Chinese herbal medicines for type 2 diabetes mellitus
(Protocol)

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BACKGROUND

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (i.e. elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group on The Cochrane Library (see 'About the Cochrane Collaboration', 'Collaborative Review Groups'). For an explanation of methodological terms, see the main Glossary on The Cochrane Library.

There are two types of diabetes mellitus: type 1 insulin dependent (IDDM) and type 2 non-insulin dependent (NIDDM). Type 2 diabetes mellitus, the most common form, is the fourth leading cause of death in developed countries with a two fold excess mortality and two to four fold increased risk of coronary heart disease and stroke. Diabetes affects women and men of all ages and every ethnic category, and many cases of diabetes remain undiagnosed because the onset of the disease occurs on average four to seven years before diagnosis (McKinlay 2000). Diabetes profoundly affects quality of life and represents a life-long burden on a patient's social support system. Diabetes places large financial demands on the health care system.

MANAGEMENT OF TYPE 2 DIABETES

For the management of type 2 diabetes mellitus, the initial recommendations include adaptation of diet, weight loss if appropriate, and exercise. If this regimen does not keep blood glucose level within the normal range, oral anti-hyperglycaemic agents are prescribed, which include metformin and sulphonylurea drugs, or insulin is given. Because of the chronicity of diabetes, the impact of the disease on quality of life, the possibility of severe complications, and the requirements for self-care, it is not unlikely that diabetic patients will seek complementary/alternative therapies (McGrady 1999), i.e. non-standard therapies, such as using food supplements or herbal medicines. The goal of these therapies is to lower blood glucose levels, to decrease dosage of oral anti-hyperglycaemic drugs, to decrease insulin resistance, and to assist in managing the complications of diabetes (Bailey 1989; Ivorra 1989; McGrady 1999).

TRADITIONAL CHINESE MEDICINE

Herbal medicine forms the main part of Traditional Chinese Medicine, which is a 3000-years-old holistic system of medicine combining medicinal herbs, acupuncture, food therapy, massage, and therapeutic exercise for both treatment and prevention of disease (Fulder 1996). Traditional Chinese Medicine has its unique theories for concepts of aetiology, systems of diagnosis, and treatment which are vital to their practice. The theories of Traditional Chinese Medicine include Yin-Yang, the five-elements (Fire, Earth, Metal, Water, and Wood), Qi (vital energy) and Blood, Zhang-Fu (five Viscera and six Bowels), and Channels and Collaterals (Meridian doctrine) (Liu 1991; Cheng 2000). Diseases are considered to result from internal causes as well as external causes, which are defined as disturbances of the body's elaborate balance (for example, the imbalance between Yin and Yang). The drug treatment of Chinese medicine consists typically of complex prescriptions of a combination of several components. The combination based on the Chinese diagnostic patterns (i.e. inspection, listening, smelling, inquiry, and palpation) follows a completely different rationale than many Western drug treatments. Herbs are used for correcting the imbalance of Yin-Yang in the body and maintaining kinetic balance under the movement of five elements. Bianzheng Lunzhi (differentiation of symptoms and prescription of drugs) is the application of the theories.
Medicinal herbs have been widely used for more than 2000 years to treat type 2 diabetes mellitus (‘Xiao Ke Bing’ in ancient records of Traditional Chinese Medicine). In the late 1970’s, clinical investigations were reported on the use of herbal medicines (both different single herbs and mixtures of herbs) as a means of treating diabetes and its complications (Zhou 1980). The mechanism of action of the herbal medicines is inferred to involve regulating glycaemic metabolism, decreasing cholesterol levels, eliminating free radicals, increasing secretion of insulin, and improving microcirculation (Chen 1997; Shen 1997; Zhu 1997; Luo 1998; Zhu 1999). Until March of 1999, 14 herbal medicines (13 mixture of herbs and 1 extract of single herb) (see Table 01) have been officially approved for the treatment of diabetes by the State Drug Regulatory Authority of China (CMH 1999); and 13 herbal medicines (see Table 02) have been listed in the “National Essential Drugs” by the State Drug Administration of China (SDA 2000). Almost of all the herbal medicines are so called ‘Chinese proprietary medicines’, i.e., they are usually based on well-established and longstanding recipes and formulated as tablets or capsules for commerce, convenience, or palatability. However, active ingredients of these herbal medicines are largely unknown and they are combined with different herbs. A number of clinical trials have been reported on the subject in Chinese medical journals during the past 20 years, and the first randomised trial was reported in 1991 (Chen 1991). The results of these trials suggest that treatment with Chinese herbal medicines may have great potential for reducing hyperglycaemia and for care of complications of type 2 diabetes mellitus. However, there are reports of liver toxicity and kidney damage or even cancer associated with using Chinese herbal medicines (Ishizaki 1996; Melchart 1999; Gottlieb 2000; Tomlinson 2000). The potential role and safety for long-term use of herbal medicines in patients with type 2 diabetes mellitus needs to be systematically reviewed to inform the current practice and direct the continued search for new treatment regimens.

