingredients</th>
<th>Control group</th>
<th>Follow-up period</th>
<th>Outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tong et al., 1999</td>
<td>Unclear</td>
<td>64</td>
<td>III and IV</td>
<td>Tangshenkang capsule</td>
<td>Bupleurum, turmeric, stiffsilkworm, astragalus, American ginseng, hedyotis diffusa, aconite, fructus polygoni orientalis, leech, semen brassicae, Allanthus altissima singule</td>
<td>Captopril</td>
<td>16 weeks</td>
<td>24-h urinal protein</td>
</tr>
<tr>
<td>Wang et al., 2005</td>
<td>55.83±10.6</td>
<td>39</td>
<td>III and IV</td>
<td>Shenhaining water pill</td>
<td>Rehmannia ia, yam, cornus, astragalus, poria, alisma, cortex moutan, mantis egg-case, angelica, hierdo, herba leonuri, mammor serpenatnatum, hedyotis diffusa</td>
<td>Benazepril</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate, 24-h urinal protein</td>
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<tr>
<td>Wang 2005</td>
<td>54.38±7.45</td>
<td>24</td>
<td>III and IV</td>
<td>Bushenhuayu decoction</td>
<td>Astragalus, cornus, yam, lycopus lucidus, salvia, achyrantes, ramulus euonymyi, rhizoma alismatis</td>
<td>Captopril</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
</tr>
<tr>
<td>Wang 2016 (Wang, 2016)</td>
<td>55.88±7.61</td>
<td>34</td>
<td>III and IV</td>
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<td>Hedyotis diffusa, cornus officinalis, Rhizoma Imperatae, peach kernel, safflower</td>
<td>Valsartan</td>
<td>12 weeks</td>
<td>Urine microalbumin, 24 h urinal protein</td>
</tr>
<tr>
<td>Wang et al., 2008</td>
<td>53.45±4.45</td>
<td>40</td>
<td>III</td>
<td>Tangshenxiao yin</td>
<td>Ogata, astragalus, angelica, cornelia, ligustrum lucidum, cooked rhubarb, leeches, salvia, ramulus euymy, herba leonuri, rosa laevigata, gorgon</td>
<td>Valsartan</td>
<td>12 weeks</td>
<td>Urine albumin excretion rate</td>
</tr>
<tr>
<td>Xiao 2014</td>
<td>51.12±6.37</td>
<td>33</td>
<td>III</td>
<td>Yiqitongluo yin</td>
<td>Astragalus, angelica, millletia, pasepartout, leech, ligisticum wallichi</td>
<td>Valsartan</td>
<td>12 weeks</td>
<td>Urine albumin-to-creatinine ratio, urine microalbumin</td>
</tr>
<tr>
<td>Yang 2014</td>
<td>53.7±2.4</td>
<td>30</td>
<td>III</td>
<td>Yiqiyangxiniao zheng tonglue decoction</td>
<td>Astragalus, centella asiatica, polygonatum, salvia, ligisticum wallichi, poria, rehmannia, earthworm, leeches, turtle shell, rhubarb, amomum villosum</td>
<td>Irbesartan</td>
<td>24 weeks</td>
<td>Urinary albumin excretion rate, end point events</td>
</tr>
<tr>
<td>Zhang and Qin 2012</td>
<td>58.3±6.7</td>
<td>34</td>
<td>III</td>
<td>Jishengxueqipill and fuangxueshuantong capsule</td>
<td>Rehmanna glutinosa, dogwood, cortex moutan, yam, poria, almond, cinnamon, aconite, achyrantes, panax notoginseng, astragalus, salvia, scrophulariaceae</td>
<td>Captopril</td>
<td>16 weeks</td>
<td>Urinary albumin excretion rate, urine albumin-to-creatinine ratio</td>
</tr>
<tr>
