SYSTEMATIC REVIEW

Review of systematic reviews and Meta-analyses investigating Traditional Chinese Medicine treatment for type 2 diabetes mellitus

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Abstract

OBJECTIVE: To conduct a review of the systematic reviews and meta-analyses on the Traditional Chinese Medicine (TCM) treatment of type 2 diabetes mellitus (T2DM).

METHODS: We searched PubMed, Cochrane, Web of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang, and other databases from database inception to May 2014 for systematic reviews and meta-analyses on TCM treatment of T2DM. Manuscripts were read by two investigators if they met the inclusion criteria, and data were extracted. A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used to classify research quality, and the evidence quality was graded by the Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) system.

RESULTS: Eighteen systematic reviews and meta-analyses were considered. Fifteen analyzed the efficacy of Chinese herbal medicines, and three investigated the efficacy of acupuncture. AMSTAR evaluation ranged from 3-10, and re-evaluation of the main results implied that treatment of T2DM with TCM has certain advantages when compared with conventional Western medicine. However, the evidence quality was generally low.

CONCLUSION: This work shows favorable evidence for the clinical treatment of TCM on T2DM. However, it is recommended that evidence-based decisions are made based on clinical trials because of the GRADE scores of the studies. To achieve higher quality of clinical research, clinical research on TCM requires specific and suitable research methods. Further trials may increase the quality of evidence to evaluate the clinical efficacy of TCM for T2DM.

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Key words: Medicine, Chinese traditional; Diabetes Mellitus, type 2; Review; Meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common disease
with a complex etiology. World Health Organization reported that in 2000 there were 151 million people suffering from diabetes worldwide, and that an estimated 300 million people will suffer from diabetes in 2025. The current pace of development of diabetes has far exceeded expectations. The prevalence of diabetes and prediabetes among Chinese adults is 9.7% and 15.5%, respectively, up from less than 1% in 1980, 2.5% in 1994, and 5.5% in 2000. Diabetes is a risk factor for cardiovascular disease and stroke, which caused 29 million deaths by 2010. T2DM can cause a variety of complications if blood glucose levels are not controlled, and results in the use of medications, high outpatient and inpatient costs, and requires expensive diagnostic tests. Furthermore, absenteeism from recurrent symptoms can cause indirect economic losses. Modern treatment for T2DM is mainly via Western Medicine. However, severe side-effects of medications make complementary and alternative therapies more appealing among patients and clinicians. These complementary treatments include herbs, acupuncture, and other Traditional Chinese Medicine (TCM). A systematic review re-evaluates collected systematic reviews on the treatment, diagnosis, and other aspects of specific disease or health problems, and can provide a higher quality of evidence for readers. Numerous systematic reviews and meta-analyses on TCM management of T2DM have been published. However, the methodological quality and limitations of individual studies has resulted in a lack of quality evidence. Therefore, this study aims to re-evaluate the systematic reviews and meta-analyses, and classify their quality of evidence using the Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) system.

MATERIALS AND METHODS

Search strategy
PubMed, Cochrane, Web of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang databases were searched on computer from database inception to May 2014. The grey literature was also searched using the CNKI and Wanfang doctor/master thesis database. Different combinations of key words and random words (Cochrane Library [MeSH], PubMed [MeSH], CBM [MeSH]) were chosen based on different databases. Meanwhile, the references attached to the article or related reviews were tracked, and interventions were excluded from the retrieval strategy. Search terms included: type 2 diabetes mellitus, systematic reviews, and meta-analysis. The search strategy was presented as follows, taking the Cochrane Library as an example.