Chinese herbal medicines for type 2 diabetes mellitus are considered collectively in this review as a special treatment. The present review deals with the effects of Chinese medicines on glycaemic control, morbidity, mortality, quality of life, and complications as well as safety in patients with type 2 diabetes.

OBJECTIVES

To assess the effects of Chinese herbal medicines on mortality, morbidity and quality of life in patients with type 2 diabetes mellitus and to assess if the use of these medicines is associated with adverse effects.

Additional objectives are as follows:
1. To assess changes in glycaemic control (glycated haemoglobin; fasting plasma glucose).
2. To assess effects on weight.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised clinical trials fulfilling the inclusion criteria will be eligible for this review. Ideally, trial participants, people administering the treatment and outcome assessors will all have been blinded, but single-blind and unblinded trials will also be considered and their effect on the overall results will be assessed in a sensitivity analysis. Special methodological techniques will be used to analyse data from crossover trials, after consulting a statistician. Trials will only be included if the treatment was given for a minimum of two months.

Types of participants

Adults (above 18 years old) with type 2 diabetes mellitus. To be consistent with changes in diagnostic criteria of type 2 diabetes mellitus through the years (WHO 1980; WHO 1985; ADA 1997; WHO 1998; ADA 1999), the diagnosis should have been established using the diagnostic criteria valid at the time of the beginning of the trial. Ideally, diagnostic criteria should have been described. These changes may have produced significant variability in the inclusion criteria, in the clinical characteristics of the patients included as well as in the results obtained. These differences will be considered and explored using sensitivity analyses.

Types of intervention

The intervention of Chinese herbal medicines includes extracts from herbs, single herbs, Chinese proprietary medicines (see Additional Tables), or compounds of herbs that are prescribed (individualised treatment) by a Chinese practitioner. Herbal medicine plus other therapies as a holistic treatment, for example, herbs plus acupuncture, will be excluded. The control intervention includes placebo, a non-pharmacological intervention (for example, exercise or diet), or any active intervention used with the intention of lowering blood glucose (for example, metformin, a sulphonylurea drug, acarbose, insulin).

Co-interventions are allowed as long as both arms of the randomised trial receive the same co-intervention(s).

Types of outcome measures

MAIN OUTCOME MEASURES

1. Mortality (diabetes-related and all-cause)
2. Quality of life (ideally, measured using a validated instrument)
3. Diabetes complications (neuropathy, retinopathy, nephropathy, sexual dysfunction)

Trials in which the major goal of the intervention is to treat the diabetic complications will be considered in separate reviews.

ADDITIONAL OUTCOME MEASURES

4. Glycaemic control (glycated haemoglobin levels (HbA1c) and fasting blood glucose levels)
5. Weight or body mass index (BMI)
6. Fasting insulin levels
7. Adverse effects (for example, liver toxicity, kidney damage)
8. Costs

**TIMING OF OUTCOME ASSESSMENT**

The main outcome measures will require trials of five years or more to yield meaningful results. For other outcomes, we will include trials of short duration (two to three months), medium duration (more than three to six months) and long duration (more than six months), assessing results of short and medium duration separately in a subgroup analysis.

**SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES**

See: search strategy

**ELECTRONIC SEARCHES**

The following electronic databases will be searched regardless of language and publication status:
- The Cochrane Library, including the Cochrane Controlled Trials Register (CCTR, 4/2001), using the search terms for type 2 diabetes and Chinese medicine given in the MEDLINE search strategy below.
- MEDLINE search 1966 to 12/2001, as follows:

**NOTES:** unless stated otherwise, search terms are free text terms; MeSH: Medical subject heading (MEDLINE medical index term); an asterisk (*) stands for "any character(s)"

**TYPE 2 DIABETES MELLITUS**

1. See search strategy of the Metabolic and Endocrine Disorders Group.

**CHINESE MEDICINE**

2. Medicine, herbal [MeSH, all subheadings and categories included]
3. Plants [MeSH, all subheadings and categories included]
4. Drugs, chinese herbal [MeSH, all subheadings and categories included]
5. Medicine, chinese traditional [MeSH, all subheadings and categories included]
6. Yang deficiency [MeSH, all subheadings and categories included]
7. TCM
8. (herb* NEAR (extract* OR singl* OR drug* OR compound* OR mixtur*))
9. herbal medic*
10. Ginseng [MeSH, all subheadings and categories included]
11. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

**TYPE 2 DIABETES AND CHINESE MEDICINE**

12. #1 AND #11

**CLINICAL TRIALS**

13. See search strategy of the Metabolic and Endocrine Disorders Group.

**TYPE 2 DIABETES AND CHINESE MEDICINE AND CLINICAL TRIALS**

14. #12 AND #13

The following additional databases will be searched, adapting the search strategy given above:
- EMBASE from 1974 to 2, 2002
- Chinese BioMedical disk (CD-ROM) from 1979 to 2001
- LILACS (www.bireme.br/bvs/lilacs.htm) from 1986 to 2, 2002
- Databases of ongoing trials (available via www.controlled-trials.com)
- Database of the grey literature (Sigle)

The full electronic search strategy for all databases will be available from the Editorial Base except the Chinese database.

**HANDSEARCHING**

We will handsearch Chinese Journal of Diabetes (1993-2001) and Chinese Journal of Endocrinology and Metabolism (1985-2001). We will try to identify potentially eligible studies by searching the reference lists of relevant trials and reviews identified.

**OTHER SEARCH STRATEGIES**

Authors of relevant identified studies and other experts will be contacted in order to obtain additional references, unpublished trials, ongoing trials or to obtain missing data not reported in the original trials. Similarly, manufacturers of the reviewed Chinese medicines will be contacted in order to retrieve information on herbs trials, published and unpublished.

Additional key words of relevance may be identified during any of the electronic or other searches. If this is the case, electronic search strategies will be modified to incorporate these terms.

**METHODS OF THE REVIEW**

**TRIALS SELECTION**

Two reviewers (MZ, WW) will assess the titles, abstract sections and keywords of every record retrieved independently. Full articles will be retrieved for further assessment if the information given suggests that the study: 1. includes patients with diabetes mellitus, 2. compares Chinese herbal medicines with placebo or any other active intervention, 3. assesses one or more relevant outcome measure, 4. uses random allocation to the comparison groups. If there is any unclear information in the title or abstract, the full
article will be retrieved for clarification. Interrater agreement for study selection will be measured using the kappa statistic (Fleiss 1981). Where differences in opinion exist, they will be resolved by a third party (JL). If resolving disagreement is not possible, the article will be added to those ‘awaiting assessment’ and the authors will be contacted for clarification. If no clarification is provided, the review group editorial base will be consulted.

QUALITY ASSESSMENT OF TRIALS
The quality of reporting each trial will be assessed based largely on the quality criteria specified by Schulz and by Jadad (Schulz 1995; Jadad 1996). In particular, the following factors will be studied:
1. Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
2. Minimisation of performance bias - were the patients and people administering the treatment blind to the intervention (where blinding is possible)?
3. Minimisation of attrition bias - a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
4. Minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, studies will be broadly subdivided into the following three categories (see Cochrane Handbook):
A - all quality criteria met: low risk of bias.
B - one or more of the quality criteria only partly met: moderate risk of bias.
C - one or more criteria not met: high risk of bias.

This classification will be used as the basis of a sensitivity analysis. Additionally, we will explore the influence of individual quality criteria in a sensitivity analysis.

Each trial will be assessed independently by two reviewers (MZ, WW) and verified by JL. Interrater agreement will be calculated using the kappa statistic. Any disagreement in the quality assessment will be resolved through discussion and a judgement will be made based on consensus.

DATA EXTRACTION
Data concerning details of study population, intervention and outcomes will be extracted independently by two reviewers (MZ, WW) using a standard data extraction form. The standard data extraction form will include at least the following items:
1. General information: published/unpublished, title, authors, source, contact address, country, urban/rural etc., language of publication, year of publication, duplicate publications, sponsoring, setting.
2. Trial characteristics: design, duration, randomisation (and method), allocation concealment (and method), blinding (patients, people administering treatment, outcome assessors), check of blinding.
3. Intervention(s): placebo included, intervention(s) (single herb or compound of herbs, dose, route, timing, mode of treatment; expertise of the practitioner), comparison intervention(s) (dose, route, timing), co-medication(s) (dose, route, timing).
4. Patients: sampling (random/convenience), exclusion criteria, total number and number in comparison groups, sex, age, baseline characteristics, diagnostic criteria, duration of diabetes, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow-up (reasons/description), subgroups.
5. Outcomes: outcomes specified above, other outcomes, length of follow-up, quality of reporting of outcomes.
6. Results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures of effect specified below; intention-to-treat analysis.

Differences in data extraction will be resolved by consensus, referring back to the original article. When necessary, information will be sought from the authors of the primary studies.

DATA ANALYSIS
Data will be summarised statistically if they are available, of sufficient quality and sufficiently similar. We expect both event (dichotomous) and continuous data.

Dichotomous data will be expressed as relative risk (RR) with 95% confidence interval (CI). We will calculate the risk difference (RD) and convert the RD into the number needed to treat (NNT) or the number needed to harm (NNH) if follow-up is similar for the different trials. Continuous data will be expressed as weighted mean differences (WMD) with 95% CI and an overall WMD will be calculated. Overall results will be calculated based on the random effects model.

Heterogeneity will be tested for using the Z score and the Chi square statistic with significance being set at p < 0.10. Possible sources of heterogeneity will be assessed by subgroup and sensitivity analyses as described below. Potential bias will be tested for using the funnel plot or other corrective analytical methods depending on the number of clinical trials included in the systematic review (Egger 1997).

The analyses will be carried out using MetaView 4.1 in Review Manager 4.1 (Cochrane software).

SUBGROUP ANALYSES
We will aim to perform subgroup analyses in order to explore effect size differences in case there is a significant result for at least one of the major outcome measures:
1. Glycosylated haemoglobin level at baseline (if this is unavailable, mean level of fasting plasma glucose at baseline will be used) (subdividing into three groups of low, medium and high level - based on data)
2. Age (18-40 years, 41-64 years, older than 65 years)
3. Gender
5. Different herbs/herbal preparations
6. Duration of intervention (short, medium, long - based on data).

SENSITIVITY ANALYSES
We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:
1. Repeating the analysis excluding unpublished studies (if there were any).
2. Repeating the analysis taking account of study quality, as specified above.
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
4. Repeat the analysis excluding studies using the following filters: diagnostic criteria, language of publication, publication status, source of funding (industry versus other), country.

The robustness of the results will also be tested by repeating the analysis using different measures of effects size (RD, RR etc.) and different statistical models (fixed and random effects models).
C O V E R S H E E T

Title
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JIANPING LIU: Protocol development, third party for searching for trials, data analysis, development of final review, corresponding author.
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WEIYA WANG: Searching for trials and quality assessment of trials, data extraction and analysis, development of final review.

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