<td>Zhang et al., 2015</td>
<td>50.1±10.6</td>
<td>30</td>
<td>III</td>
<td>Modified xiaokekang</td>
<td>Astragalus, pueraria, salvia, cassis, cox seed, rehmannia, atractylodes, dodder, cornus, leech</td>
<td>Angiotensin receptor blocker</td>
<td>12 weeks</td>
<td>24 h urinal protein</td>
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<tr>
<td>Zhang 2010</td>
<td>Unclear</td>
<td>30</td>
<td>III</td>
<td>Yishenhuangzhuo decoction</td>
<td>Rehmanna, medlar, cornus, dodder, ramuli euonymyi, Polygonum cuspidatum, berberine</td>
<td>Benazepril</td>
<td>12 weeks</td>
<td>Urinary albumin excretion rate</td>
</tr>
<tr>
<td>Zhao et al., 2008</td>
<td>39.8±1.85</td>
<td>103</td>
<td>III</td>
<td>Sutangyishen pill</td>
<td>Astragalus, ginseng, atractylodes, cornus officinals, cucumminia, cimicifuga, motherwort, bupleurum, angelica, citrus, ophiopogon, paenia suffruticosa, radix liquiritiae</td>
<td>Captopril</td>
<td>12 weeks</td>
<td>24 h urinal protein</td>
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<th>Ingredients</th>
<th>Sample</th>
<th>TCM group</th>
<th>Control group</th>
<th>Duration</th>
<th>TCM phase</th>
<th>Outcome measurement</th>
<th>Outcome</th>
<th>Follow-up period</th>
<th>Outcome</th>
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<tr>
<td>Zhao et al., 2008</td>
<td>Astragalus, epimedium, rehmannia, euonymi, rhubarb</td>
<td>5.78</td>
<td>Unclear</td>
<td>31</td>
<td>15</td>
<td>LH</td>
<td>24 h urinary protein, urinary albumin excretion rate</td>
<td>Losartan</td>
<td>12 weeks</td>
<td></td>
<td>TCM granule, Zizhaozhenxing: Rhubarb, Atractylodes, Rehmannia, Euonymi, Rhubarb</td>
<td>Hibiscus</td>
<td>48 weeks</td>
<td>Unclear</td>
<td>12 weeks</td>
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<td>Zhao et al.</td>
<td>Astragalus, epimedium, rehmannia, euonymi, rhubarb</td>
<td>5.85</td>
<td>Unclear</td>
<td>31</td>
<td>15</td>
<td>LH</td>
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<td>Losartan</td>
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<td>Hibiscus</td>
<td>48 weeks</td>
<td>Unclear</td>
<td>12 weeks</td>
<td></td>
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<tr>
<td>Zhao et al., 2010</td>
<td>Astragalus, epimedium, rehmannia, euonymi, rhubarb</td>
<td>5.86</td>
<td>Unclear</td>
<td>31.75</td>
<td>31.16–110.63</td>
<td>LH</td>
<td>24 h urinary protein, urinary albumin excretion rate</td>
<td>Losartan</td>
<td>12 weeks</td>
<td></td>
<td>TCM granule, Zizhaozhenxing: Rhubarb, Atractylodes, Rehmannia, Euonymi, Rhubarb</td>
<td>Hibiscus</td>
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<td>Unclear</td>
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<td>Losartan</td>
<td>12 weeks</td>
<td></td>
<td>TCM granule, Zizhaozhenxing: Rhubarb, Atractylodes, Rehmannia, Euonymi, Rhubarb</td>
<td>Hibiscus</td>
<td>48 weeks</td>
<td>Unclear</td>
<td>12 weeks</td>
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</table>