#1 Type 2 diabetes mellitus
#2 Type 2 diabetes mellitus [MeSH Terms]
#3 T2DM
#4 Meta-Analysis
#5 Meta-Analysis [MeSH Terms]
#6 Meta-Analysis [Publication Type]
#7 Systematic review
#8 #1 OR #2 OR #3
#9 #4 OR #5 OR #6 OR #7
#10 #8 AND #9

Inclusion criteria
(a) Systematic Review or meta-analysis on TCM treatment for T2DM as a primary intervention with at least one randomized controlled trial (RCT) either in English or Chinese. (b) The original study objects were patients with T2DM or in accordance with the relevant domestic or overseas diagnostic criteria, not limited by sex and ethnicity. (c) The interventions were mainly TCM therapy, including herbal medicine (e.g. herb compounds, single herb, Chinese patent medicine, or herbal extracts), acupuncture (e.g. acupuncture, moxibustion, acupoint injection, acupoint application, or auricular acupuncture), and massage. (d) The latest or the most detailed edition was chosen for repeatedly published literature. (e) The grey literature like conference papers meeting the above criteria was considered.

Exclusion criteria
(a) Comparative studies on different Chinese medicine therapies (e.g. Chinese herbal medicine vs acupuncture or herb compounds vs Chinese patent medicine); (b) quality assessment and methodological studies for systematic reviews; and (c) abstracts or comments for conference papers.

Literature screening and review data extraction
Two individual investigators read all titles and abstracts, and research that was obviously in accordance with the exclusion criteria was eliminated, while those initially meeting the inclusion criteria were read in full. Discrepancies were resolved by discussion or involvement of the third investigator. Information extracted from the review data included: title, author, source, object of study, inclusion criteria, exclusion criteria, treatment group interventions, control group interventions, course of treatment, quality assessment methods, indexes for therapeutic effects, and adverse events. After completing the data extraction form, crosschecking was executed between the two investigators.

Assessment of literature quality and evidence quality
The methodological quality of included systematic reviews or meta-analyses was evaluated by A Measurement Tool to Assess Systematic Reviews (AMSTAR). The AMSTAR tables include 11 items, each with comment options of “YES,” “NO,” “NOT CLEAR,” or “NOT USED.” Each item with the answer “YES” is recorded as 1 point, while answers to the rest are recorded as 0 points, for a potential total of 11."
classification by AMSTAR scores is as follows: 0-4 is low, 4-8 is medium, and 9-11 is high. The evidence quality of the systematic reviews was assessed by GRADE. Evidence classification is as follows: (a) high quality (very confident that the real effects are close to those estimated); (b) medium quality (medium confidence that the real effects are close to those estimated); (c) low quality (limited confidence that the real effects are close to those estimated); and (d) very low quality (almost no confidence that the real effects compare with those estimated).

RESULTS

Literature search results
Eighty papers were searched after preliminary retrieval. Ten repeated studies were excluded by literature management software (EndNote X6), while five did not meet the inclusion criteria. Therefore, 65 papers were initially included. After reading the full text of each paper, the following were excluded: 15 systematic reviews, three repeated conference papers/journal articles, three papers on literature quality assessment, five papers on the systematic reviews or meta-analyses whose interventions did not meet the exclusion criteria, and one research comment. Finally, 18 papers were included. There were six manuscripts published in English, including one Cochrane review, and 12 Chinese manuscripts published from 2003 to 2013. The literature screening procedure is shown in Figure 1.

Basic characteristics and quality assessment of included literature
There were 15 systematic reviews and meta-analyses on the efficacy and safety of Chinese herbal treatment for T2DM, among the 18 papers. The herbal medicines used included: (a) Chinese patent medicines, including Liuweidihuang pills; (b) herbal extracts like berberine and green tea extracts; and (c) point injection formulations (e.g., astragalus injection, puerarin injection, and Shengmai injection). The remaining three papers evaluated the efficacy of acupuncture therapy on T2DM. Two papers assessed the efficacy of point injection, and the final paper studied the efficacy of acupuncture. The methodological quality of the studies was evaluated by AMSTAR, with total points ranging from 3 to 10. Six papers were
classified as high quality and five as medium quality. Information on the included studies is presented in Table 1.

Results of re-evaluation

Ten papers evaluated the efficacy and safety of Chinese patent medicine treatment for T2DM. There was one Cochrane systematic review. The results suggested some clinical efficacy of Chinese patent medicine when compared with conventional Western medicine or placebo treatment. However, the GRADE classification ranged from low quality to very low quality, because of the low quality of eligible research. Three papers assessed the efficacy of Liuweidihuang pills in the treatment of T2DM compared with conventional Western medicine. The AMSTAR scores were 4, 4, and 9, respectively. Meta-analysis showed superior efficacy of Liuweidihuang pills for T2DM compared with conventional Western Medicine. However, limitations in the original research resulted in a GRADE classification of low quality.

Three papers evaluated the clinical efficacy of herbal extracts (berberine and the green tea extracts) for T2DM. The research to evaluate the clinical efficacy of berberine was based on randomized double-blind placebo-controlled trials. The results showed that herbal medicines have some clinical efficacy when compared with placebo treatment. Despite the high methodological quality, factors like small sample size and publication bias resulted in a GRADE classification of medium quality. One systematic review included seven clinical trials on using green tea extracts for T2DM. Meta-analysis of the trials found that green tea extracts were not significantly different in overall clinical efficacy and other indicators in patients when compared with the placebo treatment.

Two systematic reviews analyzed the efficacy of astragalus injection, puerarin injection, and Shengmai injection treatment for T2DM. Meta-analysis showed that astragalus injection was clinically effective in T2DM patients [RR = 1. 58, 95% CI (1. 20, 2. 09)] when compared with the control group, and point injection of puerarin was significantly better than the control group [RR = 1. 28, 95% CI (1. 11, 1. 47)]. However, the GRADE classification was very low quality because of limitations, wide confidence intervals, small sample size, and publication bias.

One systematic review on the treatment of T2DM by acupunctures published by Tae-Hun Kim studied the efficacy and safety of acupunctures therapy vs conventional Western Medicine interventions. The meta-analysis suggested that acupuncture improved clinical efficacy compared with conventional Western Medicine. No severe side-effects were observed. However, the bias risk for the original study resulted in a GRADE classification of low quality.

DISCUSSION

This study found that there are certain clinical effects that TCM treatment can exert on T2DM, and there are few adverse reactions, such as hypoglycemia, when compared with Western drugs alone. Furthermore, treatment by Chinese medicine plus Western Medicine was superior to that of Western Medicine alone. T2DM is categorized as "Xiao Ke" in TCM, and was first mentioned in the Chinese book Su Wen Qi Bing Lun. An alternative name for "Xiao Ke" is described in Huang Di Nei Jing as "Xiao Dan," "Fei Xiao," or "Ge Xiao" based on different pathogeneses and symptoms. TCM theorizes that the internal organs weakness, excessive intake of fat and sugar, and mood disorders are the main causes of "Xiao Ke" The pathogenesis is based on body fluid loss dryness-heat, according to TCM. Furthermore, a lack of Yin is its intrinsic factor, while dryness-heat is its extrinsic factor. The most commonly evaluated drug among the Chinese patent drugs was Liuweidihuang pills, which is composed of prepared Dihuang (Radix Rehmanniae), Shanzhuyu (Fructus Macrocarpi), Shanyao (Rhizoma Dioscoreae), Zexie (Rhizoma Alismatis), Mudanpi (Cortex Moutan Radicis), Fuling (Poria). The herbs can help to improve liver and kidney function. In diabetes patients treated with Liuweidihuang pills for 12 weeks, fasting blood glucose and HbA1c concentrations decreased, blood NO levels increased, endothelin (ET) contents decreased, and superoxide dismutase and glutathione peroxidase increased significantly the treatment group than the control group patients compared with before intervention. These results suggest that the use of Liuweidihuang pills in the early stages of diabetes can help to reduce blood glucose levels, improve oxidative stress, and recover NO-ET levels. Therefore, it can protect injured endothelial cells and prevent the subsequent macrovascular complications of diabetes. We found that TCM has advantages in the treatment of T2DM when compared with the clinically used drugs. However, the original research methodological limitations resulted in low GRADE classifications for quality of evidence and low credibility of the assessment results. The relevant herbal extracts or herbal medicine compounds have attracted the attention of global researchers because of developments in the formulation and preparation, and the controllability of clinical studies. Among them was berberine, which can control blood glucose and improve diabetes symptoms by improving the insulin resistance, inhibiting gluconeogenesis, and reducing cholesterol. Additional investigations that compare Western and Chinese medicine are required to meet the development needs of the next era. The eligible 18 systematic reviews and Meta-analyses on the treatment of T2DM by TCM were published between 2002 and 2013. There were 12 Chinese papers with AMSTAR from 3 to 10, and six English papers with AMSTAR from 5 to 10. The methodological quality was relatively low for Chinese papers when...
<table>
<thead>
<tr>
<th>Eligible study</th>
<th>n</th>
<th>Interventions for the treatment group</th>
<th>Interventions for the control group</th>
<th>Quality</th>
<th>Outcome index</th>
<th>Main results of the systematic review and meta analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naren QMG et al 2012</td>
<td>10</td>
<td>Chinese medicine (herbal compounds or herbal extracts)</td>
<td>Western drugs (glipizide, metformin, rosiglitazone, etc.) and placebo</td>
<td>Low</td>
<td>FBG, 2hPBG, HbA1c, adverse effects</td>
<td>Berberine may reduce the fasting blood glucose of T2DM, but is not superior to glipizide, metformin, rosiglitazone, or other drugs. Side-effects of berberine treatment for T2DM was less severe, mainly including gastrointestinal symptoms, and no hypoglycemia.</td>
</tr>
<tr>
<td>Li KJ et al 2008</td>
<td>4</td>
<td>Point injection</td>
<td>Blank control</td>
<td>Low Jadad scores for 1</td>
<td>Clinical efficacy</td>
<td>Astragalus injection treatment for T2DM showed a significant clinical effect, compared with the control group [RR = 1.58, 95% CI (1.20, 2.09)].</td>
</tr>
<tr>
<td>Peng JL et al 2013</td>
<td>6</td>
<td>Chinese patent medicine (Jinqijiang Tang troche)</td>
<td>Western drugs, placebo</td>
<td>Low</td>
<td>Clinical efficacy, FBG, 2hPBG, HbA1c, adverse effects</td>
<td>Jinqijiangtang troche treatment for T2DM showed a significant clinical effect compared with the placebo group [RR = 0.65, 95% CI (0.41, 1.03)].</td>
</tr>
<tr>
<td>Li JB et al 2013</td>
<td>7</td>
<td>Chinese medicine (herbal compounds or Chinese patent medicine) or combine with Western Medicine</td>
<td>Western drugs</td>
<td>No assessment</td>
<td>FBG, 2hPBG, HbA1c, adverse effects</td>
<td>Chinese medicine (alone or combined with Western Medicine) treatment for T2DM showed significant clinical effects without severe adverse effects.</td>
</tr>
<tr>
<td>Chen YJ 2011</td>
<td>5</td>
<td>Chinese patent medicine (Liuweidihuang pills)</td>
<td>Blank control</td>
<td>Low Jadad scores for 1</td>
<td>Clinical efficacy</td>
<td>Liuweidihuang pill treatment for T2DM showed a significant clinical effect compared with the blank control group [RR = 1.21, 95% CI (1.11, 1.31)].</td>
</tr>
<tr>
<td>Li KJ et al 2009</td>
<td>5</td>
<td>Chinese patent medicine (Liuweidihuang pills)</td>
<td>Blank control</td>
<td>Low Jadad scores for 1</td>
<td>Clinical efficacy</td>
<td>Liuweidihuang pill treatment for T2DM showed a significant clinical effect compared with the blank control group [RR = 1.24, 95% CI (1.07, 1.43)].</td>
</tr>
<tr>
<td>Xu ZY et al 2013</td>
<td>12</td>
<td>Chinese patent medicine (Xiaoke Wan)</td>
<td>Western drugs (Metformin, glyburide, glitazide)</td>
<td>Low Jadad scores between 1-2</td>
<td>FBG, HbA1c, adverse effects</td>
<td>Xiaoke Wan treatment for T2DM could improve total efficacy when compared with conventional medicine [OR = 3.11, 95% CI (2.38, 4.22)].</td>
</tr>
<tr>
<td>Li KJ 2009</td>
<td>4</td>
<td>Chinese patent medicine (Xiaoke Wan)</td>
<td>Blank control</td>
<td>Low Jadad scores for 1</td>
<td>Clinical efficacy</td>
<td>Xiaoke Wan treatment for T2DM showed a significant clinical effect compared with the blank control group [RR = 1.18, 95% CI (1.07, 1.30)]. There was a low incidence of adverse events [OR = 0.33, 95% CI (0.02, 4.13)].</td>
</tr>
<tr>
<td>Li KJ et al 2010</td>
<td>18</td>
<td>Chinese medicine (herbal compounds, single herbs, Chinese patent medicine, and herbal extracts)</td>
<td>Placebo, blank control</td>
<td>Low Jadad scores less than 3</td>
<td>Clinical efficacy</td>
<td>Chinese patent medicine showed better clinical efficacy compared with placebo and control groups [RR = 1.28, 95% CI (1.11, 1.47)].</td>
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Table 1 Basic features, methodology, and evidence quality of included studies

<table>
<thead>
<tr>
<th>AMSTAR scores</th>
<th>GRADE classification</th>
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<tr>
<td>10</td>
<td>1. Low [1, 4]</td>
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<tr>
<td>3</td>
<td>Very low [1, 2, 4]</td>
</tr>
<tr>
<td>7</td>
<td>Low [1, 4, 5]</td>
</tr>
<tr>
<td>4</td>
<td>Cannot judge</td>
</tr>
<tr>
<td>4</td>
<td>Low [1, 4, 5]</td>
</tr>
<tr>
<td>4</td>
<td>Low [1, 4, 5]</td>
</tr>
<tr>
<td>6</td>
<td>Low [1, 4]</td>
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<tr>
<td>3</td>
<td>Low [1, 4, 5]</td>
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<tr>
<td>3</td>
<td>Low [1, 2, 4]</td>
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<tr>
<td>3</td>
<td>Low [1, 2, 4]</td>
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<tr>
<td>Eligible study</td>
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<tr>
<td>Zhang Y 2010&lt;sup&gt;35&lt;/sup&gt;</td>
<td>87</td>
</tr>
<tr>
<td>Chen WN et al 2012&lt;sup&gt;36&lt;/sup&gt;</td>
<td>17</td>
</tr>
<tr>
<td>Li KJ et al 2009&lt;sup&gt;37&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Pu Run et al 2013&lt;sup&gt;38&lt;/sup&gt;</td>
<td>18</td>
</tr>
</tbody>
</table>
compared with English papers, according to the GRADE classifications. Numerous systematic evaluations of Chinese medicine interventions have been performed by Chinese researchers. The results generally found that incomplete literature retrieval, poor control of selection bias, and low accuracy of data combination methods are present in Chinese papers, which affected the credibility of the results. High quality of systematic reviews and meta-analyses are one of the most important sources of evidence for evidence-based medicine practice, and are the best basis from which to make the clinical decisions. The methodological quality of systematic reviews on TCM needs improvement, so high-quality clinical studies with large prospective, multi-center, double-blind and randomized designs should be conducted.

Comprehensive literature retrieval and quality assessment were strictly executed in this work, and the GRADE classification system was used to classify the evidence quality. However, there are some limitations of our study. Most research trials were executed in China, and the limitations of research design quality and sample sizes affect the extrapolation and the strength of evidence. Furthermore, stratified analysis of disease course, syndromes, and complications were excluded by the eligible research. Therefore, it is difficult to precisely evaluate the efficacy of TCM treatment for T2DM.

In summary, the present study can act as a reference for the clinical use of TCM for T2DM, but caution is advised for clinicians because of GRADE classifications of the included studies. Nevertheless, this study can engage researchers involved in evidence-based medicine, statistical methods, and the clinical health field. Professional research teams should be trained to explore the evaluation of TCM, and analyze the literature on the use of TCM in treatments. Meanwhile, quality supervision on the systematic evaluation of TCM should be carried out, and an evaluation methodology should be established along with a TCM literature database. This will ensure that TCM treatments can be evaluated objectively, which will improve the evidence quality of Chinese medicine evidence-based health policy.

REFERENCES