**Efficacy confrontation on urine albumin-to-creatinine ratio**

Two records[^23^,^25^] reported the effect of TCM and ACEI/ARB on UACR. The follow-up period of one study[^23^] was 12 weeks and the other one[^25^] was 16 weeks. Both results demonstrated that TCM had a better effect in decreasing UACR. The result of meta-analysis of these two studies also showed that
the UACR in experimental group declined more compared with control group (MD, −4.56, 95% CI, −5.76 to −3.36, \(P < 0.00001\)); [Figure 4].

**Efficacy confrontation on 24-h urinal protein**

Eleven records\[^{10,11,13,17-19,21,26,28,29,31,32}\] reported the effect of TCM and ACEI/ARB on 24-h urinal protein. In one record,\[^{31}\] the 24-h urinal protein was only measured in 15 participants (7 participants in treatment group and 8 participants in control group). Therefore, it was excluded and only 10 records were meta-analyzed. Because baselines of three studies\[^{18,26,28}\] had huge differences (<0.5 g/24 h) comparing with the other studies (between 0.5 g/24 h and 2 g/24 h), seven studies were left in the meta-analysis. Besides, subgroup analysis was used in the meta-analysis based on the follow-up period. The result of SFP (12–24 weeks) subgroup showed that experimental group had a better effect in 24 h urinal protein, decreasing 0.36 g/24 h (95% CI, −0.45 to −0.27, \(P < 0.00001\)) [Figure 5] more than the control group. As for the LFP (>24 weeks) subgroup, experimental group also had a better effect. However, the decline of 24 h urinal protein was only 0.08 g/24 h (95% CI, −0.13 to −0.03, \(P=0.0006\)) [Figure 5] more than the control group.

**Efficacy confrontation on endogenous creatinine clearance ratio and estimated glomerular filtration rate**

Among the 24 records, there were four records\[^{11,19,29,30}\] showed the efficacy confrontation on Ccr and three records\[^{10,12,31}\] showed confrontation on eGFR. As for the Ccr group, baselines of Ccr in two studies\[^{19,30}\] were higher than the upper limit of normal (120 mL/min) and the other two records\[^{17,18}\] had baselines which is lower than the normal (80 mL/min). Hence, subgroup analysis was conducted based on the baseline of Ccr. The result of the higher baseline (>120 mL/min) subgroup showed that TCM based on Zheng differentiation was better than ACEI/ARB in the effect of declining the Ccr (MD, −9.64, 95% CI, −14.45 to −4.84, \(P < 0.0001\)); [Figure 6]. In the lower baseline (<80 mL/min) subgroup, the result showed that TCM could protect renal function as well as ACEI/ARB (MD, 2.61, 95% CI, −2.04–7.27, \(P=0.27\)) [Figure 7a].

In the eGFR group, all studies showed that both TCM and ACEI/ARB had beneficial effect on protecting renal function, manifesting as maintaining the eGFR or even improving...
the eGFR. When meta-analyzing, the result showed that experiment group and control group had no significant difference on eGFR (MD, 1.00, 95% CI, −0.59–2.58, \(P = 0.22\)); [Figure 7b].

**Efficacy confrontation on endpoint event**

Only two records\(^{[12,24]}\) reported the effect of TCM and ACEI/ARB on endpoint event. The endpoint event was defined as development from stage III into stage IV (Mogensen stages of diabetic nephropathy). One study\(^{[12]}\) followed participants for 12 weeks and the other one\(^{[24]}\) followed for 24 weeks. Results of both studies showed no difference in the risk of endpoint event between TCM and ARB/ACEI group. After meta-analyzing, result were the same (RR, 0.67, 95% CI, 0.20–2.224, \(P = 0.51\)) [Figure 6].

**Assessment of publication bias**

Publication biases were examined by funnel plot. Considering the small amount of records, only the UAER subgroup was used in the assessment. After analysis, an asymmetrical funnel plot was generated [Figure 8]. It prompted that publication biases might existed.
**DISCUSSION**

*Zheng* is a distinctive conception of TCM, meaning syndrome or pattern. It is the overall physiological and pathological pattern of the human body in response to a given internal and external condition, which usually is an abstraction of internal disharmony. TCM doctor always diagnoses *Zheng* with a comprehensive analysis of the clinical symptoms and signs gathered by a practitioner using inspection, auscultation, olfaction, interrogation, and palpation of the pulses. In most cases, TCM doctors give a prescription depending on *Zheng* and disease patients get. Different patients getting the same disease always are treated by different prescriptions because of their different *Zheng*. What is more important, effectiveness of the prescription mostly depends on whether it is made basing on the *Zheng*. To get trials that can really reflect the effectiveness of TCM, only researches that have syndrome diagnostic criteria were included in this review.

As we all know, urinary albumin is an important risk factor for renal failure and is often used to estimate new treatments of DKD. In this review, 19 records reported the effect on urinary albumin of TCM based on *Zheng* differentiation and ACEI/ARB. Primary meta-analysis showed that Chinese herbal medicine had a good effect on reducing UAER and proteinuria. However, is it better than the ACEI/ARB? In this study, results of UAER subgroup showed that the TCM based on *Zheng* differentiation was more effective than ACEI/ARB and the advantage enlarged as the follow-up period lengthened. The better effect of TCM was also demonstrated in the UACR subgroup. Although the result of UACR subgroup showed no significant difference between TCM and ARB/ACEI, we could not disaffirm the better effect of TCM, considering the tiny sample of UACR subgroup. These results proved that TCM based on *Zheng* differentiation was more effective than ACEI/ARB in reducing urinary albumin.

Further, 24-h urinal protein is a usefully outcome to assess the effect of treatment for DKD, especially for the IV stage (Mogensen stages of diabetic nephropathy) patients. Many DKD can develop into nephrotic syndrome and diabetes has become the most common secondary cause of nephrotic syndrome, which is difficult to be healed. Besides, the progressing of DKD always accelerates when large amount of urinal protein appears, which means it will develop into ESRD quickly. Hence, if we could decrease the 24-h urinal protein, the speed toward ESRD would be slowed down. As we all know, ARB/ACEI can decrease proteinuria and reduce the risk of developing into ESRD. Studies have shown that combination therapy with Chinese medicine and ACEI/ARB might have polypharmacological anti-proteinuric and renoprotective effects for the management of DKD. However, which is better when they are used separately? In this study, result showed that TCM might be more effective than ACEI/ARB on the reduction of 24-h urinal protein statistically. However, the advantage is so weak that it has no clinical significance. What’s more, result will be more credible if more studies included in this review.

Renal function is what patients and doctors mostly care about. DKD has been the leader cause of ESRD. As we all know, ARB/ACEI has been proved that can slow the speed of renal failure. As well as ARB/ACEI, some decoctions based on *Zheng* differentiation also been verified to be effective in protecting renal function. What is better? In this study, Ccr and eGFR were used to access the effectiveness of renal function protection. Results showed that TCM based on *Zheng* differentiation had a beneficial effect on eGFR as well as ARB/ACEI. While results about Ccr showed that TCM had a better effect than ARB/ACEI at the stage of glomerular hyperfiltration with a Ccr higher than normal, when Ccr was lower than normal, TCM could also work as well as ARB/ACEI in improving or maintaining Ccr.

Results above proved that TCM based on *Zheng* differentiation had better effect than ARB/ACEI in proteinuria decline and no worse effect in protecting renal function, but what about the effect of reducing endpoint events? The findings of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study and IDNT (the Irbesartan in Diabetic Nephropathy Trial) study demonstrated that both losartan and irbesartan could slow the progress of kidney disease in patients with diabetes. In this study, only two records reported effects of TCM and ACEI/ARB on end point event. The endpoint event was defined as development from stage III into stage IV (Mogensen stages of diabetic nephropathy). From the results of these two studies, we could know that no difference was observed between TCM based on *Zheng* differentiation and ACEI/ARB in reduction of end point events. The result was the same when they were meta-analyzed. The result confirmed to that of renal function protection subgroup. However, considering the tiny sample and short follow-up period, conclusion cannot be made until more and longer follow-up period randomized studies are conducted.

In addition, our meta-analysis had some limitations. First, all the records were published in Chinese and conducted in...
China. It was easy to generate a language bias and location bias. Second, some low-quality studies were included. Third, many studies had carried on without blinding measure. Besides, only published studies were included in this review. Hence, high-quality randomized controlled clinical trials with larger sample, longer follow-up period, and standard blinding method should be taken in the future.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES


