Chinese herbal medicine for the treatment of people with impaired glucose tolerance and insulin resistance

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STATEMENT OF AUTHENTICATION

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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(Signature)
# Table of Contents

Acknowledgements ........................................................................................................... i  
Statement of Authentication ............................................................................................... iii  
Table of Contents ............................................................................................................. iv  
List of Tables .................................................................................................................... xi  
List of Figures ................................................................................................................... xiii  
List of Appendices ............................................................................................................. xv  
Abbreviations .................................................................................................................. xvii  

Abstract ............................................................................................................................. 1  

## Chapter 1  Overview and chapter outline ................................................................. 5  
1.1 Thesis title .................................................................................................................. 5  
1.1.1 Research rationale ................................................................................................. 5  
1.2 Research outline ........................................................................................................ 8  
1.2.1 Systematic review .................................................................................................. 8  
1.2.2 Patterns of disharmony and TCM treatment principles in people with prediabetes 9  
1.2.3 Randomised controlled trial ............................................................................... 9  
1.2.4 Reliability of Traditional Chinese Medicine (TCM) diagnosis 10  
1.3 Significance of the study ......................................................................................... 10  
1.4 Thesis outline ........................................................................................................... 11  

## Chapter 2  Prediabetes: Definitions and Current Management ............................ 14  
2.1 Definition and diagnosis ......................................................................................... 14  
2.2 Testing for prediabetes ............................................................................................ 17  
2.3 Epidemiology ........................................................................................................... 19  
2.4 Pathophysiology of prediabetes ............................................................................. 23  
2.5 Aetiology .................................................................................................................. 27  
2.6 Current management ............................................................................................... 29  
2.6.1 Intensive lifestyle modifications ......................................................................... 30  
2.6.2 Pharmaceutical interventions .............................................................................. 32  
2.7 Impact on quality of life & economic cost ............................................................... 35  
2.8 Conclusion ............................................................................................................... 36  

## Chapter 3  Traditional Chinese Medicine: Theory, Treatment and Herbal Medicine for prediabetes ................................................................. 38  
3.1 Rationale .................................................................................................................. 38  
3.2 Method ....................................................................................................................... 42  
3.2.1 Inclusion criteria ................................................................................................ 42  
3.3 Findings of the review ............................................................................................. 42  
3.3.1 Description of the literature .............................................................................. 42  
3.3.2 TCM differential diagnosis and patterns of disharmony in people with IGT . 43
Chapter 4 Chinese Herbal Medicines for IGT or IFG - A Systematic Review

4.1 Background

4.2 Objectives

4.3 How the intervention might work

4.4 Adverse effects of the intervention

4.5 Method

4.6 Results - Description of studies

4.7 Risk of bias in included studies

4.8 Effects of interventions

4.6.1 Results of the search

4.6.2 Included studies

4.6.3 Participants

4.6.4 Diagnosis

4.6.5 Interventions

4.6.6 Outcomes

4.6.7 Excluded studies

4.7.1 Allocation

4.7.2 Blinding

4.7.3 Incomplete outcome data

4.7.4 Selective reporting

4.7.5 Other potential sources of bias

4.8.1 Herbal medicine plus lifestyle modification versus lifestyle modification alone

4.8.2 Normalisation of fasting blood glucose and incidence of diabetes

4.8.3 Fasting blood glucose and 2hr blood glucose after an oral glucose tolerance test (OGTT)
Chapter 5 Individual Herbs for Prediabetes and Jiangtang Xiaozhi

5.1 Approach ................................................................. 100
5.2 Individual herbs ......................................................... 103
5.2.1 Shan yao ................................................................. 107
5.2.2 Ren shen ................................................................. 111
5.2.3 Fu ling ................................................................. 112
5.2.4 Huang jiang ............................................................ 113
5.2.5 Ge gen ................................................................. 114
5.2.6 Tian hua fen .......................................................... 115
5.2.7 Di huang ............................................................... 115
5.2.8 Nu zhen zi ............................................................ 116
5.2.9 Huang qi ............................................................... 118
5.2.10 Huang lian .......................................................... 120
5.2.11 Li zhi he ............................................................... 123
5.2.12 Kun bu ............................................................... 125
5.2.13 Jiang huang ......................................................... 126
5.3 Clinical trial formulation – Jiangtang Xiaozhi .................. 129
5.3.1 Composition of Jiangtang Xiaozhi ......................... 129
5.4 Preclinical Studies ....................................................... 129
5.5 Clinical Study ........................................................... 130
5.6 Conclusion .............................................................. 132

Chapter 6 Randomised Clinical Trial – Method ..................... 135
6.1 Research objectives .................................................... 135
6.2 Research design ......................................................... 136
6.3 Setting .................................................................... 136
6.4 Participants .............................................................. 136
6.4.1 Principles guiding selection of criteria ....................... 136
6.4.2 Inclusion criteria .................................................... 137
6.4.3 Exclusion criteria ................................................... 138
6.4.4 Recruitment ........................................................ 139
6.4.5 Screening procedures and interview ......................... 142
6.5 Interventions ............................................................ 143
6.5.1 Jiangtang Xiaozhi tablets ................................................... 144
6.5.2 Jiangtang Xiaozhi tablets manufacturing process .......... 144
6.5.3 Placebo tablets ................................................................. 146
6.5.4 Placebo tablets manufacturing process ......................... 146
6.5.5 Labelling ........................................................................... 146
6.5.6 Medication compliance ...................................................... 147
6.6 Sample size ........................................................................... 147
6.7 Randomisation and blinding ................................................... 148
6.7.1 Generation of allocation sequence .................................. 148
6.7.2 Allocation concealment and blinding ............................... 148
6.8 Primary outcome measure: glycaemic control ................. 149
6.9 Secondary outcomes ............................................................. 151
6.9.1 Insulin .............................................................................. 151
6.9.2 C-reactive protein ............................................................. 153
6.9.3 Obesity and waist girth ...................................................... 153
6.9.4 Lipids ............................................................................... 154
6.9.5 Blood pressure ................................................................. 154
6.9.6 Health-related quality of life (HRQoL) ......................... 155
6.9.7 Adverse effects and safety tests ...................................... 157
6.10 Treatment and assessment procedure ............................... 157
6.11 Outcome measure protocols .............................................. 158
6.11.1 Interview protocol ......................................................... 159
6.11.2 Initial enrolment questions ............................................. 159
6.11.3 Blood sampling procedures .......................................... 160
6.11.4 Height and weight ......................................................... 161
6.11.5 Waist and hip girth .......................................................... 162
6.11.6 Blood pressure ............................................................... 162
6.11.7 Physical activity and nutritional intake ...................... 162
6.12 Safety monitoring ................................................................. 163
6.12.1 Adverse events ............................................................... 164
6.13 Data analysis ....................................................................... 166
6.13.1 Approach to analysis ...................................................... 166
6.13.2 Missing data ................................................................. 166
6.13.3 Statistical analysis .......................................................... 167

Chapter 7 Randomised Controlled Trial: Results .................. 169
7.1 Recruitment ................................................................. 169
7.2 Participant discontinuation ............................................... 170
7.3 Baseline characteristics of participants ............................ 171
7.3.1 Risk factors for diabetes ................................................ 171
7.3.2 Other medical history ....................................................... 174
7.3.3 Anthropometric measurements .................................... 175
7.3.4 Biochemical measurements .......................................... 176
7.3.5 Physical activity, fruit and vegetable intake .................. 178
7.4 Primary Outcomes ............................................................. 179
7.4.1 Fasting blood glucose levels ....................................... 179
7.4.2 2hr Post-prandial glucose ............................................. 181
7.4.3 Glycosylated haemoglobin (HbA1c) ......................... 183
7.5 Secondary Outcomes ......................................................... 184
7.5.1 Insulin ................................................................. 185
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.3.2</td>
<td>Practitioners</td>
<td>269</td>
</tr>
<tr>
<td>9.3.3</td>
<td>Data collection and diagnostic framework</td>
<td>269</td>
</tr>
<tr>
<td>9.3.4</td>
<td>Statistical analysis</td>
<td>270</td>
</tr>
<tr>
<td>9.3.5</td>
<td>Definition of agreement on TCM pattern diagnosis</td>
<td>272</td>
</tr>
<tr>
<td>9.4</td>
<td>Results</td>
<td>273</td>
</tr>
<tr>
<td>9.4.1</td>
<td>Patient characteristics</td>
<td>273</td>
</tr>
<tr>
<td>9.4.2</td>
<td>TCM diagnostic patterns</td>
<td>273</td>
</tr>
<tr>
<td>9.4.3</td>
<td>The TEAMSI-TCM instrument</td>
<td>275</td>
</tr>
<tr>
<td>9.4.4</td>
<td>TCM patterns of disharmony and biomarkers for people with prediabetes</td>
<td>276</td>
</tr>
<tr>
<td>9.5</td>
<td>Discussion</td>
<td>278</td>
</tr>
<tr>
<td>9.7</td>
<td>Conclusion</td>
<td>284</td>
</tr>
</tbody>
</table>

References ........................................................................................................ 285
Appendices........................................................................................................... 239
# List of Tables

| Table 2-1 | Diagnostic Criteria for Diabetes Mellitus, IGT and IFG | 15 |
| Table 2-2 | Global Burden: Prevalence and Projections, 2010 and 2030 | 19 |
| Table 2-3 | Key defects associated with isolated Impaired Fasting Glucose (IFG) and isolated Impaired Glucose Tolerance (IGT) | 23 |
| Table 2-4 | Main pharmaceutical interventions for prediabetes and diabetes | 31 |
| Table 3-1 | Prediabetes: Patterns of Disharmony | 43 |
| Table 3-2 | TCM Signs and Symptoms in People with IGT According to Four Common Patterns of Disharmony | 44 |
| Table 3-3 | Patterns of Disharmony, Prevalence and Biomechanical Markers in 156 People with IGT | 46 |
| Table 3-4 | Patterns of Disharmony, Prevalence and Biomechanical Markers in 55 People with IGT | 47 |
| Table 3-5 | Treatment principles in order of prevalence | 50 |
| Table 4-1 | Preparation and composition of Chinese herbal medicines in the included trials | 73 |
| Table 5-1 | Chinese herbs used in complex formulas in 33 controlled trials and one unpublished trial involving people with IGT | 104 |
| Table 5-2 | Summary of major constituents and pharmacologic activities of Chinese single herbs for IGT with hypoglycaemic effects | 108 |
| Table 5-3 | Comparison of outcome measures before and after treatment | 131 |
| Table 5-4 | Effect of Jiangtang Xiaozhi Treatment (n=30) on Inflammation Markers | 132 |
| Table 6-1 | Summary of recruitment media coverage | 141 |
| Table 6-2 | Composition of Jiangtang Xiaozhi tablets | 144 |
| Table 6-3 | Composition of Jiangtang Xiaozhi allotype tablet (placebo) | 146 |
| Table 6-4 | Timing of Outcome Measures | 158 |
| Table 6-5 | Pathology order of collection and normal values | 161 |
| Table 6-6 | Timing of safety measures | 164 |
| Table 7-1 | Between-group comparison of risk factors for diabetes at baseline | 172 |
| Table 7-2 | Between-group comparison of anthropometric measures at baseline | 175 |
| Table 7-3 | Between-group comparison of biochemical measures at baseline | 177 |
| Table 7-4 | Between-group comparison of number of participants with adequate physical activity, and fruit & vegetable intake at baseline | 178 |
| Table 7-5 | Outcome: Fasting Blood Glucose (mmol/L) | 180 |
| Table 7-6 | Outcome: 2hr Post prandial glucose (mmol/L) | 182 |
| Table 7-7 | Outcome: HbA1c% values | 184 |
| Table 7-8 | Outcome: Insulin values | 186 |
| Table 7-9 | Outcome: Insulin Resistance (HOMA-IR) | 189 |
| Table 7-10 | Outcome: Beta-cell function (HOMA%B) | 191 |
| Table 7-11 | Outcome: Insulin sensitivity (HOMA%S) | 194 |
| Table 7-12 | Sensitivity analysis: HOMA-IR, HOMA%S and HOMA%B | 196 |
| Table 7-13 | Outcome: C-reactive protein | 198 |
| Table 7-14 | Outcome: Total cholesterol | 199 |
List of Figures

Figure 2-1 Preclinical and clinical stages of type 2 diabetes. ........................................ 22
Figure 2-2 Multiple defects contributing to the progression to type 2 diabetes .... 25
Figure 3-1 Research strategies in drug trials and the proposed CAM strategy. ..... 56
Figure 4-1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection .................................................. 70
Figure 4-2 Risk of bias summary ................................................................................ 80
Figure 4-3 Forest plot of outcome of normalisation of FBG................................ 84
Figure 4-4 Forest plot of outcome ‘diabetes incidence’ ............................................ 85
Figure 5 1 Comparison of approaches to research on novel and traditional treatments........................................................................................................... 101
Figure 6-1 Flow of participants from recruitment to trial completion .......... 137
Figure 7-1 Participant flow through recruitment to trial completion ............... 170
Figure 7-2 Effect of intervention over time on Fasting Blood Glucose .......... 181
Figure 7-3 Effect over time of Intervention on 2hr Post-prandial Glucose .... 183
Figure 7-4 Effect of treatment over time on Insulin ............................................. 187
Figure 7-5 Effect Over Time of Treatment on HOMA-IR .................................. 190
Figure 7-6 Effect Over Time of Treatment on HOMA%B .............................. 192
Figure 7-7 Effect Over Time of Treatment on HOMA%S .............................. 195
Figure 7-8 Effect Over Time of Treatment on HDL Cholesterol ................. 203
Figure 7-9 Effect Over Time of Treatment on Weight ................................. 208
Figure 7-10 Effect Over Time of Treatment on BMI ................................. 210
Figure 7-11 Effect Over Time of Treatment on Waist ...................................... 213
Figure 7-12 Effect Over Time of Treatment on WHR ....................................... 216
Figure 7-13 Comparison of Baseline Group with Australian normative data .... 218
Figure 7-14 SF-36 Dimension T-Scores at Week 16 ..................................... 223
Figure 7-15 Prediabetes subgroup: Fasting Blood Glucose ............................... 227
Figure 7-16 Prediabetes subgroup: Insulin ...................................................... 228
Figure 7-17 Diabetes subgroup: Effect of treatment over time on insulin ....... 235
Figure 9-1 Primary TCM Diagnosis for Prediabetes Symptom Overlap .......... 280
List of Appendices

Appendix A-1 Systematic review: Medline search strategy for systematic review . 239
Appendix A-2 Systematic review: characteristics of included studies .................. 242
Appendix A-3 Systematic review: overview of study populations ................. 267
Appendix A-4 Systematic review: characteristics of excluded studies ............ 270
Appendix A-5 Systematic review: data analysis of the effects of interventions ..... 278
Appendix B-1 Chemistry and preparation of Jiangtang Xiaozhi Capsule .......... 317
Appendix B-2 Preclinical studies of Jiangtang Xiaozhi Capsule .................... 322
Appendix B-3 Clinical study of Jiangtang Xiaozhi Capsule ......................... 334
Appendix C-1 Phone screening criteria ......................................................... 344
Appendix C-2 OGTT patient information sheet ............................................. 347
Appendix C-3 Informed consent form ............................................................ 349
Appendix C-4 Participant information sheet ............................................... 351
Appendix C-5 Australian SF-36 version 2.0 questionnaire .......................... 354
Appendix C-6 Nutritional and physical activity survey ................................ 361
Appendix C-7 Case report form ................................................................. 363
Appendix D-1 TEAMS-TCM patient pack ............................................... 373
Appendix D-2 TEAMS-TCM practitioner pack ......................................... 384
Appendix D-3 TEAMS-TCM pattern differentiation form ............................. 393
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPK</td>
<td>5’ adenosine monophosphate-activated protein kinase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BBMV</td>
<td>brush-border membrane vesicles</td>
</tr>
<tr>
<td>CAM</td>
<td>complementary and alternative medicine</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>FBG</td>
<td>fasting blood glucose</td>
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<tr>
<td>FPG</td>
<td>fasting plasma glucose</td>
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<tr>
<td>GLUT4</td>
<td>glucose transporter type 4</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>HbA1c</td>
<td>glycated haemoglobin</td>
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<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
</tr>
<tr>
<td>HOMA</td>
<td>homeostasis model assessment</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health related quality of life</td>
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<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>IFG</td>
<td>impaired fasting glucose</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat</td>
</tr>
<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
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<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
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<tr>
<td>PCOS</td>
<td>polycystic ovarian syndrome</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>peroxisome proliferator-activated receptors</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
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<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<tr>
<td>STZ</td>
<td>streptozotocin</td>
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<tr>
<td>TCM</td>
<td>traditional Chinese medicine</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<td>WHR</td>
<td>waist hip ratio</td>
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This research was undertaken to investigate Chinese herbal medicine for the treatment of impaired glucose tolerance and insulin resistance. The prevalence of diabetes is a rapidly growing with considerable social and economic costs to our community. It is desirable that progress from prediabetes to frank diabetes be stopped or delayed. There has been considerable research undertaken in lifestyle and pharmaceutical prevention or delay or diabetes but there is no cure, pharmaceutical interventions often have side effects and lifestyle interventions are not always achieveable. There have been a number of clinical trials of Chinese herbal medicine interventions in recent years but there has been no review undertaken of Chinese herbal medicine interventions.

The objective of this research was to review the evidence for the treatment of prediabetes with traditional Chinese herbal medicine and examines the traditional Chinese medicine approach to the treatment of prediabetes. This involved two main pieces of research a systematic review to evaluate the efficacy and safety of Chinese herbal medicine for the treatment of impaired glucose tolerance or impaired fasting blood glucose; and a double blinded, randomised and placebo-controlled clinical trial to evaluate the effectiveness of a Chinese herbal formula, Jiangtang Xiaozhi for the treatment of impaired glucose tolerance and insulin resistance in persons with prediabetes and mild diabetes.

In the preparation for the conduct of the clinical trial and systematic review an examination of the traditional Chinese medicine (TCM) patterns of disharmony and treatment principles was undertaken. An inter-rater reliability study of the TCM diagnosis of people with prediabetes using a subset of the clinical trial participants was also conducted.

The systematic review was undertaken using the Cochrane review methodology and examined 16 trials lasting four weeks to two years involving 1391 participants receiving 15 different Chinese herbal medicines in eight different comparisons. No
trial reported on mortality, morbidity or costs. No serious adverse events like severe hypoglycaemia were observed. Meta-analysis of eight trials showed that those receiving Chinese herbal medicines combined with lifestyle modification were more than twice as likely to have their fasting plasma glucose levels return to normal levels compared to lifestyle modification alone. Those receiving Chinese herbs were less likely to progress to diabetes over the duration of the trial. However, all trials had a considerable risk of bias and none of the specific herbal medicines comparison data was available from more than one study. Moreover, results could have been confounded by rates of natural reversion to normal glucose levels.

The positive evidence in favour of Chinese herbal medicines for the treatment of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) was constrained by the following factors: lack of trials that tested the same herbal medicine, lack of details on co-interventions, unclear methods of randomisation, poor reporting and other risks of bias.

A randomised placebo controlled trial was conducted to investigate the efficacy and safety of a Chinese herbal medicine, Jiangtang Xiaozhi, in the treatment of impaired glucose tolerance and insulin resistance. The trial was conducted over 20 month in 71 people in three centres in Sydney and Gosford. The primary outcome measures were indicators of glycaemic control.

The null hypothesis that the Chinese herbal formula, Jiangtang Xiaozhi, has no added value in treating impaired glucose tolerance or insulin resistance in persons with prediabetes and early diabetes compared to placebo is partially rejected. We found evidence that Jiangtang Xiaozhi showed benefits in improving insulin resistance, maintaining insulin levels and improving HDL-cholesterol compared to a placebo. We also found that Jiangtang Xiaozhi was able to improve postprandial glucose compared to baseline levels. But we found no evidence that Jiangtang Xiaozhi was effective in lowering fasting blood glucose or HbA1c in a 16 week trial in people with impaired glucose tolerance and mild diabetes. The herbal formula was well tolerated.

The trial was conducted according to rigorous methodology with minimal risk of bias. The main limitation of the trial was that it was inadequately powered. Our
results do not fully support the findings of a previous clinical trial of Jiangtang Xiaozhi where evidence was found for the treatment of fasting blood glucose in people with diabetes compared to baseline levels. However our trial was shorter in length and in a smaller sample. An additional two critical differences seem to have been the more severe baseline symptoms of participants and the dosage. Nonetheless, our trial supports the findings of this earlier study on the capacity of Jiangtang Xiaozhi to improve insulin measures and HDL cholesterol compared to a placebo.

There is evidence that Jiangtang Xiaozhi exerts a positive effect on serum insulin and insulin resistance that warrants further investigation. To our knowledge this is the first study outside of China and Japan to investigate a Chinese herbal medicine for the treatment of prediabetes using a rigorous RCT design. In conclusion, a small sample of participants with IGT and early diabetes exhibited significant benefits in terms of both insulin and HDL cholesterol over a relatively short intervention period using Jiangtang Xiaozhi.

In light of the growing epidemic of diabetes worldwide, preventing or delaying the onset of diabetes may likewise reduce the microvascular and macrovascular complications of the disease. It is worthwhile investigating the potential of Jiangtang Xiaozhi to decrease blood glucose levels and reduce or prevent the incidence of diabetes in a longer, adequately powered trial.

This robust study further contributes to the growing body of scientific knowledge of Chinese herbal medicine. Findings from quality RCTs are important to inform the community, health professionals and regulatory authorities on the role of Chinese herbal medicine in health care.

The findings of our inter-rater reliability study indicated that TCM practitioners diagnosing patients with prediabetes commonly selected one of three patterns: Qi and Yin deficiency, Spleen qi deficiency or Yin deficiency. There was a moderate level of inter-rater reliability between practitioners. The methodology of inter-rater reliability studies of TCM diagnosis would benefit from further refinement, building on research that has already been conducted. The continued improvement of the face
and content validity of the TEAMS-I-TCM instrument will result in a robust tool for the conduct of clinical trials.
CHAPTER 1

Overview and chapter outline

1.1 Thesis title

Effectiveness of Chinese herbal medicine in the treatment of impaired glucose tolerance and insulin resistance in persons with mild diabetes and prediabetes.

1.1.1 Research rationale

Worldwide it is estimated 285 million adults - equivalent to 6.4% of the population aged 20 to 79 yrs - have diabetes. A further 344 million have impaired glucose tolerance (IGT) (International Diabetes Federation, 2008). These individuals show higher than normal blood sugar (glucose) levels, but not high enough to be classified as having type 2 diabetes. Over time however, the impaired glucose tolerance of many of these individuals will deteriorate and a diagnosis of diabetes will be made. Evidence from a large scale clinical study in the United States of America (USA) found that, without intervention, 7.8 percent of overweight individuals with impaired glucose tolerance can be expected to become diabetic within any three year period (Diabetes Prevention Program Research Group, 2009). The diagnosis of diabetes signifies a shift from minor and barely noticeable symptoms, with some additional risk for cardiovascular disease, to symptoms and pathology indicative of increasingly significant detriment to health and wellbeing.

Diabetes is a lifelong condition that seriously and adversely affects a person's quality of life. As well has having to curtail their lifestyle, monitor blood glucose, use multiple drugs and injections, individuals with the disease can expect permanently disabling complications and risk premature death. Heart attack and stroke are more often fatal if diabetes is present than not (Stevens, 2004). Diabetes is a leading cause of death, new cases of end-stage renal disease (ESRD), lower-limb amputations, blindness, and cardiovascular disease.
Evidence of the severity of diabetes’ burden on international health is startling. Diabetes is estimated to be the cause of 3.96 million excess deaths among the worldwide adult population in 2010. This is equivalent to 6.8% of global all-ages mortality (Roglic & Unwin, 2010). Increasingly sedentary lifestyles coupled with obesity, ageing of the population and better health care improving the longevity of people with diabetes, are postulated reasons for increasing rates of diabetes related mortality (Shaw, Sicree, & Zimmet, 2010). The World Health Organisation (WHO) projects that, without urgent intervention, deaths caused by diabetes will increase by more than 50% in the next 10 years (WHO, 2008). In recognition of the threat posed by diabetes to human wellbeing throughout the world, the United Nations unanimously adopted a resolution in December 2006 calling upon all countries to develop national policies for the prevention, care and treatment of diabetes (United Nations, 2007).

Impaired glucose tolerance, independent of diabetes, carries an increased risk of cardiovascular disease and all-cause mortality (Barr, et al., 2007; Coutinho, Gerstein, Wang, & Yusuf, 1999; DECODE study group, 1999). There is a linear relationship between glucose levels and the likelihood of myocardial infarction independent of other risk factors such as smoking and lipid levels (Pais, et al., 1996). Research has continued to show that increased blood glucose levels, prior to frank diabetes, are associated with the acceleration of artherosclerotic plaques (Redgrave, Lovett, Syed, & Rothwell, 2008), endothelial dysfunction (Su, et al., 2008) and sudden death (Curb, et al., 1995).

At present, the best course of action to reduce higher than normal blood sugar is rigorous behavioural change to modify diet and increase levels of physical activity. For some this is not easy. The built environment with limited footpaths, parks or public gyms is not necessarily conducive to affordable regular exercise. Healthy food choices may not be available at the neighbourhood grocery store and even if they are, may not be affordable. Other critical requisites for major behaviour change include optimal mental health and social support. These too are often in short supply. For others, rigorous and sustained behavioural change isn’t enough. In these cases pharmaceutical interventions such as metformin may delay or suppress the onset of diabetes. The cost effectiveness of this option however, has been challenged.
Experimental data suggests that if all persons with impaired glucose tolerance were to take metformin for ten years, then the onset of diabetes would be delayed by only two cases per 100 person years (Herman, et al., 2005; Misra, 2009). As well as low cost effectiveness, metformin is contraindicated for some individuals. When used as directed, documented adverse events for Metformin include an increased prevalence of peripheral neuropathy and has been associated with life-threatening lactic acidosis (Merck P/L, 2007).

Lifestyle interventions – exercise and diet – can achieve remarkable reductions in the incidence of diabetes among at-risk individuals, with a 58% reduction in incidence compared to placebo reported in a major large-scale 3-year study (Diabetes Prevention Program Research Group, 2009). When the same individuals were followed for a total of 10 years however, the reduction in incidence of diabetes among the lifestyle intervention group was less marked: 34% compared to placebo. The authors found that much of the initial weight loss was regained. There is clearly a need for low-risk low-cost alternatives to pharmaceutical interventions where lifestyle modifications have failed to adequately improve glucose tolerance.

Chinese herbal medicines have long been used for the treatment of impaired glucose tolerance and diabetes in China, Korea and Japan, with strong anecdotal evidence of their effectiveness (Liu, Zhang, Wang, & Grimsgaard, 2004). An estimated 800-1,200 species of plants exhibit hypoglycaemic properties, including many common plants such as pumpkin, wheat, celery, and bitter melon (Evans, 2009; Jia, Gao, & Xiao, 2003; Leach, 2007).

To our knowledge, the earliest documented randomised clinical trial using Chinese herbal medicine in the treatment of diabetes was conducted in 1991(Liu, et al., 2004). Randomised clinical trials in prediabetes have been conducted since 2000 (Grant, et al., 2009). A Cochrane Database Systematic Review of Chinese Herbal Medicine used in the Treatment of Diabetes identified 66 randomised controlled trials involving 8,302 participants and concluded that some herbal medicines show hypoglycaemic effects and insulin sensitising effects (Liu, et al., 2004). However, these findings need to be carefully interpreted due to the low methodological quality of the studies, small sample size, and limited number of trials. Nonetheless, in the
light of some positive findings, Chinese herbal medicines deserve further examination.

1.2 Research outline

This research reviews and establishes evidence for the treatment of prediabetes with traditional Chinese herbal medicine and examines the traditional Chinese medicine approach to the treatment of prediabetes. The research comprises four parts:

1. An examination of the traditional Chinese medicine (TCM) patterns of disharmony and treatment principles evident in the clinical trials of herbal medicines for the treatment of people with prediabetes.

2. A Cochrane systematic review to evaluate the efficacy and safety of Chinese herbal medicine for the treatment of impaired glucose tolerance or impaired fasting blood glucose when compared with a placebo, no treatment, or conventional treatment.

3. A double blinded, randomised and placebo-controlled clinical trial to evaluate the effectiveness of a Chinese herbal formula, Jiangtang Xiaozhi for the treatment of impaired glucose tolerance and insulin resistance in persons with prediabetes and mild diabetes.

4. An inter-rater reliability study of the TCM diagnosis of people with prediabetes using a subset of the clinical trial participants.

1.2.1 Patterns of disharmony and TCM treatment principles in people with prediabetes

Traditional Chinese Medicine (TCM) is a system of healing that originated probably two millenia ago (Kaptchuk, 2000). It has evolved into a well-developed, coherent system of medicine that uses several modalities to treat and prevent illness. TCM focuses on the whole person, diagnosing through careful examination and identifying patterns of disharmony. When a disorder exists, a Pattern of Disharmony (Bian Zheng) has occurred in the body. There are numerous Patterns of Disharmony. They are named according to the Organs, Meridians, or Substances affected or what
Chapter 1: Overview and chapter outline

Pathogenic Factor is involved. These terms characterize the Chinese medicine understanding of the disease process. At the heart of TCM, is the selection of a treatment for a disease guided specifically by the prevailing pattern of disharmony (Maciocia, 1989).

People with prediabetes exhibit certain patterns of disharmony. These patterns guide treatment and herbal medicine selection. The extent to which this clinical approach is considered in randomised controlled trials was explored together with the prevalent patterns of disharmony.

1.2.2 Systematic review

A systematic review of all randomised controlled trials of Chinese herbal medicine in the treatment of prediabetes was conducted. The review was undertaken within the guidelines set out by the Cochrane Collaboration (Higgins & Green, 2008).

The use of explicit, systematic methods in reviews limits bias (systematic errors) and reduces chance effects. Cochrane collaboration reviews use meta-analysis to provide more precise estimates of the effects of healthcare than those derived from the individual studies included in a review.

The objectives of the review were: (a) to identify all randomised controlled trials conducted in people with prediabetes and undertake a quality assessment of the methodology of these studies, and (b) to analyse the outcomes of the randomised controlled trials and provide comment on the efficacy of Chinese herbal medicine for the treatment of prediabetes.

1.2.3 Randomised controlled trial

A randomised controlled clinical trial (RCT) was undertaken to determine the effectiveness of a Chinese herbal medicine, Jiangtang Xiaozhi, in the treatment of people with impaired glucose tolerance or prediabetes. It was a rigorous study designed to exclude error and bias, and provide a sound estimate of the probability that any effects could have been caused by chance alone (Pocock, 1993).
The objectives of the RCT were to: (a) design a research methodology with outcome measures that effectively answered the research question; (b) conduct a randomized controlled trial of a Chinese herbal formula for prediabetes; and (c) analyse, prepare and publish findings from the randomised controlled trial.

### 1.2.4 Reliability of Traditional Chinese Medicine (TCM) diagnosis

The diagnostic and clinical reasoning in Chinese medicine is central to the selection of treatment. When conducting clinical trials of acupuncture and Chinese herbal medicine it is preferable to group participants so as to reflect clinical practice. However, a lack of consistency of diagnoses, and the absence of a reliable and valid instrument make the incorporation of the TCM diagnostic framework into the structure of clinical trials difficult. Several formal attempts have been made to evaluate the validity and reliability of TCM diagnoses and this area of research is growing (MacPherson, Thorpe, Thomas, & Campbell, 2004; O’Brien, et al., 2009).

This component of the research: (a) assessed the interrater reliability of a Chinese medicine diagnosis using a structured assessment instrument; (b) identified TCM patterns for prediabetes along with the biochemical markers that predominate; and (c) piloted a prediabetes module for the TCM version of the Traditional East Asian Medicine Structured Interview (TEAMS1) instrument, (Schnyer, et al., 2005).

### 1.3 Significance of the study

There have been few rigorous RCTs of Chinese herbal medicines. There had previously been no systematic review of Chinese herbal medicine in the treatment of prediabetes. Nor, to our knowledge, had there been any review of TCM approaches generally to people with prediabetes. The conduct of both a systematic review and a clinical trial of a promising Chinese herbal medicine for treatment of prediabetes addressed a significant gap in the research literature.

Central to treatment with traditional Chinese herbal medicine is the identification of the pattern of disharmony. This identification of a pattern of disharmony comes from a diagnostic framework and clinical reasoning that involves the careful assessment of all the signs and symptoms of the presenting patient. Any disease may
have numerous patterns of disharmony. To use TCM diagnosis in RCTs requires confidence that the diagnoses are reliable and consistent across TCM practitioners. This part of my research contributes to the development of a valid and reliable instrument that will enable TCM diagnosis to be incorporated into clinical trials of traditional Chinese medical therapies.

1.4 Thesis outline

Chapter Two defines prediabetes and other relevant terminology. It describes the epidemiology of diabetes and prediabetes, and discusses current management options (lifestyle modification, and oral hypoglycaemic agents). The impact on quality of life and the cost of diabetes and prediabetes are considered.

Chapter Three examines Traditional Chinese Medicine theory in the context of prediabetes, its pathogenesis and diagnostic criteria. In traditional Chinese medicine (TCM), treatment of disease is carried out according to the identification of a pattern of disharmony. A review was conducted of randomised controlled trials to identify the main patterns of disharmony in people with prediabetes and the main TCM treatment principles being utilised. Commonly used treatment principles and herbs were also reviewed.

Chapter Four is a systematic review utilising the Cochrane methodology of randomised controlled trials of Chinese herbal medicines used in the treatment of people with prediabetes.

Chapter Five provides details of animal and human studies of Chinese herbs in use for the treatment of impaired glucose tolerance and diabetes. The ingredients used in the clinical trial formula, Jiangtang Xiaozhi are also reviewed. The traditional uses, chemical constituents and available toxicity studies are provided. This provides the scientific background and rationale for the clinical trial.

Chapter Six describes the aims, objectives and research methodology of the randomised controlled clinical trial. Details of the trial are documented in accordance with the CONSORT statement (Altman, Schulz et al. 2001).
Chapter Seven reports the primary and secondary outcome results of the randomised controlled trial of Jiangtang Xiaozhi in people with prediabetes and mild diabetes.

Chapter Eight discusses the principal findings of the trial, external validity, the strengths and limitations of the trial.

Chapter Nine assesses the inter-rater reliability of Chinese medicine diagnosis using a structured assessment instrument; and identifies TCM patterns for prediabetes along with their biochemical markers that predominate in people in the West.
Chapter 1: Overview and chapter outline
This chapter explains important definitions and criteria for diagnosis and testing prediabetes, including discussion of how this has evolved in recent decades. The epidemiology, pathophysiology and aetiology of prediabetes are then explored, together with identification of controversies and uncertainties. The largest part of the chapter describes management options for diabetes and prediabetes which include lifestyle modifications, and anti-hypoglycaemic agents. Select herbs and herbal medicines as treatment options are explored in later chapters. The chapter closes with discussion of the cost effectiveness of prevention, delay and treatment of prediabetes.

2.1 Definition and diagnosis

The term “diabetes” in this thesis refers to type 2 diabetes mellitus. Much of the epidemiological and research data however, does not differentiate between type 1 and type 2 diabetes. The International Diabetes Federation in their influential Diabetes Atlas acknowledges this limitation and points out that type 1 diabetes accounts for only a minority of the total burden of diabetes in a population (International Diabetes Federation, 2008). The concept of “prediabetes” is relevant only to type 2 diabetes.

Prediabetes refers to the intermediate metabolic states between normal and diabetic glucose homeostasis. While noting that population plasma glucose is a continuum, the prediabetes concept recognises that somewhere on that continuum glucose levels become sufficiently high as to be harmful. Prediabetes comprises two distinct states,
Chapter 2: Prediabetes: definitions and current management

those of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) or a combination of both. Neither IFG nor IGT are considered clinical entities in their own right. In 2002, the American Diabetes Association defined prediabetes as the condition in which blood glucose levels are elevated above the normal range but do not satisfy the diagnosis for diabetes mellitus (Twigg et al. 2007).

IGT was first introduced by the World Health Organisation (WHO) in 1979 to replace ‘pre-state' of diabetes or 'prediabetes' and other categories of hyperglycaemia that did not appear to carry a risk of microvascular complications (Unwin, Shaw, Zimmet, & Alberti, 2002). The criteria for diagnosing IGT and IFG, as revised by the WHO in 1999, are set out in Table 2-1. Australia has adopted the WHO criteria (Twigg et al. 2007). People with IGT have abnormal fasting plasma glucose and abnormal 2-h plasma glucose (2-HPG) values. People with IFG only have abnormal fasting plasma glucose not 2-HPG.

IGT is diagnosed when plasma glucose two-hours after a glucose load is in the range of 7.8-11.0 mmol/L. Although greater than normal, these concentrations are not sufficiently elevated to meet the criteria established for the diagnosis of diabetes. IGT is conceptualised as a transitional state from normoglycemia to frank diabetes.

The diagnostic lower limits for diabetes are intended to represent true thresholds, below which the there is no risk of diabetic retinopathy (World Health Organisation, 1999a). Many studies show increased risk for retinopathy above thresholds of about 11.1 mmol/L 2 hours after an OGTT (Tapp, Zimmet et al. 2006; DPP 2007; Wong, Liew et al. 2008). However, recent studies call into question the notion of an absolute threshold. The Diabetes Prevention Program observed retinopathy in 7.9 percent of subjects with IGT. That is, people whose plasma glucose two-hour post-glucose load is less than the diabetic threshold of 11.0 mmol/L but above the accepted normal levels.
Table 2-1 Diagnostic Criteria for Diabetes Mellitus, IGT and IFG (World Health Organisation, 1999)

<table>
<thead>
<tr>
<th></th>
<th>Glucose concentration, mmol/l (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma Venous</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting and/or</td>
<td>≥ 7.0 (126)</td>
</tr>
<tr>
<td>2-h post-glucose load</td>
<td>≥ 11.1 (200)</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance (prediabetes)</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting concentration (if measured) and</td>
<td>&lt; 7.0 (126)</td>
</tr>
<tr>
<td>2-h post-glucose load</td>
<td>7.8–11.0 (140–199)</td>
</tr>
<tr>
<td><strong>Impaired fasting glucose (prediabetes)</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting and</td>
<td>6.1–6.9 (110–125)</td>
</tr>
<tr>
<td>2-h (if measured)</td>
<td>&lt; 7.8 (140)</td>
</tr>
</tbody>
</table>

This thesis included people with early diabetes in the investigation of the efficacy of Jiangtang Xiaozhi in treating impaired glucose tolerance. Early or mild diabetes has varyingly been defined as people with an HbA1c below 7.5% (Wagner et al., 2006), a FPG between 5.5 mmol/L and 7.8 mmol/L and a 2-h post-load plasma glucose measurement ≥ 11.1 mmol/L (Kirkman et al., 2006); mild hyperglycaemia (glycosylated haemoglobin of 6.2–7.5%) (Mari et al., 2008).
2.2 Testing for prediabetes

The diagnostic glycaemic test was first developed in 1841 (Barr, Nathan, Meigs, & Singer, 2002). The fasting plasma glucose (FPG) test assesses the level of glucose in the blood in a fasting state. The oral glucose tolerance test (OGTT) was introduced as a research tool in the 1920s and widely adopted as a diagnostic method in the 1950s (McCance et al., 1997). The OGTT is a laboratory method to assess how the body metabolizes blood glucose - a “stress test” for the pancreas to see how it reacts to an overload of sugar.

Standards for interpreting the OGTT have been unchanged since 1979 in the U.S and WHO (Sorkin, Muller, Fleg, & Andres, 2005), whereas the standards for interpreting the FPG have changed over the years. In 1999, the diabetic threshold was reduced from an FPG of 7.8 mmol/L to 7.0 mmol/L and the criteria for impaired glucose tolerance or prediabetes likewise amended (World Health Organisation, 1999b).

A number of studies have examined the relationship of the FPG and the OGTT (DECODE 1999; Simons, Friedlander et al. 2000; Sorkin, Muller et al. 2005). Diagnosing diabetes on the basis of an FPG alone has been found to be insensitive in the detection of early type 2 diabetes in at-risk subjects (Perry, Shankar, Fineberg, McGill, & Baron, 2001). A review of current data on postprandial hyperglycaemia found that around 33% of people diagnosed with type 2 diabetes have normal FPG (Leiter et al., 2005). In a study examining the relationship of subclinical or prediabetes with mortality, Sorkin et al found a combination of FPG and 2hPG to be a better predictor of mortality risk than FPG alone (Sorkin, et al., 2005).

The upper limits for IGT and IFG are based on consensus and are intended to represent levels above which diabetic retinopathy or microvascular complications are likely (Alberti, Zimmet, & WHO, 1998). As evidence from the Diabetes Prevention Program shows there is no perfect correlation between levels of hyperglycaemia and microvascular and/or macrovascular problems (Diabetes Prevention Program Research Group, 2002). The choice of diagnostic level will continue to be problematic.
Chapter 2: Prediabetes: definitions and current management

The tests themselves are not without limitations. While both tests are initiated in a fasting state so that food intake is not a variable, time of day and stress have both been shown to alter glucose concentration as does age (Santaguida, 2005). The OGTT is inconvenient for participants. For three days prior to the test the participants must be on a diet containing approximately 150g of carbohydrate daily. The test requires participants to fast for between 8-12 hours the night prior to the test. Blood is drawn prior to the administration of a 75g glucose drink and over the next two hours. During this time participants must sit quietly. There is also a high level of reversion to normal blood glucose from IGT and IFG in some individuals. One review stated that up to 53% of dysglycemic individuals may revert to normal glycaemia within a year, without intervention (Santaguida, 2005).

With development of a test for glycated haemoglobin (HbA1c) there has been a push to drop the OGTT and instead use the HbA1c for assessing glycaemic control and diagnosing IGT and diabetes. Glycated haemoglobin is a measure of glycaemic control over the two to three months prior to testing, which is different to the snap-shot in time provided by plasma glucose tests. The merits of substituting the HbA1c have been the subject of lengthy debate. The issues include: lack of standardisation, poor correlation between HbA1c and FPG and a lack of sensitivity in detecting prediabetes.

HbA1c was first introduced as a method of monitoring (not diagnosing) diabetes in 1977. A lack of international standardization led several countries to develop their own standards. At present, clinical laboratories do not provide a measure of true HbA1c rather they provide a method-dependent indicator of HbA1c content (Collier, Ghosh, Davidson, & Kilpatrick, 2009). Standards have begun to emerge in recent years. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a highly specific reference method for HbA1c. However, the levels from the new technique are between 1.5% and 2% lower than the results relating to the influential Diabetes Control Complications Trial (DCCT) and are not interchangeable (Hoelzel, Weykamp et al. 2004; Dhatt, Agarwal et al. 2005). There are concerns that using the new levels may generate confusion among patients and clinicians (Kilpatrick, 2008).
Chapter 2: Prediabetes: definitions and current management

In 2003 the American Diabetes Association reported on their review of diagnostic tests for diabetes together with their new diagnostic criteria, and concluded the HbA1C “remains a valuable tool for monitoring glycaemia, and is not currently recommended for the diagnosis of diabetes” (2003b, p. S15). Lack of standardisation of laboratory methods was their primary concern. A more recent review, reflecting cross-sectional studies where laboratory methods have become increasingly standardised, found the HbA1c accurate to detect diabetes with a cut off of 6.1%, sensitivity ranging from 78% to 81% and specificity from 79% to 84% when compared with using the reference standard of FPG and 2hr-OGTT. However they found that neither HbA1c nor FPG were effective in detecting IGT, and therefore an OGTT is still required for the detection of IGT (Bennett, 2007).

Improved sensitivity and standardisation in assessing HbA1c culminated in July 2009 when an International Expert Committee, comprising members of the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation, recommended that the HbA1c level of 6.5% be set as the diagnosis for diabetes (International Expert Committee on Diabetes, 2009). The Committee recommended that the categorical clinical states of IGT, IFG and prediabetes be phased out and replaced by HbA1c measurements as glucose measurements. Those with HbA1c levels below the diagnostic threshold but above ≥6% should receive demonstrably effective preventive interventions. Importantly for the present research, adopting HbA1c as a standard clinical reference is complemented by its adoption in epidemiological, clinical trials and other research. The generalisability of findings from research to practice will be improved as a consequence of this consistency.

2.3 Epidemiology

In 2010, an estimated 344 million adults worldwide have impaired glucose tolerance (see Table 2-2). This is equivalent to 7.9% of the age group 20 to 79 years and is projected to rise to 472 million, or 8.4% by 2030 (International Diabetes Federation,
2008). The International Diabetes Federation dataset does not include figures for impaired fasting glucose (IFG).

Table 2-2 Global Burden: Prevalence and Projections, 2010 and 2030

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total world population (billions)</td>
<td>7.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Adult population (20-79 years, billions)</td>
<td>4.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Diabetes and IGT (20-79 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global prevalence (%)</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Comparative prevalence (%)</td>
<td>6.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Number of people with diabetes (millions)</td>
<td>285</td>
<td>439</td>
</tr>
<tr>
<td>IGT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global prevalence (%)</td>
<td>7.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Comparative prevalence (%)</td>
<td>7.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Number of people with IGT (millions)</td>
<td>344</td>
<td>472</td>
</tr>
</tbody>
</table>


Australia’s large scale AusDiab study is longitudinally tracking the glucose status of 11,247 adults. In its baseline report, the prevalence of IGT and IFG was found to be 16.4% (Dunstan et al., 2002). A five-year follow-up found that, each year six percent of Australians who have either IGT or IFG at the start of the year, will progress to diabetes by year end (International Diabetes Institute, 2006). The incidence of progression to diabetes is greater among those who have both IFT and IGT. In this group, 9.3% can be expected to progress to diabetes per year (Engberg 2009). The predicted cumulative 5 to
6 year incidence of development of type 2 diabetes for people with either IGT or IFG is 20% to 34%; those with both IGT and IFG have a progression rate of 38% to 65% (American Diabetes Association, 2003a).

While the presence of both IGT and IFG is strongly predictive of progression to diabetes, isolated-IGT is independently and linearly associated with an increased risk of cardiovascular disease (Perry & Baron, 1999; Tominaga et al., 1999). The degree of additional risk for cardiovascular disease that is imposed by isolated-IGT compared to normoglycemic individuals is a matter of some contention. Some studies report significantly increased relative risk ranging from 3.51 to 8.63 (for example, de Vegt et al., 2001; Gerstein et al., 2007; Li, Tsai, & Chou, 2003). Others such as the meta-analysis of 18 published prospective observational studies conducted by Ford, Zhao and Li (2010) are more conservative. Ford, Zhao and Li (2010) concluded that isolated-IGT is associated with only a modest increase in risk for cardiovascular disease in the order of 0.97 to 1.30. While the degree of additional relative risk may only be modest it is nevertheless significant given the sizeable and growing percentage of adults who have prediabetes. A small increase in the mortality or harm rate from cardiovascular disease which may be causally associated with prediabetes still translates into substantial numbers of people.

Not all those with IGT will develop diabetes and about one third will return to normal IGT and one third will continue to have IGT. Patients classified as IFG or IGT may revert to apparently normal glucose metabolism and a proportion of patients do. Several studies have reported rates of reversion to normal glucose tolerance of from one third to one half for subjects identified with IGT (Li, Tsai, & Chou, 2005; Saad, Knowler, Pettitt, Nelson, & Bennett, 1988; Santaguida P, 2005). Rates of reversion to normal appeared independent of the duration of follow-up, with a range of 2 months to 10 years (Forrest, Jackson, & Yudkin, 1988; Ko et al., 1998; Saad, et al., 1988).

Some studies distinguish between transient and persistent IGT. Persistent IGT is defined as someone who has been diagnosed with IGT on at least two occasions (Li, et al., 2005). The progression of transient prediabetes (trIGT) to diabetes is unclear. A study
of Pima American Indians with trIGT were found to be at high risk for developing type 2 diabetes (Saad, et al., 1988), while a 4-year prospective study in South African Indians, concluded that transient IGT was not associated with a risk of progression to type 2 diabetes (Motala, Omar, & Gouws, 1997). Both of these studies found that people with persistent IGT were more at risk of progressing to diabetes.

IGT and/or IFG are frequently present for many years until health checks reveal raised plasma glucose levels or diabetic symptoms develop. By the time a diagnosis of type 2 diabetes is made around half of all subjects have diabetes related tissue damage (Azad et al., 1999). After diagnosis, management of type 2 diabetes is not easy as near normal glucose levels are difficult to achieve. Normal glucose levels can rarely be maintained and long-term complications pose particular problems.

The clinical consequences of not treating prediabetes are apparent from observational studies of relevant population cohorts and intervention studies. The DECODE study of 22,000 people found that as 2hr post load blood glucose increased from 5.3 to 11.1 mmol/L so too did the hazard ratio for all-cause mortality (DECODE study group, 1999). In the IGT placebo arm of the Diabetes Prevention Program there was an increase in clinical cardiovascular events by approximately 50% (Skyler, 2004). A meta-analysis of 38 prospective studies confirmed that hyperglycaemia in the non-diabetic range was associated with increased risk of both fatal and non-fatal cardiovascular disease. Cardiovascular events seemed to increase linearly even in the range below concentrations diagnostic of diabetes, without a clear threshold (Levitan, 2005).

Retinopathy, characteristic of diabetes, is present in persons with elevated fasting glucose and impaired glucose tolerance and no known history of diabetes. The Diabetes Prevention Program, observed diabetic retinopathy in 7.9% of patients with IGT compared to 12.6% in patients with IGT that progressed to diabetes during the course of the study (Skyler, 2004). Preliminary findings of participants in the ‘Hoorn study’, a longitudinal cohort-study, suggests that the cognitive impairment associated with type 2 diabetes already develops in prediabetic stages and progresses gradually thereafter (Van den Berg, Biessels, Nijpels, & Dekker, 2009).
These findings suggest that adults with untreated IGT and IFG experience a progression to diabetes together with cognitive, microvascular and macrovascular harm (Garber et al., 2008).

### 2.4 Pathophysiology of prediabetes

The progression from normal glucose regulation through the prediabetic states to overt type 2 diabetes and the consequences for symptomology, microvascular and macrovascular complications is outlined in Figure 2-1. The pathophysiology of this progression is however, not completely understood. It involves rising blood glucose, decreasing sensitivity of the body to insulin (insulin resistance) and beta-cell dysfunction. Beyond these basics, the underlying pathophysiology of IGT is the subject of considerable research and debate (Ahren & Pacini, 1997).

*Figure 2-1 Preclinical and clinical stages of type 2 diabetes. (Adapted from Norberg, 2006) Notes. MI is myocardial infarction; ERD is end stage renal disease*
Danish researchers Faerch, Borch-Johnsen, Holst and Vaag stimulated the debate in their 2009 review wherein they proposed quite distinct pathophysiological processes for IFG and IGT. The implication of their conclusion is that impaired glucose regulation may be a binary state rather than a continuum as is the more dominant paradigm at present. Table 2-3 summarises the defects Faerch and colleagues (2009) found associated with each condition.

Table 2-3 Key defects associated with isolated Impaired Fasting Glucose (IFG) and isolated Impaired Glucose Tolerance (IGT)

<table>
<thead>
<tr>
<th>IFG</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced hepatic insulin sensitivity</td>
<td>reduced peripheral insulin sensitivity</td>
</tr>
<tr>
<td>near normal hepatic insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>stationary beta cell dysfunction and/or</td>
<td>progressive loss of beta cell function</td>
</tr>
<tr>
<td>chronic low beta cell mass</td>
<td></td>
</tr>
<tr>
<td>altered glucagon-like peptide-1 secretion</td>
<td>reduced secretion of glucose-dependent</td>
</tr>
<tr>
<td></td>
<td>insulinoactive polypeptide</td>
</tr>
<tr>
<td>inappropriately elevated glucagon secretion</td>
<td>inappropriately elevated glucagon secretion</td>
</tr>
</tbody>
</table>

When both IFG and IGT are present, Faerch and colleagues (2009) found severe defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of beta cell function. Probability of progression to diabetes is higher when IGT and IFG coexist (Unwin, et al., 2002). Understanding the role of insulin in glucose metabolism may be helpful.

Insulin secretion and insulin sensitivity display a hyperbolic relation with compensatory increased insulin secretion when insulin sensitivity is reduced (Best JD, 1996). When a
normal concentration of insulin produces less than normal response the person is said to be insulin resistant (Wallace & Matthews, 2002). Causal processes are unclear. Studies have shown that there is an inadequate compensation in insulin secretion when insulin sensitivity is reduced in IGT (Taniguchi et al., 1994). Another study concluded that beta-cell dysfunction rather than insulin resistance determines the progression from IGT to diabetes in a high-risk Caucasian population (Nijpels, Popp-Snijders, Kostense, Bouter, & Heine, 1996). The degree to which insulin resistance in muscle and liver and beta-cell failure lead to hyperglycaemia are debated but their role in the pathogenesis of diabetes are now fairly well understood and documented (Tonelli, Kishore, Lee, & Hawkins, 2005).

Decreased insulin secretion, insulin resistance in the liver and beta cell dysfunction are part of a range of defects that contribute to progression as shown in Figure 2-2. DeFronzo (2009) adds to this ‘triumvirate’, the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), [alpha]-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance).

We are familiar with the role of the pancreatic beta cell in the pathogenesis of diabetes but the glucagon production of the pancreatic alpha cell also seems to plays a role. Elevated fasting plasma glucagon levels have been found in contribute to hepatic glucose production effectiveness (Færch, Borch-Johnsen, Holst, & Vaag, 2009).

The role of the fat cell occurs with elevated free fatty acid, or increased ‘lipolysis’ as it is known, decreases insulin secretion (Tonelli, et al., 2005).

The gut is also involved with abnormalities in the incretin axis, specifically the beta-cell resistance to the stimulatory effect of inhibitory polypeptide (GIP) on insulin secretion (DeFronzo, 2009).
The brain also has a role to play. Insulin is an appetite suppressant. Yet in obese people there is elevated insulin. Some studies propose that the brain also becomes resistant to the action of insulin (DeFronzo, 2009; Obici, Feng, Karkanias, Baskin, & Rossetti, 2002).

The stage of progression of glucose intolerance during which these metabolic abnormalities develop is still a matter of debate (Schianca, Rossi, Sainaghi, Maduli, & Bartoli, 2003). Importantly for preventative and early intervention efforts, the UK Prospective Diabetes Study (UKPDS) suggest that impaired β-cell function begins 10-12 years before a diagnosis of diabetes (Færch, et al., 2009). By the time diabetes has become manifest, it is may be too late in many cases to reverse the glucotoxic effects of hyperglycaemia on beta cell function. Individuals with IGT are maximally or near-maximally insulin resistant, beta-cell function is reduced in the vicinity of 80%, and they have an approximate 10% incidence of diabetic retinopathy (DeFronzo, 2009). DeFronzo (2009) concludes that “By both pathophysiological and clinical standpoints,
these pre-diabetic individuals with IGT should be considered to have type 2 diabetes”. Acting on the prediabetic state is therefore important if the onset of diabetes is to be prevented or at least delayed.

Theoretically, type 2 diabetes could be prevented or delayed by three types of interventions to address IGT and/or IFG:

1) Interventions that limit fat accumulation in the body (less obesity = less insulin resistance);

2) Interventions that uncouple obesity from insulin resistance (less insulin resistance = less beta cell failure);

3) Interventions that directly preserve beta cell mass and/or function, despite the high secretory demands imposed by insulin resistance (better beta cell function = less diabetes) (American Diabetes Association, 2003a).

The pathophysiology of prediabetes described above points to a difference between the mechanisms that prevent diabetes compared to the mechanisms that delay its onset. True prevention of diabetes requires that the natural progressive increase in blood glucose is altered. Agents that lower blood glucose without altering insulin sensitivity or preserving beta-cell function delay diabetes rather than prevent it (Anderson, 2005).

2.5 Aetiology

Since 1980, the World Health Organisation and the International Diabetes Federation and, more recently, the United Nations, have spearheaded a concerted international effort to survey diabetes and improve understanding of its complications, mortality and risk factors. This epidemiological knowledge has had a profound impact on diabetes research, care and prevention (Zimmet, 1999). However, the causal agents of diabetes are still unclear (Van Tilburg et al., 2003).
At present, the prevailing and widely accepted aetiological theory is that diabetes and its precursor hyperglycaemic conditions result from a combination of genetic susceptibility and external risk factors (DeFronzo & Ferrannini, 1991; Grant, Moore, & Florez, 2009). The external factors known to be associated with prediabetes are identical to those associated with diabetes (Edelstein et al., 1997) and include:

- Smoking;
- Obesity, in particular central adiposity;
- Saturated fat intake;
- Sedentary lifestyle;
- Increasing age;
- Hypertension;
- Blood lipids;
- Low birthweight and short adult stature;
- Ethnicity.

In a review of six prospective studies involving a total of 2,389 people with IGT, Edelstein and colleagues, (1997) found that the most consistent predictor of progression from IGT to diabetes was fasting and post-load glucose concentrations and BMI at baseline. Family history of diabetes was clearly linked with diabetes but not consistently predictive of progression from IGT to diabetes. Similarly, gender and age were not consistent predictors in the six analysed data sets. The relationship between age and the progression to NIDDM was inconsistent among the study populations. A more recent review of the evidence found that IGT is predominantly related to physical inactivity, unhealthy diet and abnormalities associated with short adult stature (Færch, et al., 2009).
Exactly how these external risk factors interact with genes has been the subject of genome-wide association studies that have, in the view of one commentator “quickly turned from a trickle to a flood” (Rich, Norris, & Rotter, 2008). Nearly two dozen genes have been identified as associated with diabetes and include variants that appear to modify responses to treatment interventions (Grant, Moore et al., 2009).

Genome research aside, there are now several well developed models for detecting prediabetes and predicting diabetes (Chen & et al, 2010; Griffin, Little, Hales, Kinmonth, & Wareham, 2000; Heikes, 2008). These ‘risk calculators’ use a combination of demographic, anthropometric and lifestyle risk factors to identify people who may benefit from intervention. Recently, there have been moves to incorporate biomarkers into predicting risk (Meigs, 2009; Schmidt et al., 1999). These models incorporate a range of biological phenomena that appear in the pathophysiology of diabetes including abnormal adipocyte signalling, inflammation identified through markers such as C-reactive protein, and interleukin-6, endothelial dysfunction, excessive iron, and variation in the Circadian system (Meigs, 2009). A model using six of these biomarkers (adiponectin, C-reactive protein, ferritin, interleukin-2 receptor A, glucose, and insulin) was tested and performed better than single risk indicators in providing a quantitative estimate of the 5-year risk of developing type 2 diabetes (Kolberg, 2009).

2.6 Current management

Available therapies for the management of prediabetes are:

- Intensive lifestyle modifications
- Pharmaceutical interventions
- Alternative medicine (e.g. herbal medicine, vitamin and mineral supplements)
Diabetes prevention trials have been underway to investigate the efficacy of lifestyle modifications and pharmacological interventions in delaying the progression from IGT to diabetes. Most of these studies have run for 2-6 yrs. A number of rigorous herbal medicine trials in people with IGT have also been undertaken. The main mechanisms of action underpinning the pharmaceutical and herbal interventions to delaying diabetes or the onset of its complications are:

1) Stimulate pancreatic islet beta cell release of insulin

2) Inhibit hormones that increase blood glucose

3) Increase the number, affinity, or sensitivity of the insulin receptor to insulin

4) Decrease the release of glycogen

5) Enhance the use of free radicals, resist lipid peroxidation, and correct the lipid and protein metabolic disorder; and

7) improve the microcirculation in the body (Jung 2006; DeFronzo 2009).

2.6.1 Intensive lifestyle modifications

Lifestyle interventions are undoubtedly the most effective way to reduce progression to diabetes while directly addressing the risk factors of poor nutrition, obesity and lack of physical activity. There have been a number of good quality trials conducted in the last 20 years consistently strengthening lifestyle intervention as the first tool of choice in addressing prediabetes.

The Da Qing IGT and Diabetes Study was the first randomized controlled trial, commencing in 1986, to examine the effect of intensive lifestyle intervention on the development of type 2 diabetes (Pan 1997). In this trial there was a significant decrease in the incidence of diabetes over a 6-year period in the intervention groups. These
results were repeated in a Finnish study (Lindstrom & Tuomilehto, 2003) and the Diabetes Prevention Program (DPP 2002).

In the Finnish study 522 middle-aged, obese subjects with IGT were randomized to receive either brief diet and exercise counselling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects.

In the Diabetes Prevention Program, the 3,234 enrolled subjects were slightly younger (mean age 51 years) and more obese (mean BMI 34 kg/m²) but had nearly identical glucose intolerance compared with subjects in the Finnish study (DPP Research Group, 2002). Subjects were randomized intensive lifestyle intervention, metformin, or placebo. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years (range 1.8–46 years), a 58% relative reduction in the progression to diabetes was observed in the lifestyle group (absolute incidence 4.8%), and a 31% relative reduction in the progression of diabetes was observed in the metformin group (absolute incidence 7.8) compared with control subjects (absolute incidence 11.0). The intensive lifestyle intervention, but less so with metformin, improved the cardiovascular risk and glucose tolerance profile simultaneously (Goldberg et al., 2009).

Lifestyle interventions have fewer and less serious side effects than pharmaceutical interventions but multiple external barriers, limited understanding of diabetes risk and prevention by both providers and the public combined with limited behaviour change skills impede the implementation of these types of initiatives on a large scale (Simmons, Unwin, & Griffin). A clinical trial which randomised participants to a personalised exercise program or no treatment concluded that “Long-term behavioural intervention programs, providing individualized exercise prescription, are not sufficient to change sedentary behaviour and/or improve glycaemic control in insulin treated, type 2 diabetes patients” (Willeke et al., 2010).
2.6.2 Pharmaceutical interventions

Where individuals are not able to undertake the intensive lifestyle interventions prescribed in these trials, pharmaceutical interventions may be necessary. The main class of drugs used are outlined in Table 2-4 along with their mode of action and known side-effects. The degree of metabolic derangement dictates the treatment options. The most commonly prescribed drugs are sulphonylureas and the biguanide, metformin. When the major metabolic defect is (a) impaired pancreatic β-cell insulin production, then sulphonylureas, such as glipizide or glyburide might be used, or (b) increased hepatic glucose production, then metformin might be used (DeFronzo, 1979).

Table 2-4 Main pharmaceutical interventions for prediabetes and diabetes

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mode of action</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Prevents degradation of complex carbohydrates into glucose,</td>
<td>Gastrointestinal (flatulence, diarrhoea, abdominal bloating and cramping)</td>
</tr>
<tr>
<td>(eg acarbose)</td>
<td>carbohydrates remain in the intestine</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Biguanide (eg metformin)</td>
<td>Improves glycaemic control by sensitising the liver and the periphery to the</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>effects of insulin.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones (eg</td>
<td>Activating PPAR(γ) which decreases insulin resistance is decreased, modifies</td>
<td>Rosiglitazone associated with a sevenfold increase in heart failure,</td>
</tr>
<tr>
<td>troglitazone, rosiglitazone)</td>
<td>adipocyte differentiation is modified, levels of certain interleukins (e.g. IL-6)</td>
<td>although the number of such cases was small; Troglitazone withdrawn from the</td>
</tr>
<tr>
<td></td>
<td>fall and adiponectin levels rise</td>
<td>market due to an increase in hepatitis and potential liver failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas (eg tolbutamide)</td>
<td>Increasing insulin release from the beta cells in the pancreas, also</td>
<td>Hypoglycaemia, weight gain, gastrointestinal, headache</td>
</tr>
<tr>
<td></td>
<td>sensitise β-cells to glucose</td>
<td></td>
</tr>
</tbody>
</table>

Notes: PPAR - peroxisome proliferator-activated receptors
Metformin is recommended as first-line treatment in diabetes. Metformin improves glycaemic control by sensitising the liver and the periphery to the effects of insulin (Bailey et al., 2005; Pavo et al., 2003). The Diabetes Prevention Program (DPP, 2002) found the drug metformin reduced the incidence of diabetes by 31% compared to placebo. A meta-analysis of metformin showed that if it is used for up to 3 years, the likelihood that prediabetes will progress to diabetes decreases (Lilly 2009). Whilst still the best drug currently on the market metformin does have some limitations. The efficacy of metformin has been found to be variable among sub-groups, being less effective in those over-60s, those with a BMI <35, and those with FPG below 6.1 mmol/l. Gastrointestinal symptoms including diarrhoea, flatulence, nausea and vomiting occurred in 77 of every 100 persons on metformin in the study (Diabetes Prevention Program Research Group, 2002).

The class of drugs called alpha-glucosidase inhibitors (AGIs) are sometimes used where blood glucose levels are not being stabilized through diet and exercise, or where metformin is not suitable or tolerated. The main alpha-glucosidase inhibitor currently used is acarbose. Acarbose prevents the degradation of complex carbohydrates into glucose; the carbohydrates will remain in the intestine. In the colon, bacteria will digest the complex carbohydrates, thereby causing gastrointestinal side effects such as flatulence (78% of people) and diarrhoea (14% of people). A systematic review of acarbose in people with IGT found that the use of acarbose reduces the incidence of type 2 diabetes, but the effects on glycaemic control are limited (Van de Laar, 2004). A 3 year study found that treatment with acarbose was associated with beneficial effects on 2-h plasma glucose levels but not with improvement of beta-cell function (Nijpels et al., 2008). Acarbose has also been associated with a 49% risk reduction in CVD (Chiasson et al., 2003).

In the STOP-NIDDM study, protection provided by acarbose from progression along the diabetes continuum was lost shortly after discontinuation of the drug therapy. After a 3 month wash out 15% of acarbose-treated patients developed diabetes compared with
10.5% of placebo-treated patients (Chiasson, et al., 2003). Side effects include abdominal bloating and cramping (30% withdrew from the STOP-NIDDM study).

In a trial of another AGI, voglibose, 750 (85%) of 881 participants in the placebo group reported an adverse event. Serious adverse events (all one each) in the voglibose group were cholecystitis, colonic polyp, rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid haemorrhage, and in the placebo group were cerebral infarction and cholecystitis. The trial was terminated early (Kawamori et al., 2009).

Thiazolidinediones (TZDs) are more potent insulin sensitisers than metformin, which work not just at the liver but in the muscle and adipose tissue also hold promise to improve beta cell function (DeFronzo, 2010; Wallace, Levy, & Matthews, 2004). Currently available TZDs are pioglitazone and rosiglitazone; troglitazone was withdrawn from the market because of the significant increased risk of liver damage and in some cases fatal hepatic toxicity.

Pioglitazone has been shown to enhance insulin sensitivity in the liver and the periphery (DeFronzo, 1979; Pavo, et al., 2003; Wallace, 2004). Five studies of TZDs have shown that the progression to diabetes from IGT has been lowered to between 50% and 80% (Buchanan et al., 2002; DeFronzo, 2010; The DREAM Trial Investigators, 2006). Treatment with thiazolidinediones decreases haemoglobin A1C (HbA1c) over 6 to 12 months and sustains these lower levels over several years. Rosiglitazone was recently found to have significant improvements in measures of beta-cell function over time in pre-diabetic subjects (Hanley, 2010). However, the side effects of TZDs can be considerable and include congestive heart failure (Prato, Bianchi, Miccoli, & Penno, 2007), weight gain and oedema (Kimmel & Inzucchi, 2005), and most recently long-term thiazolidinedione use doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes (DTB, 2008; Meier et al., 2008).

The fourth major class of drugs are sulfonylureas. Many studies have shown that, following an initial decline in HbA1c, sulfonylureas were associated with a progressive
decline in beta-cell function with an accompanying loss of glycaemic control (DeFronzo, 2010). Sulfonylureas cause an initial decrease in HbA1c over the initial 6 to 12 months of therapy, but thereafter there is a progressive increase in HbA1c due to the progressive loss of beta-cell function. Weight gain and hypoglycaemia are common side effects of sulfonylureas (Al-Ozairi, 2007; Nauck, Meininger, Sheng, Terranella, & Stein, 2007).

In summary, none of the drugs are able to exert a protective effect on the beta-cell. Diabetes is progressive and eventually these drugs fail to maintain normal glycaemic control. This is a major concern, since progressive beta-cell failure is the primary pathogenic abnormality responsible for the development of overt diabetes and the progressive rise in HbA1c (DeFronzo, 2010). Further, about one third of type 2 diabetic patients are treated with anti-hyperglycaemic agents to stimulate insulin secretion. These drugs however risk inducing hypoglycaemia and, over time, lose their efficacy. A Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (Kahn et al., 2006).

2.7 Impact on quality of life & economic cost

The Australian Institute of Health and Welfare (AIHW, 2005), ranked diabetes fifteenth out of 200 diseases in terms of total recurrent health expenditure.

Costs of diabetes care can be considered in context of three issues (Al-Ozairi, 2007). Firstly, the real costs of diabetes come from failures of preventative medicine. When complications develop, the disease progresses, and cost increases. Secondly, the increasing prevalence of diabetes, driven by overeating and underactivity, together with increased life expectancy and the increase in people developing diabetes at a younger age (International Diabetes Federation, 2008). The third issue is the increased costs of new technologies, notably, medications and methods of administering treatment - insulin.
pumps; inhaled insulin can easily double or triple the total costs (not just the drug costs) of diabetes care.

The dependency on pharmacological medication to maintain blood glucose control combined with the increasing numbers of diagnosed people with diabetes will continue to see health care costs rise. The cost of metformin is 3- to 5-fold higher than that of the cheapest generic sulphonylureas, and 30-fold higher for thiazolidinediones (Vuksan & Sievenpiper, 2005).

DiabCost Australia, the first large scale national study into the burden of type 2 diabetes, estimated that the cost in Australia is an estimated $3 billion a year, with average costs per person at $5,360 plus $5,540 in benefits, totalling $10,900 (Colagiuri, 2003). The cost per person increases with the onset of complications: $4,020 without complications; and $9,625 with both microvascular and macrovascular complications (2.8 times higher), with the average health expenditure per known case of diabetes in 2000-01 at $1,469.

In the USA the total annual economic cost of diabetes in 2007 was estimated to be $174 billion (American Diabetes Association, 2008). One out of every five health care dollars is spent caring for someone with diagnosed diabetes, while one in ten health care dollars is attributed to diabetes.

A gradual decrease in quality of life across categories of glucose tolerance status has been found in recent research. Those with IGT reported difficulty performing physical tasks (walking, climbing stairs, and bending), compared to those with normal glucose tolerance (Tapp et al., 2006). Whereas the microvascular complications, heart failure, depression and a high number of medications taken by people with diabetes were each strong independent correlates of decreased quality of life (Wexler et al., 2006).

2.8 Conclusion

With regard to prescribing a pharmacological intervention to delay or prevent the onset of diabetes, this will increase a patient’s drug exposure and may increase the likelihood
of adverse effects (American Diabetes Association, 2003a). Of all drugs used in prevention trials, glitazones have been the only ones matching results obtained with lifestyle modification (Prato, et al., 2007). However the possible side effects noted above do not translate into a viable intervention for people with prediabetes that are asymptomatic and may or may not go on to develop diabetes. Further, individuals with IGT may differ with regard to the underlying mechanisms of glycaemic dysregulation, and treatment that is inaccurately targeted may pose an unnecessary risk with reduced likelihood of benefit (Prato, et al., 2007).

Most anti-hyperglycaemic drugs with the exception of metformin increased body weight by 1 to 5 kg. Sulfonylureas were associated with greater risk for hypoglycaemia, thiazolidinediones with greater risk for heart failure, and metformin with greater risk for gastrointestinal problems compared with other oral agents (Bolen et al., 2007).

Lifestyle modification is the ideal method of delaying or preventing diabetes as it also reduces cardiovascular risk profile. However, not all individuals will be able to undertake the intensive lifestyle interventions prescribed in these trials. Long term adherence to the interventions described is problematic (Padwal, Majumdar et al. 2005; Lindahl, Nilsson et al. 2009). Patient adherence to medical recommendations is a problem that has been studied over decades. Data from medication adherence studies indicate that between 20 and 60% of patients fail to follow prescriptions. Since preventive medications do not provide the positive reinforcement of symptom control or relief, compared with effective therapeutic medications, adherence may be even more of a challenge (Walker et al., 2006).

In view of the high proportion of subjects with IGT that go on to develop overt diabetes, and cardiovascular disease, there is considerable interest in exploring therapeutic approaches that will reduce the risk of diabetes in subjects with IGT with minimal or no adverse effects where lifestyle modifications have failed, and pharmaceutical interventions are not warranted or suitable.
CHAPTER 3

Traditional Chinese Medicine
Theory, Treatment and Herbal Medicine for Prediabetes

This chapter examines prediabetes, its pathogenesis and diagnostic criteria from the perspective of Traditional Chinese Medicine (TCM) theory.

A review of the main TCM patterns of disharmony found in the contemporary literature, their prevalence within the population, and links to biochemical markers are presented. The predominant patterns of disharmony are then considered in conjunction with the treatment principles and herbs being used in TCM RCTs for people with IGT. The findings and implications for research are then discussed. This chapter informs the inter-rater reliability study of Chinese medicine diagnosis which is presented in Chapter 9.

3.1 Rationale

Traditional Chinese Medicine (TCM) is a system of healing that originated thousands of years ago. It has evolved into a well-developed, coherent system of medicine that uses several modalities to treat and prevent illness. It focuses on the whole person, diagnosing through careful examination and identifying patterns of disharmony. The aim of treatment is to harmonise imbalances and enhance self-healing. Treatment is adjusted at each visit to meet the dynamic nature of the disease. It differs from Western medicine diagnosis which focuses on the ‘macromolecular’ level (Bensoussan, 1996).

At the heart of TCM, is the selection of treatment for a disease guided specifically by the full range of presenting symptoms and the individualisation of a treatment strategy based on those symptoms. Of the many diagnostic tools used in TCM, a commonly used paradigm is the identification of patterns of disharmony (Bian
Chapter 3 Traditional Chinese Medicine Theory, Treatment and Herbal Medicine for Prediabetes

Zheng) (Maciocia, 1989). This diagnostic framework consists of looking, hearing, smelling, asking and feeling in such a way that extends well beyond what is considered typical in Western medicine. For example, asking may reveal the absence of thirst thereby indicating a cold or damp condition; asking, looking and feeling may expose problems with the sinews and tendons and thereby points to a disharmony with the Liver\(^1\). Looking at face areas and colours reflect the health of the inner Organs and the eyes reveal the health of *shen* or the spirit (Maciocia, 1989). Feeling by palpation along the meridians may also help to guide clinical reasoning and diagnosis. These clinical signs and symptoms are drawn together to identify a pattern of imbalance or disharmony. Any disease may have numerous patterns of disharmony, depending on the individual’s manifestation of the disease.

For example, a patient with prediabetes may present with symptoms of obesity/overweight, heaviness of the limbs, loose stools, abdominal distension, fatigue, vaginal discharge (or recurrent thrush), a pale tongue, possibly teethmarks and a distinct coat on the tongue. The pulse may be considered “soggy” (Flaws B, 2002). These symptoms would be referred to in TCM as ‘dampness’ and ‘heat’ damaging the Spleen. Damp stagnation is seen as pathological body fluids clogging the organs and channels, similar to peripheral tissue resistance, due to obesity. The main treatment principle is to tonify the Spleen qi and dry damp and clear heat.

Regulating blood, which has often been used in modern times for its ability to penetrate congested tissues, may also be valuable in overcoming tissue resistance.

Diabetes appeared in one of the earliest texts of Chinese herbal medicine, the *Yellow Emperor’s Inner Classic* (the “Neijing”) compiled roughly 2000 years ago. The Chinese called diabetes – *xiao ke* meaning ‘thirst-emaciation’. In TCM, prediabetes or IGT has not typically been treated as a distinct disease entity. Traditionally diabetes is divided into three types of *xiao ke* depending on the predominance of three main symptoms: thirst, hunger and excessive urination, related to the Lung, Spleen and Kidney respectively (Choate, 1999; Flaws, 2002).

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\(^1\) Bodily organs and fluids in TCM do not correspond directly to the Western medicine equivalent. When an organ or fluid is referred in the TCM sense it is capitalised.
Upper *xiao ke* refers to the lack of body fluids due to Lung heat which manifests mainly as excess thirst along with other symptoms of yin with additional symptoms such as dry mouth, dry throat, and a dry cough. Middle *xiao ke* refers to the injury of yin by Stomach dryness which manifests as excessive hunger which may be accompanied by bad breath, burning in the epigastric region and restlessness. Lower *xiao ke* involves the exhaustion of Kidney essence (jing) and Kidney yin with the main symptom of excessive urination accompanied by symptoms such as lower back pain, weakness at the knees, and malar flush. These patterns rarely present so neatly and often overlap. Treatment is individualised to meet these variations.

These three ‘classical’ patterns have been expanded by recent authors to include early stage diabetes and impaired glucose tolerance (Flaws, 2002; Maclean, 2010; Wei-bin, 2008). In recent years, TCM endocrinologists have begun to group TCM symptoms with the biochemical markers of impaired glucose tolerance. Treating people with IGT may be considered as part of TCM theory called *zhi wei bing* – treating the disease before its onset and/or preventing the further development of the disease.

In TCM, prediabetes is typically considered to be caused by congenital deficiency, inappropriate diet, overwork and insufficient rest (Lu, 1999). It is reported that most patients are overweight with an occasional sweet taste in the mouth (Lu, Gao, & Yang, 1999). Although, in thin patients it could be due to a congenital weakness (Liu, 2008). Recent theorists in TCM have posited that prediabetes has its origins in the following dysfunctions.

1. Poor innate constitution, specifically Spleen and Kidney deficiency which leads to the impairment of the transportation and transformation of fluids and yin deficiency (Li, 2006; Liu, 2008).

2. Inappropriate diet, excessive consumption of sweet, rich and greasy foods may generate phlegm and damp which impairs the Spleen and Stomach, damages the Spleen qi, and damages the jing. This damage leads to the generation of heat and damp which consumes yin and fluid (Flaws, 2002; Maclean, 2010; Wu, 2004).
3. Disorders of the emotions (Wang, 1999; Lian, 2004; Sun, 2005): In TCM when Liver qi stagnates it disturbs the proper ascending and descending of qi, leading to heat and consumption of both Lung and Kidney yin (Li, 2006).

4. Too much work and insufficient rest can lead to Spleen deficiency which is the source of fluid and excessive sex can consume the Kidney jing (Li, 2006; Wu, 2004). In TCM organ pathology, the pancreas is not mentioned but is functionally included within the “Spleen” (Maciocia, 1989).

5. The pathophysiology of the progression from a pre-diabetic state of impaired glucose tolerance to diabetes can be seen in TCM as a progression from a deficiency of Spleen qi with an ensuing stagnation of damp, the generation of heat, consumption of fluids and the emergence of yin and qi deficiency as the dominant pattern. As the patient progresses through this continuum, different medicinals become appropriate.

A Chinese medicine practitioner tends to the individual, not the disease. In clinic, there is no absolutely definitive way to treat a disease or a pattern of disharmony. It has been argued that because in traditional Chinese medicine treatment is individualised, scientific methods are inappropriate for research. However, as the pioneer of RCTs and advocate of the search for causation, Sir Austin Bradford Hill noted 40 years ago: “If each patient is unique, how can a basis for treatment be found in the past observations of other patients?” The number of patterns of disharmony is not infinite, and probably only a few hundred are common. It is arguably legitimate that patients with the same pattern of disharmony be prescribed similar treatments.

A final qualifier though concerns the effect of the context within which the TCM practitioners is working. Treatment protocols are adapted to the contexts of specific local biologies so that protocols for people in Australia may look different to those in China (Volker, 2007). Notwithstanding these cultural differences, patterns of disharmony guide practitioners in their clinical reasoning and treatment decisions and should form a meaningful basis for research paradigms.
Chapter 3 Traditional Chinese Medicine Theory, Treatment and Herbal Medicine for Prediabetes

3.2 Method

The objective of the literature review was to identify the main TCM patterns of disharmony, their prevalence within the population, and the treatment principles being used in RCTs for people with impaired glucose tolerance. The search was conducted as part of the Systematic Review reported in Chapter Four. Sources were the same but the search terms were broadened.

3.2.1 Inclusion criteria

Clinical trials that satisfied all of the following criteria were included:

- Participants diagnosed or otherwise properly classified as having IGT or prediabetes.

- Controlled clinical trials that were reported as randomised, irrespective of blinding, publication status, or language.

- Studies that compared a Chinese herbal medicine or herb with a co-intervention, pharmaceutical or placebo were included.

- Reports with a discussion of at least one TCM pattern of disharmony or TCM principle of treatment.

Reviews:

- Reviews on the prevalence of the patterns of disharmony in people with prediabetes.

3.3 Findings of the review

3.3.1 Description of the literature

The initial search retrieved 1926 records and from these 83 full papers were identified for further examination. Thirty-six randomised controlled trials (RCTs) met the inclusion criteria. The characteristics, quality and risk of bias of these trials have been assessed in Chapter Four (Grant et al., 2009) and are further documented.
in Appendix A-2 and A-4. Trials that were excluded from the systematic review reported in Chapter Four on the grounds of risk of bias are included in the analysis presented here. The purpose of this section is to identify the nominated patterns of disharmony and treatment principles not to examine the quality of the studies.

In addition to trials, eight reviews were identified for inclusion. Four of these were studies of the prevalence of patterns of disharmony in people with prediabetes (Liu, 2003; Lian, 2004; Dong, 2005; Chen, 2007). The other four reviews discussed TCM patterns of disharmony in people with IGT.

### 3.3.2 TCM differential diagnosis and patterns of disharmony in people with IGT

There were nine patterns of disharmony identified in eight reviews as shown in Table 3-1 (Lu 2003; Lian 2004; Wu 2004; Dong 2005; Li 2006; Chen 2007; Song 2007; Chai 2008). Of these eight reviews, four examined existing literature and proposed patterns of disharmony from this analysis. The other four studies conducted a TCM diagnosis on a population cohort with IGT and to determine the prevailing patterns of disharmony. Some of the studies in this latter group also paired the patterns with biomarkers.

Table 3-1 shows the patterns discussed in the reviews. Nearly all reviews found Spleen deficiency with damp, and qi and yin deficiency to be dominant patterns in people with IGT. Blood stasis was a common accompanying pattern.

According to Chai (2008), people with IGT can be differentiated according to qi deficiency, yin deficiency, deficiency of both qi and yin, phlegm-damp and blood stasis. He proposes that phlegm-damp constitution tends to be the most prevalent pattern among those with IGT.

Wu concluded that the primary pattern in people with IGT was Spleen deficiency and damp-heat. The Spleen deficiency arises from an inappropriate diet, lack of exercise, too much thinking, emotional disturbance and/or too much work (Wu, 2004).
Table 3-1 Prediabetes: Patterns of Disharmony

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Spleen deficiency with damp (or damp-heat)</td>
<td>Lu, 2003; Lian 2004; Wu 2004; Li SL 2006; Chen 2007; Song 2007</td>
</tr>
<tr>
<td>2. Qi and Yin deficiency</td>
<td>Lu Y 2003; Dong 2005; Li SL 2006; Chen 2007; Song 2007; Chai 2008.</td>
</tr>
<tr>
<td>4. Yin deficiency (with empty-heat or blood stasis)</td>
<td>Lu Y 2003; Dong 2005; Li SL 2006; Song 2007; Chai 2008.</td>
</tr>
</tbody>
</table>

Chen and colleagues (2007) are the only reviewers to identify a pattern of blood stasis and yang deficiency. However, this group only represented a small proportion (11%) of the 156 cases Chen and colleagues analysed. Many reviewers identified blood stasis as an accompanying pattern (Dong 2005; Li 2006; Song 2007; Chai 2008).

In one of the most comprehensive reviews, Song (2007) identifies four main patterns: Spleen deficiency with damp; yin deficiency with empty-heat; Qi and yin deficiency; phlegm and blood stasis. In the treatment principle for this last pattern of stagnation,
also combines strengthening the Spleen and tonifying qi, alongside activating blood and unblocking channels, expelling damp and phlegm.

Li and colleagues (2006) identify a similar four patterns of disharmony: Spleen deficiency with damp; yin deficiency and blood stasis; qi and yin deficiency; Liver qi stagnation and blood stasis. The four main patterns of disharmony identified above are set out in Table 3-2 with the typical signs and symptoms.

Table 3-2 TCM Signs and symptoms in people with IGT according to four common patterns of disharmony

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qi &amp; Yin deficiency</td>
<td>Fatigue, lack of strength</td>
</tr>
<tr>
<td></td>
<td>Thirst</td>
</tr>
<tr>
<td></td>
<td>Five palm heat (<em>Wu xin fan re</em>)</td>
</tr>
<tr>
<td></td>
<td>Polyphagia</td>
</tr>
<tr>
<td></td>
<td>Polyuria</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath, reluctance to talk</td>
</tr>
<tr>
<td></td>
<td>Spontaneous sweating</td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Red tongue with scanty coat or fat tongue with teethmarks</td>
</tr>
<tr>
<td></td>
<td>Bowstring, fine or rapid, forceless pulse</td>
</tr>
<tr>
<td>Accompanying blood stasis</td>
<td>Stuffiness in the chest, chest pain</td>
</tr>
<tr>
<td></td>
<td>Numbness in the limbs</td>
</tr>
<tr>
<td>Spleen deficiency with damp</td>
<td>Stuffiness in the chest</td>
</tr>
<tr>
<td></td>
<td>Torpid intake</td>
</tr>
<tr>
<td></td>
<td>Heaviness of limbs</td>
</tr>
<tr>
<td></td>
<td>Lack of strength</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td></td>
<td>Loose stools</td>
</tr>
<tr>
<td></td>
<td>Pale red tongue with slimy white coat, soggy pulse</td>
</tr>
</tbody>
</table>
Pattern | Signs and symptoms
---|---
Yin xu with empty-heat | Dry mouth and parched throat
| Fear of heat
| Heart vexation
| Thirst
| Rapid hungering
| Tension, agitation & easy anger
| Frequent, profuse urination
| Possible constipation
| Red tongue with scanty and or yellow coat
| Bowstring, rapid or slippery rapid pulse

### 3.3.3 The prevalence of TCM patterns of IGT and correlation to biochemical markers

Four papers examined the prevalence of TCM patterns of disharmony among people with IGT (Lu, 2003; Lian 2004; Dong 2005; Chen 2007). The studies ranged in size from 156 (Chen et al., 2007) to 55 (Lu, 2003) people with IGT. All studies were conducted in a Chinese population. The symptoms and patterns were provided in two of the studies together with information about biochemical markers. Tables 3-3 and 3-4 summarise the data from these four studies in terms of the patterns identified, their prevalence and biochemical markers.

Variations of Spleen qi deficiency with damp or phlegm were found to be the most common pattern in four of the studies. Of 156 cases in one study, 56% were diagnosed with damp heat and phlegm stagnating and damaging the Spleen (Chen, et al., 2007). A similar prevalence was found in two of the other three studies, 62% (Lu Y, 2003) and 40% (J. Lian, 2004). Biomarkers for those with Spleen qi deficiency were found to be a higher BMI (Chen, et al., 2007), higher triglycerides (Chen, et al., 2007), insulin resistance (Chen, et al., 2007; Lu Y, 2003) and central obesity (Chen, et al., 2007; J Lian, 2004).
Table 3.3 Patterns of Disharmony, Prevalence and Biochemical Markers in 156 People with IGT (Chen, et al., 2007)

<table>
<thead>
<tr>
<th>Pattern of Disharmony</th>
<th>Symptoms</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damp heat and phlegm damaging the Spleen</td>
<td>Stuffiness in the chest, fogginess, tinnitus, heaviness in the body, fatigue in the limbs, excessive phlegm, a sense of something stuck in the throat, loss of appetite, bitter taste in the mouth, bad breath, sticky stool, a red tongue with a white or yellow greasy coat and a wiry, thready and deep pulse.</td>
<td>higher BMI, higher triglycerides, higher insulin, larger waist measurements</td>
</tr>
<tr>
<td>Qi and yin deficiency</td>
<td>Dryness in the throat and mouth, a lack of strength, thirst, lack of saliva, tendency to drink, irritability, restlessness, night sweats, dizziness, palpitations, depression, lots of dreams. A tongue body that is light red but with little or no coat, and a pulse that is thready and fast but without strength.</td>
<td>Hypertension, Higher LDL</td>
</tr>
<tr>
<td>Yang deficiency and Blood stasis (10.9%)</td>
<td>Lack of strength, spiritual fatigue, a preference for warmth, coldness in the limbs, hands and feet, dizziness, reluctance to talk, lower back pain, sore knees, shortness of breath, nocturia, irregular stools, sighing, numbness in the limbs, muscle pain, purple or dark lips. A tongue body that is purple or pale, and a pulse that is weak or wiry.</td>
<td>Older cohort, Higher HbA1c</td>
</tr>
</tbody>
</table>
Table 3-4 Patterns of Disharmony, Prevalence and Biochemical Markers in 55 people with IGT (Lu Y, 2003)

<table>
<thead>
<tr>
<th>Pattern of Disharmony</th>
<th>Prevalence</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen qi deficiency with damp</td>
<td>66%</td>
<td>Higher insulin</td>
</tr>
<tr>
<td>Qi and yin deficiency</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Yin deficiency with empty-heat</td>
<td>22%</td>
<td>Lower insulin levels</td>
</tr>
</tbody>
</table>

Of the people with IGT examined, qi and yin deficiency was found in 52% (Dong, 2005a), 33% (Chen, et al., 2007), 16% (Lu, 2003) and not at all in one study (Lian, 2004). The biomarkers found in this pattern included insulin resistance (Dong, 2005b), hypertension and elevated LDL cholesterol (Chen, et al., 2007) and elevated insulin, although not as severely as those with Spleen qi deficiency (Lu, 2003).

Yin deficiency with dry heat was diagnosed in two of the studies; 31% (Dong, 2005b), and 22% (Lu, 2003) of the study population with IGT. Insulin levels were found to be significantly lower in those with yin deficiency with empty-heat in both studies.

Lian diagnosed two other patterns not noted above: Liver and Spleen disharmony (33%), a group who tended to be more insulin resistant, and the remainder were diagnosed with Lung heat with fluid damage (27%), a pattern more typical of being further along the diabetes continuum (Lian, 2004).

Chen also diagnosed a small proportion of the 156 IGT cases examined with yang deficiency and blood stagnation (11%). This group was characterised by a higher HbA1c and were significantly older than the other two groups (Chen, et al., 2007).

In considering the biomarkers of insulin, those with qi deficiency were more likely to have insulin higher than normal whereas those with yin deficiency had low levels of insulin (Fang, 2008). Lu (2003) supports this analysis of insulin levels in his examination of the insulin and glucose levels of 55 people. Like Chen’s study,
insulin levels were highest in those with Spleen qi deficiency with damp (23.84 ± 12.51).

In conclusion, the population prevalence studies indicate that Spleen qi deficiency with damp is the main pattern of disharmony in people with IGT. Only in Dong’s (2005) analysis was qi and yin deficiency seen as the main pattern. The data on biomarkers indicates that insulin resistance may be seen as damp and phlegm stagnation due Spleen qi deficiency (Chen, et al., 2007). When the functions of the Spleen fail to work, fluids fail to be transported and transformed. Following from this is the heat and the consumption of fluids impairing and consuming yin.

These findings are supported by Lu Ren-he who calls the initial stage of diabetes or the pre-xiao ke stage - “splenic pure heat’ and Lu Jing-zhong focuses treatment at the initial stage of diabetes on the Spleen (Lu, 1999; Wei-bin, 2008).

The data from the population prevalence studies indicates that two main pathologies appear to dominate — Spleen qi deficiency typically accompanied by damp or phlegm; and qi and yin deficiency. The different TCM patterns evident in people with IGT make standardisation of treatment problematic (Wang, 2004). For treatment to be effective differentiation should occur prior to enrolment in a clinical trial or undertaking treatment.

3.3.4 Treatment principles and formulations

Of the 36 RCTs reviewed only seven of the designs involved a differential diagnosis and limited participation to those with a predetermined TCM pattern of disharmony (Fan, Luo et al. 2004; Luo 2005; Fang 2007; Liu 2007; Xin 2007; Wei 2008; Xu 2008).

Both Yang (2004) and Fan (2004) enrolled only people with yin deficiency and empty heat or qi and yin deficiency. These participants received the same base formula with additions according to symptoms. Luo (2005) enrolled people with either qi deficiency or yin deficiency. Participants received the same formula and treatment effect was assessed by the change in TCM symptoms. Fang (2007) had a set inclusion criteria of enrolling only people with qi and yin deficiency or blood stagnation. Wei (2008) included only people diagnosed with Spleen qi deficiency
and damp-heat. Xu (2008) differentiated participants into phlegm damp or heat Toxin treatment groups.

Three trials provided variations in treatment according to symptoms of an additional pattern of disharmony (Zhou 2001; Fan, Luo et al. 2004; Xue 2008). Xin (2007) did not specify inclusion criteria. The set treatment principle of tonifying the Spleen & Kidney; nourish yin and qi and herbs were modified to accommodate five different additional patterns: Stomach heat and yin xu; Liver and Kidney yin xu; yin and yang xu; damp heat attacking the Spleen; and blood stagnation. The characteristics of these trials are set out in Appendix A-2 and A-4.

The utilisation of diagnostic patterns of disharmony in clinical trials is complex. There can be considerable variation in practitioner diagnostic assessment techniques and the diagnostic categories that are assigned. This can make TCM diagnosis apparently ‘unreliable’ or ‘inconsistent’. The TCM diagnostic categories and sub-categories presented may use different terminology or hold different meaning to different practitioners. These complexities are explored further in Chapter Nine. Nonetheless scoping out previous research contributes to understanding of these complexities. The patterns of disharmony used in clinical trials of Chinese herbal medicines for the treatment of people with IGT are examined in 36 clinical trials, seven main treatment principles were identified as shown in Table 3-5.

Table 3-5 Treatment Principles in order of Prevalence

<table>
<thead>
<tr>
<th>Treatment principle</th>
<th>Number of trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonify Qi and nourish (Ki) Yin</td>
<td>16</td>
</tr>
<tr>
<td>Strengthen the Spleen (and tonify qi)</td>
<td>10</td>
</tr>
<tr>
<td>Nourish yin (and clear empty-heat)</td>
<td>7</td>
</tr>
<tr>
<td>Invigorating blood and removing stasis</td>
<td>3</td>
</tr>
<tr>
<td>Expel phlegm, dry damp</td>
<td>3</td>
</tr>
<tr>
<td>Regulate the Liver and strengthen the Spleen</td>
<td>2</td>
</tr>
<tr>
<td>Heat toxin</td>
<td>1</td>
</tr>
</tbody>
</table>

*A trial with more than one treatment principle is counted here only once according to the first principle of treatment.
In some trials two main treatment principles were combined. Common accompanying principles were to expel phlegm; drain damp; remove blood stasis; or generate fluids. Thirty-one of the 36 trials involved nourishing yin or nourishing the Kidneys as the main or accompanying treatment principle. Each of the seven treatment principles are discussed below together with herbal interventions. Details of the herbal interventions were not available for three of the trials. Two trials examined the same herbal formula, Ketang Ling (Cai, 2001; Dai, 2005).

**Tonify qi and nourish yin**

The main treatment principle identified in 16 trials was to “tonify qi and nourish yin”. Herbal formulae include Jiangtang Bushen Tang (Fan, Luo, & Qin, 2004); Danzhi Jiang Tang (Fang, 2007); Tang Ping San (Qu, 2002); Jianpi Zishen Huo Xue (Tang, 2007); and Shengqi Di Huang Tang (Wang, 2008).

Common qi tonics in these formulae included Huang qi, Shan yao, Ren shen. Some of the commonly selected herbs to nourish Kidney yin: Shu di huang, Sheng di, Mai dong, Nu zhen zi, Han lian cao.

**Strengthen Spleen (and tonify qi)**

Tonifying qi and/or strengthening the Spleen was encountered as the main treatment principle in ten trials (Wei, 2001; Li, 2002; Huang, 2003; Hao, 2004; Luo, 2005; Yin, 2007). The trial of Xiaoke Yuye (Hao, 2004) included the principle of removing blood stasis. Common qi tonics such as Huang qi were frequently combined with damp draining herbs such as Fu ling (Huang, 2003; Li, 2002).

**Nourish yin (and clear empty-heat)**

Nourishing yin appeared as the main treatment principle in seven trials. Herbal formulae included Ketangling (Dai, 2005), Qimai Jiang Tang (Li, 2004), and Liu Wei Di Huang Tang (Zeng YH, 2000). One study combined nourishing yin and expelling phlegm (An, 2007). Nourishing yin was combined with generating fluids using herbs such as Tian hua fen (Dai, 2005) and Ge gen (Zhou, 2001); and clearing heat. Herbs such as Huang lian were added along with Xia ku cao and Mu dan pi (Zhou, 2001; Fan, Luo et al. 2004; Yang, 2004; Luo, 2005).
Regulate the Liver and strengthen the Spleen

Only two trials reported regulating the Liver and strengthening the Spleen as the main treatment principle (Ding, 2007; Luo, 2008). The main liver herb included was Chai hu.

Expel phlegm and Dry damp

The treatment principle of expel phlegm-damp was combined with remove blood stasis in two trials (Huang, 2005; Shi, 2005). In one trial, treatment of IGT was administered according to two patterns of disharmony: phlegm-damp and heat Toxins (Xu, 2008). Herbs used to address phlegm-damp included Ban xia, Gua lou, and Cang zhu.

Invigorating blood and removing stasis

Invigorating blood and removing stasis appeared as a distinct treatment principle in only three trials (Huang, 2005; Fang, 2007; Liu, 2007).

Heat toxin

Xu (2008) differentiated participants into phlegm damp or heat toxin treatment groups.

Accompanying treatment principles

Invigorating blood and removing stasis was the main accompanying treatment principle found in the trials being apparent in eleven trials (Cai 2001; Qu 2002; Hao 2004; Li 2004; Dai 2005; Huang 2005; Lu 2005; Shi 2005; Li 2007; Tang 2007; Yuan 2008). Other common accompanying treatment principles included ‘to generate fluids’ which was used five trials (Huang 2003; Li 2004; Dai 2005; Chen 2006; Yin 2007) and ‘to eliminate or drain damp’ also used in five trials.

The hypothesis tested in the majority of these trials was whether a particular herbal formula was effective in the treatment of impaired glucose tolerance. The use of TCM patterns of disharmony and principles of treatment seemed to bear little relevance to the hypothesis or research design. The characteristics of the participants described showed no differentiation on the basis of treatment. Inclusion and
exclusion criteria did not refer to patterns of disharmony with the exception of the seven trials that enrolled according to predetermined patterns of disharmony.

### 3.4 Discussion

The evidence from this review of the clinical trial literature and narrative reviews is that the prevalent pattern of disharmony in people with IGT is Spleen (qi) deficiency with damp. Recent findings have expanded the symptoms of TCM patterns of disharmony to include a correlation to distinct biochemical markers. Spleen qi deficiency with damp is characterised by higher levels of insulin, a higher BMI and higher triglycerides. The second major pattern of disharmony was qi and yin deficiency. Biomarkers associated with yin deficiency were more likely to have lower levels of insulin and higher levels of fasting blood glucose.

Curiously, if most people with IGT are diagnosed with Spleen qi deficiency with damp then there is a mismatch with the main treatment principle of clinical trials seeking to tonify qi and nourish yin. There may several explanations for this disparity.

Firstly, the patterns of Spleen qi deficiency and qi and yin deficiency featured strongly in the reviews and disharmony prevalence studies of IGT population and the clinical trials. This information has a high risk of bias and limitations. The information from the reviews was based on a scanning of the literature, not a consistent systematic review, and is therefore subject to bias. There was only scanty prevalence data available and this may not have captured the full extent of the qi and yin deficiency. Further, this prevalence data may be flawed by inconsistent diagnostic frameworks.

Secondly, herbal formulae that have a treatment principle ‘to tonify qi and yin’ have a broader fit to the diabetic population not the IGT population. So the research approach may simply be one of expedience to treat people with IGT the same as people with diabetes. The most readily available formulae are being used to create generic or ‘one size fits all’ herbal formulae.
In this review, we found little attention paid to TCM differential diagnosis in clinical trial design. Only six of the 36 RCTs conducted a differential diagnosis to enrol people diagnosed with a specific pattern of disharmony. The most commonly encountered clinical trial design was the use of a standard herbal formula, coupled with a loose treatment principle, administered to a cohort of people with IGT without any pattern discrimination. In a small number of trials the formula may have been modified to take into account individual symptoms such as constipation or insomnia.

For the most part, the clinical trials enrolled participants based on one system, a biomedical diagnosis, yet described and prescribed their treatments based another system, TCM. But the population in which the herbal formulae were trialled were not, in the large majority of the trials we reviewed, related to the treatment principles. The relevance of this type of research to practitioners is questionable. And to researchers it is often unclear the question the research was seeking to answer due to the incongruence between the diagnostic system, the treatment system and the trial design. One could conclude the audience for the research is unclear, a problem that appears in much complementary and alternative medicine (CAM) research (van Haselen, 2005).

The incongruence found in our review of clinical trials reflects the general trend of research in TCM (Shea, 2006). A review of randomised controlled trials appearing in 28 Chinese language journals of disease found that the disease was usually defined and diagnosed according to conventional medicine; while trial outcomes may be assessed with objective or subjective (or both) methods of conventional medicine and, at times, traditional Chinese methods (Tang, Zhan, & Ernst, 1999). This trend is likely a pragmatic approach to undertaking simple, less costly research to prove the effectiveness of Chinese herbal medicine or to develop a product for market and mass consumption. Unfortunately this type of research does not reflect clinical practice where individual diagnosis (pattern of disharmony) informs individual treatment decisions.

The implications of these findings are manifold. We require clinical trials that report rigorous, as well as clinically relevant, protocols (Linde, 2007). But there are many problems with trying to conduct an RCT that reflects TCM clinical practice. Not least of these is the lack of evidence for the reliability of TCM diagnosis to form the
foundation of an “authentic” trial (O’Brien et al., 2009). If treatment according to a differential diagnosis and individualisation is arguably the most effective way in which to use the materia medica of Chinese medicine then the continued investigation of clinical trial tools that enable a reliable and repeatable TCM diagnosis is required. This will enable the design of rigorous trials that allow for pattern differentiation and individualisation of herbal formulae.

The results in this review are consistent with the trend reported elsewhere (Aickin, 2007; Verhoef et al., 2005) that the use of the randomised controlled trials result in a ‘treatment situation’ that is so far removed from clinical relevance that no practitioner considers it a valid reflection of what happens in the clinic (Shea 2006; Fonnebo, Grimsgaard et al. 2007; Lewith 2008). So while these randomised clinical trials may have powerful internal validity, they often have poor external validity (Verhoef, et al., 2005). The isolation of components of herbal formulae or provision of set formulae regardless of the presentation of the patient departs from everyday treatment routines. As we break things down into smaller parts to focus on the ‘mechanism’, we lose sight of the whole.

Not only does the synthesis of the parts influence and indeed constitute the whole, the whole in its turn impresses its character on each individual part, which feels its influence in the most real and intimate manner (Smuts, 1927, pp. 131 cited in (Paterson, 2008).

RCT methodology has dominated research in Chinese medicine for over 30 years. Liang (1998) notes the consequences:

Since the early 1990s, the search for the nature of disease has descended into a downward spiral. All the breakthroughs once cheerily anticipated seemed to have become an illusion. The entire traditional Chinese medicine research is currently in a state of disarray. Basic research had come to a standstill. What has gone wrong? Where should we go from here?

The reasons for this disarray are numerous and full explication is beyond the scope of the present study. Suffice to say that there has been a lack of resources in Chinese medicine research and considerable decision making power wielded by institutions dependent on systematic reviews and randomised controlled trials. The cost of this dominance is, we suggest, a paucity of clinically applicable research findings and
widespread misunderstanding of the complexities of a Chinese medicine intervention. The findings of this review are not encouraging about the prospects of any paradigm shift in the near future.

Fonnebo (2007) and Macpherson (2008) however, argue a way forward. They suggest inverting the present research paradigm as shown in Figure 3-1. Although developed for the broader field of CAM, the findings of this review indicate that Fonnebo and Macpherson’s model is strategically sound for sub-fields such as TCM.

**Figure 3-1 Research strategies in drug trials and the proposed CAM strategy**

Phases that contrast the proposed phased research strategy in CAM (dark arrows) with that conventionally used in drug trials (light arrows). Source: Fønnebø et al. *BMC Medical Research Methodology* 2007 7:7

Focusing first and foremost on clinical practice guides us to questions that are relevant to the practitioner and patient. Only when effectiveness has been established does it make sense to break the treatment down into its component parts, and then, using a placebo-controlled trial, determine which of the components are active (Fonnebo et al., 2007; Lewith, 2008). Safety is perhaps assumed through
Chapter 3 Traditional Chinese Medicine Theory, Treatment and Herbal Medicine for Prediabetes

historical use but toxic loads and safety parameters should be established. Such a model demands redistribution of limited research resources away from the present RCT-style study of effectiveness, efficacy and mechanisms in favour of research at the case-study and clinical front-end. Successful implementation of the model will require research designs, such as whole systems research and pragmatic trials (Verhoef, et al., 2005), capable of sustained methodological rigour as well as clinical relevance. Discussion of the risks and opportunities posed by such a paradigm shift is beyond the scope of the present study, as is discussion of the means by which to develop and test new research designs.

In summary, people with impaired glucose tolerance seem to fall into one of two main patterns of disharmony – Spleen qi deficiency with damp or qi and yin deficiency. There is some early work that has commenced linking biomarkers with the dominant patterns of disharmony. However, TCM differential diagnosis into patterns of disharmony appears infrequently in the RCTs of Chinese herbal medicines in people with IGT. This incongruence between patterns of disharmony in people with IGT, treatment principles and clinical trial design appears to be part of a wider trend. This supports a shift away from the dominant paradigm of commencing research with RCTs to a paradigm that seeks first to address clinical and comparative effectiveness and to research designs that are clinically relevant.
CHAPTER 4

Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose

A Systematic Review

4.1 Background

Reviews of herbs used in the treatment of diabetes include three narrative reviews (Jia, Gao, & Xiao, 2003; Li, Zheng, Bukuru, & De Kimpe, 2004; Yeh, Eisenberg, Kaptchuk, & Phillips, 2003) and one systematic review (Liu, Zhang, Wang, & Grimsgaard, 2004). There were no systematic reviews of Chinese herbs for the treatment of impaired glucose tolerance.

The results of clinical trials of Chinese herbal medicines for the treatment of diabetes have typically been positive. However, the reviewers of these trials recommend caution when drawing conclusions regarding the efficacy of Chinese herbs for diabetes. The clinical trials were frequently at high risk of bias through poor randomisation procedures, unclear reporting and small sample size (Liu, et al., 2004; Yeh, et al., 2003). Another limiting factor is the lack of trials of the same herbal medicine. In the Cochrane Systematic Review of 66 randomised controlled trials involving 8302 participants there were sixty-nine different herbal medicines tested.

Herbs with a known effect on insulin include: Astragalus membranae, Radix Rehmanniae, Radix Puerariae, Radix Ginseng, Fructus Cini, Ligustrum Lucidii and Cortex Lycii Radicis have protective effect on beta cells of pancreatic islets (Li, Xie, Huang, Li, & Li, 2004; You & Wang, 2000). Coccina indica and American ginseng have been trialled with positive results in good quality clinical trials (Yeh, et al., 2003). These individual herbs are discussed in more detail in Chapter Five.
In the light of positive findings in clinical trials, reviewers conclude that some herbal medicines deserve further examination in high-quality trials (Jia, et al., 2003; Liu, et al., 2004; Yeh, et al., 2003).

No systematic review on the efficacy of Chinese herbal medicines in people with IGT or IFG has been undertaken. In view of the high proportion of people with IGT that go on to develop overt diabetes, and potentially cardiovascular disease, there is considerable interest in exploring therapeutic approaches that will reduce the risk of diabetes in individuals with IGT with minimal or no adverse effects where lifestyle modifications have failed and pharmacological treatment is inappropriate.

4.2 Objectives

To assess the effects and safety of Chinese herbal medicines for the treatment of people with impaired glucose tolerance or impaired fasting glucose.

4.3 How the intervention might work

One of the main mechanisms of action identified in some of the hypoglycaemic herbs seems to be derived from the polysaccharides in the herbs (Jia, et al., 2003; Mao et al., 2007). In a review of seven antidiabetic drug products of plant origin that have been approved for clinical use in China, most have significant quantities of polysaccharides (Jia, Gao et al. 2003). It is generally thought that the polysaccharides in the herbal drugs may protect pancreatic islets and beta cells, help the regeneration of beta cells, and therefore, increase the insulin secretion from the pancreas (Gao et al., 2007; Jia, et al., 2003; You & Wang, 2000).

Other pharmacological studies of the Chinese herbal formulas for the treatment of diabetes indicate that the mechanisms of action of these interventions might be multifactorial. It has been suggested that in addition to the herbs containing polysaccharides, other herbs within a formula may enhance the microcirculation, increase the availability of insulin and facilitate the metabolism in insulin dependent processes (Jia 2003; Yu 2006). Herbal formulas that exert such a combined effect on insulin and blood glucose control in people with diabetes have relevance to IGT and IFG.
4.4 Adverse effects of the intervention

The chronic nature of prediabetes and diabetes means that people are potentially on treatments for a long period of time which increases the likelihood of adverse effects (American Diabetes Association, 2003). Chinese herbal medicines have a long history of being used to treat diabetes and prediabetes in broad and varied population groups. As a consequence there is an accumulated knowledge of the safety in the use for many of the herbal substances. However, all medicinal agents have potentially unexpected effects including toxicity, and herbals are no different. Adverse effects of herbal medications may be intrinsic such as predictable toxicity, overdosage, interaction with other pharmaceutical or idiopathic (allergy, anaphylaxis etc). They may also be extrinsic, relating to misidentification, contamination, lack of standardisation and so on (Bensoussan, 1996).

4.5 Method

The criteria for considering studies for this review are as follows.

4.5.1 Types of studies

Randomised clinical trials were included irrespective of blinding, publication status or language.

4.5.2 Types of participants

People with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), existing or newly diagnosed.
4.5.3 Types of interventions

**Intervention**

Chinese herbal medicines involving extracts from herbs, single or mixture herbal preparations regardless of their compositions or forms or Chinese herbal medicines combined with a pharmacological intervention.

**Control**

- placebo;
- no treatment;
- pharmacological compounds (for example biguanides such as metformin, sulphonylureas);
- non-pharmacological interventions (for example diet, exercise).

Co-interventions were allowed as long as all arms of the randomised trial received the same co-intervention(s). Only interventions performed for a minimum duration of four weeks were included.

4.5.4 Types of outcome measures

**Primary outcomes**

- glycaemic control: glycosylated haemoglobin levels A1c (HbA1c), fasting and post-load blood glucose levels;
- incidence of type 2 diabetes mellitus: as diagnosed with at the time of the diagnosis prevailing diagnostic criteria (for example, (American Diabetes Association, 1999, 2003; Gavin, Alberti, Davidson, DeFronzo, & al., 1997; World Health Organisation, 1985, 1999);
- adverse effects.

**Secondary outcomes**

- morbidity related to impaired glucose metabolism, the metabolic syndrome or type 2 diabetes: vascular complications (angina pectoris, myocardial infarction, stroke, peripheral vascular disease, amputation), neuropathy,
retinopathy, nephropathy, erectile dysfunction, hyperosmolar nonketotic dysregulation);

- mortality: mortality related to impaired glucose metabolism, the metabolic syndrome or type 2 diabetes (death from myocardial infarction, stroke, renal disease, or sudden death, death from hyperosmolar nonketotic coma), death from any cause;
- insulin: fasting and post-load insulin;
- insulin sensitivity;
- plasma lipids (triglycerides, total-, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol);
- blood pressure (diastolic and systolic blood pressure);
- body weight (or body mass index);
- inflammatory markers (for example, C-reactive protein);
- quality of life (using a validated instrument);
- costs.

### 4.5.5 Covariates, effect modifiers and confounders

Compliance.

Timing of outcome measurement.

Possible influence of treatment duration was addressed in a sensitivity analysis.

### 4.5.6 Search methods for identification of studies

Electronic searches

The following sources for the identification of trials were searched:

- The Cochrane Library
- PubMed (contains MEDLINE and a number of additional life science journals);
- EMBASE;
- Allied and Complementary Medicine Database (AMED);
- Chinese Biomedical Literature Database (CBM);
- Chinese Medical Current Contents (CMCC);
Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS);
Chinese Dissertation Database (CDDB);
Chinese Academic Conference Papers (CACP);
China Medical Academic Conference (CMAC);
The System for Information on Grey Literature in Europe (SIGLE).
The Centralised Information Service For Complementary Medicine (CISCOM) was not searched as the database was not operating when the search was finished (February 2009).
Databases of ongoing trials:
Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials);
UK National Research Register (www.update-software.com/National/nrr-frame.html);
USA - CenterWatch Clinical Trials Listing Service (www.CenterWatch.com);
USA - National Institutes of Health (www.clinicaltrials.gov)

Three different search strategies were combined where the database allowed as follows:

for IGT and IFG we used the strategy from a previous systematic review of western medicine for IGT and IFG (Van de Laar, Lucassen, Akkermans, Van de Lisdonk, & De Grauw, 2004);
for Chinese herbal medicines we employed strategies used for other Cochrane reviews of Chinese herbal medicines;
for controlled trials we used a sensitive validated search strategy (Robinson KA, 2002).

All the above databases were searched from the available date of inception until the latest issue (Feb 2009). For a detailed MEDLINE search strategy please see Appendix A-1.
4.5.7 Searching other resources

The authors of significant publications or experts in the relevant field were contacted for potential studies. We telephoned authors who had published two or more papers on clinical trials of prediabetes (three authors). When we contacted authors to collect details on included and excluded studies they were asked if they had participated in any other clinical trials of Chinese herbal medicines and IGT. Details of contact are provided in the tables of included and excluded studies. Relevant pharmaceutical companies which produced relevant products, were to be checked and contacted. However none were contacted, the products on the market are aimed at type 2 diabetes not prediabetes.

We searched the reference lists of included trials to identify additional trials. Studies published in any language were included.

4.5.8 Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Where information was ambiguous or missing in the article the author was contacted where possible. If the author could not be contacted, the decision to include the trial was resolved by consensus. An adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Liberati et al., 2009) flow-chart of study selection is provided in Figure 4.1.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we tried to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) obtained priority.

Data extraction and management
For studies that fulfilled the inclusion criteria, two authors abstracted relevant population and intervention characteristics using standard data extraction templates, with any disagreements resolved by discussion, or if required by a third party. Any relevant missing information on the trial was sought from the original author(s) of the article. For studies published in Chinese, we worked together with bilingual staff at the Beijing Centre for Evidence-based Medicine in Beijing to extract data according to a set data extraction form.

**Assessment of risk of bias in included studies**

Two authors independently assessed the risk of bias of each of the included studies against key criteria: random sequence generation; allocation concealment; blinding of participants, outcome assessors and intervention providers; incomplete outcome data; selective outcome reporting; and other sources of bias. Studies that did not adequately meet these criteria were considered at high risk of bias. These methods have been updated since the publication of the protocol for this review to reflect guidance from the Cochrane Collaboration (Higgins 2008).

### 4.5.9 Measures of treatment effect

**Dichotomous data**

Dichotomous data were expressed as relative risk (RR) ratios rather than odds ratios (OR). This method has been changed since the publication of the protocol to reflect the approach used by other studies in this modality of treatment. It is also a more easily understood statistic in presenting these outcomes.

**Continuous data**

Weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated for continuous data using a random-effects model. A random-effects model was used in preference to a fixed-effect model due to the expected heterogeneity of the trials. The actual measure of effect of all continuous variables was the differences from baseline to endpoint. The standard deviations (SD) of these differences were essential for the data to be included in the meta-analysis. All SDs of the difference were reported, and it was not necessary to impute SDs.
4.5.10 Time-to-event data

We planned to summarise time-to-event data using methods of survival analysis and express the treatment effect as a hazard ratio.

4.5.11 Unit of analysis issues

Data were summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis was performed according to the statistical guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2008).

4.5.12 Dealing with missing data

Relevant missing data were obtained from authors, where possible. Important numerical data such as screened, eligible and randomised participants as well as intention-to-treat (ITT) and per-protocol (PP) population were evaluated. Drop-outs, misses to follow-up and withdrawn study participants were also investigated where possible. Issues of last-observation-carried-forward (LOCF), ITT and PP were critically appraised and compared to specification of primary outcome parameters and power calculation.

4.5.13 Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results were not combined in meta-analysis. Heterogeneity was identified by visual inspection of the forest plots, by using a standard $\chi^2$-test and a significance level of $\alpha = 0.1$. Heterogeneity was also examined with I² (Higgins & Thompson, 2002), where I² values of 75% and more indicate a considerable level of heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

4.5.14 Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot. Therefore, we
4.5.15 Data synthesis

Data concerning details of study population, intervention and outcomes were extracted independently by two reviewers using a standard data extraction form. The standard data extraction form included at least the following items:

- general information: published/unpublished, title, authors, source, contact address, country, urban/rural, language of publication, year of publication, duplicate publications, sponsoring, setting;
- trial characteristics: design, duration, randomisation (and method), allocation concealment (and method), blinding (participants, people administering treatment, outcome assessors), check of blinding;
- 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);
- participants: 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;
- outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes;
- results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures.

4.5.16 Subgroup analysis and investigation of heterogeneity

Subgroup analyses were to be performed if one of the primary outcome parameters demonstrated statistically significant differences between treatment groups. The following subgroup analyses were planned:
glycosylated haemoglobin A1c (HbA1c) level at baseline (subdivided into groups, based on data);
- age (subdivided into groups, based on data);
- gender;
- body mass index (BMI) (subdivided into groups, based on data);
- duration of intervention (subdivided into groups, based on data).

### 4.5.17 Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results was also to be tested by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed- and random-effects models).

### 4.6 Results - Description of studies

#### 4.6.1 Results of the search

The initial search identified 1926 records, from these 83 full papers were identified for further examination. If there was unclear information in the title or abstract, the full article was retrieved for clarification. The other studies were excluded on the basis of their abstracts because they were not relevant to the question under study, obvious duplicates were removed. After screening the full text of the 83 selected papers, 16 studies finally met the inclusion criteria (Figure 4-1), and one study is awaiting classification (Liu, Wang, Kan, & Zheng, 2007).
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

Figure 4-1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection

4.6.2 Included studies

There were 16 randomised clinical trials included in this review. They reported random allocations of participants with impaired glucose tolerance (IGT) to Chinese herbal medicines versus controls. Nine studies randomised participants to receive Chinese herbal medicines with a co-intervention of lifestyle modification versus a control of lifestyle modification alone (Fan, Luo, & Qin, 2004; Hao, Hang, & Wang, 1992; Li, et al., 2004; Tang, 2007; Wei, Sun, & Long, 2001; Yang B, 2004; Yao, 2001; Zeng YH, 2000; Zhou D, 2003). Three trials compared Chinese herbal medicines with placebo (Fang, 2007; Hioki, Yoshimoto, & Yoshida, 2004; Wang, Jiao, & Chen, 2008), two of these trials included a co-intervention of a lifestyle
intervention. Two trials compared Chinese herbal medicines with the biguanide metformin (Qu, 2002; Shi, 2005). There was one three-arm trial comparing Jian Pi Zhi Shen Huo Xue with lifestyle modification versus the alpha-glucosidase inhibitor, acarbose versus lifestyle modification alone (Tang et al., 2007). One trial compared Jinqi Jiang Tang and basic IGT education with basic IGT education alone (Wang, et al., 2008). Finally, there was a single trial that compared Yi Qi Yang Yin Huo Xue with a co-intervention of an antihypertensive medication (vasodilator) versus the same antihypertensive medication alone (Lu, 2005). The details of the trials are listed under Appendix A-2.

The duration of the trials ranged from four weeks to two years (mean 9.3 months). Of the 16 included trials, eight trials ran for over 12 months ((Fan, et al., 2004; Li, et al., 2004; Tang, et al., 2007; Wang YF, 2008; Wang, Zhu, & Wang, 2005; Wei, et al., 2001; Zeng et al., 2006; Zhou & Chen, 2003). There were three large trials (more than 100 participants) that ran for over 12 months (Tang, et al., 2007; Wang, et al., 2005; Zeng, et al., 2006).

All trials had a parallel design. Fourteen trials were two-armed and two were three-armed (Tang, et al., 2007; Zeng, et al., 2006). The third control arm of the Zeng (2006) trial was not included in the comparisons or this result section. The control arm had a simple education intervention differing to the co-intervention of the herbal medicine. This comparison did not meet the inclusion criteria set for this review. Data from this arm are not included in the results section.

The trials were all conducted from 2001 onwards. One study is still awaiting classification.

### 4.6.3 Participants

The sixteen trials included 1391 participants. The average number of participants in the trials was 87, ranging from 42 to 168.

Mean age of the participants was 52, ranging from 44 to 66 years (missing data from (Fang, 2007). This is consistent with population prevalence which shows that the 40 to 59 years age group currently has the greatest number of persons with impaired glucose tolerance and diabetes (International Diabetes Federation, 2008).
There were 719 males and 659 females (no gender data available on 13 withdrawals). One trial (Hioki, et al., 2004) chose to enrol female participants only (n = 81). The aim of this study was primarily to assess insulin resistance and visceral adiposity. One other trial (Hao AZ, 2004) had an over-representation of males to females (121:47). The overall ratio of the trials is not consistent with the population prevalence of diabetes and prediabetes which shows a female predominance with females ranging 10% higher than males for diabetes, and females ranging 20% higher than males for impaired glucose tolerance (International Diabetes Federation, 2008).

Two trials enrolled obese or overweight participants only (Hioki, et al., 2004; Shi, 2005). Three studies (Yang et al., 2004; Zeng, et al., 2006; Zhou & Chen, 2003) included participants with a mean body mass index (BMI) in the healthy weight range (ranging from 20.8 to 24.3). Five studies (Tang, et al., 2007; Wang, et al., 2008; Wang, et al., 2005; Wei, et al., 2001; Yao, 2001) included participants with a mean BMI in the obese range (ranging from 25.3 to 27.2).

One trial enrolled hypertensive participants only (Qu, 2002).

With regard to ethnicity, all trial participants, with the exception of one trial which involved Japanese women (Hioki, et al., 2004) were Chinese.

All trials included participants with impaired glucose tolerance, only with the exception of one trial (Wang, et al., 2005) which involved those with impaired fasting tolerance (IFG) in addition to those with IGT.

All trials recruited outpatients from hospitals or clinics.

For an overview of the study populations of the trials, like randomised individuals, intention-to-treat populations and participants finishing the study, please refer to Appendix A-3.

### 4.6.4 Diagnosis

The diagnostic criteria used in the trials were mainly based on the WHO criteria. Eight trials used WHO 1999 and three trials used WHO 1985 criteria (Yao, 2001; Zeng, 2006; Zhou, 2003). Four trials used the American Diabetes Association (ADA
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

1997) criteria (Fang, 2007; Lu, 2005; Qu, 2002; Yang, 2004). One trial used a combination of the WHO 1999 and the ADA 1997 criteria (Wang, 2005). The ADA criteria rely on a fasting plasma glucose level equal or greater than 6.1 mmol/L and less than 7.0 mmol/L. This differs from the WHO 1999 criteria which uses both a fasting plasma glucose less than 7.0 mmol/L AND a 2hr blood glucose after oral glucose tolerance test (oGTT) equal or greater than 7.8 and less than 11.0. The WHO 1985 criteria had a slightly higher range for including people as IGT - fasting plasma glucose less than 7.8 mmol/L. The different diagnostic criteria were subjected to a sensitivity analysis but no significant differences were detected.

4.6.5 Interventions

Fifteen Chinese herbal medicine interventions were examined in the 16 randomised trials (see Appendix A-2). Chinese herbal medicine Jinqi Jiang Tang was tested in two trials (Wang, 2005; Zhou, 2003). The trials all tested compounds of complex herbal formulas (see Table 4-1 'Preparation and compositions of the Chinese herbal medicines'). Preparations of herbs were as decoctions, pills, capsules or granules.

The herbal composition of the interventions varied. However, some individual herbs were prevalent in the different formulas. Astragalus membranecus was present in 10 of the 15 interventions for which the ingredients were known. Where Astragalus membranecus was a major part of the formula (either in amounts equal or greater than 20 g or only one of six herbs) it was analysed in a separate analysis. Other commonly used herbs included Shan yao (eight of the 15 interventions) and Ge gen (four of the 15 interventions).

Table 4-1. Preparation and composition of Chinese herbal medicines in the included trials

<table>
<thead>
<tr>
<th>name of herbal formula</th>
<th>preparation</th>
<th>composition</th>
<th>study ID</th>
</tr>
</thead>
</table>

74
<table>
<thead>
<tr>
<th>name of herbal formula</th>
<th>preparation</th>
<th>composition</th>
<th>study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bofu-tsusho-san</td>
<td>powder</td>
<td>Scutellariae Radix, Glycyrrhizae Radix, Platycodi Radix, Gypsum Fibrosum,</td>
<td>Hioki C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atractylodis Rhizoma, Rhei Rhizoma, Schizonepetae Spica, Gardeniae Fructus,</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paeoniae Radix, Cnidium Rhizoma, Angelicae Radix, Menthae Herba, Ledebouriellae</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radix, Ephedrae Herba, Forsythiae Fructus, Zingiberis Rhizoma, Talcum,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Natrium Sulphuricum</td>
<td></td>
</tr>
<tr>
<td>Yi Qi Yang Yin</td>
<td>decoction</td>
<td>Astragali Radix 30g, Angelicae sinensis Radix 20g, Dioscoraea Rhizoma 20g,</td>
<td>Lu X</td>
</tr>
<tr>
<td>Huo Xue</td>
<td></td>
<td>Mori Cortex 50g, Mori Folium 30g, Mori Ramulus 30g</td>
<td>2005</td>
</tr>
<tr>
<td>Jian Pi Zhi Shen</td>
<td>powder</td>
<td>Dioscorae Rhizoma, Crategi Fructus 30g, Astragali Radix</td>
<td>Tang</td>
</tr>
<tr>
<td>Huo Xue</td>
<td></td>
<td>20g, Poria 20g, Corni Fructus 15g, Persicae Semen 10g</td>
<td>2007</td>
</tr>
<tr>
<td>Dan zhi jiang tang</td>
<td>capsules</td>
<td>Moutan Cortex, Hirodu, Cuscutae Semen, Polygonati Rhizoma, Pseudostellariae</td>
<td>Fang</td>
</tr>
<tr>
<td>jiao</td>
<td></td>
<td>Radix, plus Rehmanniae glutinosae, Corni of cinalis, Dioscoreae oppositae,</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alismatis orientalis, Poriae cocos, Moutan radicis.</td>
<td></td>
</tr>
<tr>
<td>Fufang cangzhu</td>
<td>decoction</td>
<td>Atractylodis Rhizoma 15g, Coicis Semen 24g, Mori Fructus 20g, Dioscoraeae</td>
<td>Shi J</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhizoma 30g, Phellodendri Cortex 10g, Litchi Semen 20g, Pheretima 10g</td>
<td>2005</td>
</tr>
<tr>
<td>Jiangtang bushen</td>
<td>decoction</td>
<td>Cibotii Rhizoma 10g, Dipsaci Radix 10g, Ligustri lucidi Fructus 15g,</td>
<td>Fan GJ</td>
</tr>
<tr>
<td>tang</td>
<td></td>
<td>Ecliptae Herba 15g, Lycii Cortex 15g, Astragali Radix 15g, Rehmanniae Radix</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15g, Puerariae Radix 12g, Coptidis Rhizoma 5g, Mori Cortex 10g, Moutan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortex 6g</td>
<td></td>
</tr>
<tr>
<td>name of herbal formula</td>
<td>preparation</td>
<td>composition</td>
<td>study ID</td>
</tr>
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<td>------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Jie yu huo xue</td>
<td>decoction</td>
<td>Angelicae sinensis Radix 15g, Bupleuri Radix 15g, Polygonati odorati Rhizoma 10g, Astragali Radix 30g, Chuanxiong Rhizoma 10g, Paenoiae Radix rubra 15g, Notoginseng Radix 3g, Puerariae Radix 15g, Polygonati Rhizoma 15g, Curcumae Radix 15g, Ginseng Radix 25g, Prunellae Spica 10g; If heat in palms, thirst, increased drinking: + Anemarrhenae Rhizoma 20g, Schisandrae Fructus 10g; if restlessness, tendency to anger, insomnia: + Platycladi Semen 20g, Polygoni multiflora Caulis 15g, Coptidis Rhizoma 10g; if dizziness, stuffiness in eyes, reddish face &amp; ears with heat: + Moutan Cortex 15g, Uncariae Ramulus cum Uncis 15g</td>
<td>Liu DQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2007</td>
</tr>
<tr>
<td>Jinqi Jiangtang</td>
<td>pill</td>
<td>Astragali Radix, Lonicera Flos etc</td>
<td>Zhou</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Jinqi Jiangtang</td>
<td>pill</td>
<td>Astragali Radix, Lonicera Flos etc</td>
<td>Wang</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2005</td>
</tr>
<tr>
<td>Liu wei di h ung</td>
<td>pill</td>
<td>Rehmanniae glutinosae, Corni of cinalis, Dioscoreae oppositae, Alismatis orientalis, Poriae cocos, Moutan radicis.</td>
<td>Zeng</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2006</td>
</tr>
<tr>
<td>Qimai Jiangtang</td>
<td>decoction</td>
<td>Astragali Radix 20g, Puerariae Radix 20g, Ophiopogonis Radix 10g, Ligustri lucidi Fructus 10g, Notoginseng Radix 10g, Curcumae Radix 10g, Rehmanniae Radix 25g</td>
<td>Li</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2008</td>
</tr>
<tr>
<td>Tang Kang Yin</td>
<td>decoction</td>
<td>Ginseng Radix 6g, Coptidis Rhizoma 10g, Ligustri lucidi Fructus 15g, Prunellae Spica 30g, Alumen 30g</td>
<td>Yang B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2004</td>
</tr>
</tbody>
</table>
### Table 1: Summary of key herbal formulas

<table>
<thead>
<tr>
<th>Name of Herbal Formula</th>
<th>Preparation</th>
<th>Composition</th>
<th>Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang ping san</td>
<td>powder</td>
<td>Astragali Radix 30g, Dioscoreae Rhizoma 10g, Rehmanniae Radix 10g,</td>
<td>Qu LX 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rehmanniae Radix preparata 10g, Lycii Fructus 10g, Polygoni multiflori</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radix preparata 10g, Epimedi Herba 10g, Salviae miltiorrhizae 30g,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alismatis Rhizoma 10g, Mori Folium 10g</td>
<td></td>
</tr>
<tr>
<td>Xiaoke Huayu Pian</td>
<td>tablet</td>
<td>Anemarrhena Rhizoma, Euonymi Ramulus etc</td>
<td>Hao 2004</td>
</tr>
<tr>
<td>Xiaoke Yuye decoction</td>
<td>decoction</td>
<td>Astragali Radix, Polygoni Rhizoma, Polygoni multiflori Radix preparata,</td>
<td>Wei 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemarrhena Rhizoma</td>
<td></td>
</tr>
</tbody>
</table>

The 16 trials had eight distinct comparisons:

- nine trials compared nine Chinese herbal medicines with lifestyle modification as a control and co-intervention (Jiangtang bushen decoction (Fan GJ 2004), Jinqi Jiang Tang pills (Zhou 2003), Liu wei di huang wan pills (Zeng 2006), Qimai Jiangtang Yin decoction (Li 2004), Tang Kang Yin decoction (Yang B 2004), Tang Heng I (Yao 2001), Xiaoke huayu tablets (Hao 2004), Xiaoke Yuye decoction (Wei 2001) and Jian Pi Zhi Shen Huo Xue (Tang 2007);
- two trials compared Chinese herbal formulas with a placebo with lifestyle modification as a co-intervention: Bofu-tsusho-san (Hioki C 2004) and Dan zhi jiang tang jiao (Fang ZH 2007);
- one trial compared Qiwei tangping capsules with a placebo (Wang 2008);
- one trial compared Tang ping san with metformin, with a lifestyle modification as co-intervention (Qu LX 2002);
- one trial compared Fufang cangzhu decoction with metformin (Shi J 2005);
- one trial compared Jian Pi Zhi Shen Huo Xue with acarbose (Tang 2007);
one trial compared Yi Qi Yang Yin Huo Xue combined with an antihypertensive medication with an antihypertensive medication alone (Lu X 2005);

- one trial compared Jinqi Jiang Tang pills with a basic education on IGT as a co-intervention and as a control (Wang 2005).

Tang 2007 and Zeng 2006 were three-arm trials. Tang 2007 compared a Jian Pi Zhi Shen Huo Xue plus lifestyle modification versus acarbose plus lifestyle modification versus lifestyle modification alone. Zeng 2006 compared Liu Wei Di Huang Tang plus lifestyle modification versus lifestyle modification alone versus a control receiving a diabetes educational pamphlet only.

Lifestyle modification typically involved diet, exercise and education about the disease. In most cases the specific nature of this intervention was poorly documented with the exception of Hioki C 2004 and Zeng 2006.

The studies yielded widely differing estimates of effect (a high level of heterogeneity) when results were pooled on most outcomes. This was expected with a review that includes a range of Chinese herbal medicine interventions composed of differing herbs and formulations.

### 4.6.6 Outcomes

The outcomes reported were mainly metabolic parameters including fasting blood glucose (reported in all studies except Qu LX 2002), 2hr fasting glucose (reported in all studies) and 'normalisation of fasting blood glucose' (reported in 10 studies). Normalisation was defined as fasting blood glucose $<7.0$ mmol/L and 2hr OGTT $\leq 7.8$ mmol/L according to WHO 1999 criteria for all trials except Yao 2001, which used the ADA 1997 criteria for normal glucose tolerance of fasting blood glucose less than 6.1 mmol/L. Outcomes on normalisation of blood glucose were recorded as dichotomous data.

Ten studies measured the incidence of diabetes (Fan GJ 2004; Hao 2004; Li 2004; Tang 2007; Zhou 2003; Wang 2008; Wang 2005; Wei 2001; Yao 2001). Incidence of diabetes refers to the number of participants that have converted to diabetes by the
completion of the trial. Eight of the ten trials reporting on this outcome used WHO 1999 criteria to define diabetes (FPG >7.0 mmol/L and 2hr oGTT >11.0 mmol/L).

Four studies measured glycosylated haemoglobin A1c (HbA1c) (Hao 2004; Hioki C 2004; Tang 2007; Wei 2001). Zeng nominated HbA1c as an outcome but did not report the data.

Eleven studies measured lipids, either total cholesterol, triglycerides or both. Five studies measured HDL-cholesterol. Nine studies measured fasting insulin.

No study investigated mortality, morbidity or cost effectiveness. Lu X 2005 was the only study to measure quality of life. Adverse effects were reported in two of the studies. Other outcomes measured were body mass index (BMI), waist-hip-ratio (WHR) and blood pressure.

### 4.6.7 Excluded studies

Most of the references identified by the search update were excluded at the first screening step by one reviewer, as they were clearly irrelevant (see Appendix A-4 Characteristics of excluded studies). The most frequent reasons for exclusion at this level were: article was a review or a commentary; studies of people with diabetes; and clearly non-randomised design.

The full text of 83 studies was retrieved. Sixty-six studies had to be excluded after careful evaluation of the full publication. Seventeen studies were excluded due to inadequate methods of randomisation (odd-even, alternation, and based on clinician's decision). Sixteen studies were non-randomised trials and 15 were case series. A further 18 studies were excluded as they did not meet the review criteria for the population group, outcomes, duration or intervention. Of these, five studies were excluded due large sampling discrepancies indicating there was no true randomisation. In each case we were unable to contact the authors to resolve the discrepancy. One study was excluded as it was a duplicate.
4.7 Risk of bias in included studies

Most published reports of trials were lacking in details of trial methodology (see Figure 4.2). We tried to contact all primary trial authors to clarify randomisation methods. When details were obtained (through phone calls) it was apparent that eleven of the trials had used an adequate sequence generation. The method was not reported for five trials and we were unable to contact the trial authors (Hao 2004; Li 2004; Qu LX 2002; Wang 2005; Yao 2001).

Most of the trials provided data on important baseline characteristics of the intervention and control groups to judge the comparability of the two groups.

Three trials (Fang ZH 2007; Hioki C 2004; Wang 2008) could be considered as having a low risk of bias reporting adequate sequence generation, adequate allocation concealment, participants blinded, all participants accounted for and no other apparent bias.

4.7.1 Allocation

Allocation concealment was adequate in only five trials (Fang ZH 2007; Hioki C 2004; Wang 2008; Wei 2001; Zeng 2006). It was unclear in nine trials and not adequate in two.
4.7.2 Blinding

Participants were blinded in three trials (Fang ZH 2007; Hioki C 2004; Wang 2008). The lack of blinding in the other trials could have resulted in an over- or
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

underestimation of the outcomes as it may have affected the behaviour of the participants.

**4.7.3 Incomplete outcome data**

Attrition was low or adequately accounted for in most trials.

**4.7.4 Selective reporting**

In all trials but one (Zeng 2006), nominated and expected outcomes were reported. As no trials reviewed had published protocols of their data collection or analysis it is not known if some outcomes were not published.

**4.7.5 Other potential sources of bias**

Some authors were contacted by phone for further information on methods of randomisation, sequence generation, allocation concealment and, in some cases, clarify data issues. Authors were relying on recall and this may have led to some bias.

Six trials clearly reported the number of drop-outs and withdrawals (Fan GJ 2004; Hioki C 2004; Tang 2007; Wang 2008; Wang 2005; Wei 2001), although ITT analysis was not implemented; nor was it used in any of the other included trials. Reasons for drop-outs or withdrawals were not always clear.

Small study and reporting bias were considered. It is possible that the results are biased as it is possible that studies with negative outcomes have not been published. Outcomes for the first comparison group of studies were explored through funnel plots. However, these cannot be considered reliable as there were fewer than 10 studies; in addition funnel plot asymmetry may occur by chance. A sensitivity analysis was conducted to determine if the positive results of the small trial of Tang Heng I (Yao 2001) had influenced the meta-analysis of normalisation of fasting blood glucose (RR 1.99; 95% confidence interval (CI) 1.47 to 2.71 versus RR 2.07; 95% CI 1.52 to 2.82).
4.8 Effects of interventions

There were no outcome data in any of the trials on death from any cause, morbidity, diabetes complications, or costs. No serious adverse events or hypoglycaemic episodes were reported.

We were only able to perform meta-analyses on two outcomes in this review and these should be interpreted cautiously. This is mainly due to issues of heterogeneity and because none of the specific herbal medicines comparison data was available from more than one study. Forest plots of the data analysis of the effects of interventions are presented in Appendix A-5.

4.8.1 Herbal medicine plus lifestyle modification versus lifestyle modification alone

Nine trials involving 792 participants compared herbal medicines along with lifestyle intervention with lifestyle intervention alone (Fan GJ 2004; Hao 2004; Li 2004; Tang 2007; Wei 2001; Yang B 2004; Yao 2001; Zeng 2006; Zhou 2003). The average number of trial participants was 50, ranging from 42 to 168 participants. Average trial duration was 8.3 months, ranging from one month to 24 months.

Nine different herbal medicines were investigated: Jiangtang Bushen decoction, Xiaoke Huaya tablet, Qimai Jiangtang Yin decoction, Jinqi Jiang Tang tablets, Xiaoke Yuye decoction, Liu Wei Di Huang Tang, Tang Kang Yin decoction, Tang Heng I decoction and Jian Pi Zhi Shen Huo Xue.

In all trials, with the exception of Zeng 2006, the lifestyle intervention was poorly documented.

4.8.2 Normalisation of fasting blood glucose and incidence of diabetes

Normalisation of fasting blood glucose refers to the number of participants who returned to normal blood glucose range at the end of the trial.

Eight trials involving 625 participants reported on the normalisation of fasting blood glucose levels following the intervention.
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

Of the eight trials analysed, those receiving the Chinese herbal intervention were more than twice as likely (RR 2.07; 95% confidence interval (CI) 1.52 to 2.82) to have normalised their fasting blood glucose compared to those receiving lifestyle modification only (Figure 4-3).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Herbs + lifestyle Events</th>
<th>Total Events</th>
<th>Lifestyle alone Events</th>
<th>Total Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
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<tbody>
<tr>
<td><strong>1.1.1 Jiangtang Bushen decoction</strong></td>
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<tr>
<td>Fan GJ 2004</td>
<td>18</td>
<td>23</td>
<td>10</td>
<td>22</td>
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<td>Subtotal (95% CI)</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 2.11 (P = 0.04)</td>
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<tr>
<td><strong>1.1.2 Xiaoke Huaya tablet</strong></td>
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<tr>
<td>Hao AZ 2004</td>
<td>66</td>
<td>86</td>
<td>21</td>
<td>82</td>
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<tr>
<td><strong>1.1.3 Qimai Jiangtang Yin decoction</strong></td>
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<td>LIUK 2004</td>
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<td>31</td>
<td>7</td>
<td>33</td>
<td>9.9%</td>
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<td>Subtotal (95% CI)</td>
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<td><strong>1.1.4 Jian Pi Zhi Shen Huo Xue</strong></td>
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<tr>
<td>Tang QZ 2007</td>
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<td><strong>1.1.5 Tang Kang Yin</strong></td>
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<tr>
<td>Yang B 2004</td>
<td>25</td>
<td>40</td>
<td>6</td>
<td>36</td>
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<td><strong>1.1.6 Xiaoke Yuge decoction</strong></td>
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<tr>
<td>Wei JG 2001</td>
<td>22</td>
<td>32</td>
<td>12</td>
<td>33</td>
<td>13.5%</td>
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<td>Subtotal (95% CI)</td>
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<td>Total events</td>
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<td>Yao Z 2003</td>
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<td>20</td>
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<td><strong>1.1.8 Jing jiang tang</strong></td>
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<tr>
<td>Zhou DY 2003</td>
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<td>48</td>
<td>28</td>
<td>42</td>
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<td>Subtotal (95% CI)</td>
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</table>

Total (95% CI) 318 307 100.0% 2.07 [1.52, 2.82]

Total events 217 102
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

Figure 4-3. Forest plot of outcome of normalisation of fasting blood sugar at trial completion (herbal medicines plus lifestyle modification plus lifestyle modification versus lifestyle modification alone.

The incidence of diabetes refers to the number of participants who had progressed to type 2 diabetes according to WHO or ADA criteria by the end of the trial.

Eight trials reported on the incidence of diabetes in the groups Figure 4-4. There was a significant difference in the incidence of diabetes in favour of the Chinese herbal medicines following Tang Keng Yin tablets (Yang B 2004). When the results of the eight trials were pooled there was a significant difference found in favour of the Chinese herbal medicines compared to the lifestyle intervention alone (RR 0.33; 95% CI 0.19 to 0.58). All except three of these trials had a duration of more than 12 months (Yang 2004 ran for one month, Hao 2004 ran for two months, and Yao 2001 for three months).
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

**Figure 4-4.** Forest plot of outcome ‘diabetes incidence’ (herbal medicines plus lifestyle modification versus lifestyle modification alone)

In the pooling of results on these two measures there was no considerable statistical heterogeneity among the comparisons (normalisation of fasting blood glucose: I² = 66%; incidence of diabetes: I² = 0%). It is important to note that there was clinical heterogeneity. The Chinese herbal medicines used in the clinical trials analysed are
wide ranging in their ingredients. These ingredients are used for a variety of different clinical purposes. However, they may still be considered as 'class' or 'group' of oral hypoglycaemic herbal medicines. But any pooled effect size should be interpreted only as crude indicator of the overall direction of the findings. Nevertheless, these findings show that participants receiving Chinese herbal medicines were less likely to develop diabetes and more likely to have normal blood glucose than those in the control group.

4.8.3 Fasting blood glucose and 2hr blood glucose after an oral glucose tolerance test (OGTT)

Fasting blood glucose refers to the fasting plasma glucose (FPG) levels (mmol/L) measured in all nine trials in this comparison (continuous data).

In four of the nine trials, the Chinese herbal medicines combined with lifestyle modification were significantly better at reducing fasting blood glucose levels than lifestyle modification alone. Jinqi Jiang Tang tablets (Zhou 2003) showed a significant reduction (MD -0.58 mmol/L; 95% CI -0.74 to -0.42), as did Hao 2004 (MD -1.40 mmol/L; 95% CI -1.72 to -1.08), Yang B 2004 (MD -0.21 mmol/L; 95% CI -0.33 to -0.09), and Zeng 2006 (MD -0.31 mmol/L; 95% CI -0.58 to -0.04). There was no significant difference of fasting blood glucose in the trials of Jiangta ng Bushen decoction (Fan GJ 2004), Qimai jiangtang Yin (Li 2004), Jian Pi Zhi Shen Huo Xue (Tang 2007), Xiaoke Yuye (Wei 2001), and Tang heng I (Yao 2001).

Two hour fasting blood glucose refers to blood glucose levels (mmol/L) measured after an oGTT. Six of the nine trials in this comparison reported significantly better results for reducing 2hr fasting blood glucose levels than the lifestyle modification control. There was no significant difference in the trials of Jiangtang bushen decoction (Fan GJ 2004) Tang Heng I decoction (Yao 2001) and Liu Wei Di Huang Tang (Zeng 2006).

When these studies were pooled, considerable heterogeneity was found among the studies (I² = 90%). This may be due to the type of the intervention, the duration of the intervention or both which prevented a meaningful meta-analysis of these outcomes.
4.8.4 Glycosylated haemoglobin A1c (HbA1c)

Only three studies reported HbA1c outcomes. Xiaoke Huayu tablets (MD -0.6%; 95% CI -1.0 to -0.3) (Hao 2004), Xiaoke Yuye decoction (Wei 2001) (MD -0.9%; 95% CI -1.4 to -0.3) and Jian Pi Zhi Shen Huo Xue (MD -0.1%; 95% CI -0.1 to 0.0) (Tang 2007) combined with lifestyle modification were all statistically significant in reducing HbA1c compared to the control of lifestyle modification alone. No meta-analysis was conducted due to considerable statistical heterogeneity (I² = 88%).

4.8.5 Insulin

In the six trials that measured insulin levels, significantly lower levels were detected in those taking Jiangtang bushen decoction (Fan GJ 2004), Qimai jiangtang decoction (Li 2004), and Jinqi Jiang Tang tablets (Zhou 2003). No significant differences in insulin levels were found in those participants taking Tang Kang Yin (Yang B 2004) and Tang Heng I decoction (Yao 2001) compared with the lifestyle modification control group. In the trial of Jian Pi Zhi Shen Huo Xue (Tang 2007) insulin levels of the lifestyle modification control group were significantly lower than those in the Chinese herbal intervention group.

Insulin active index (IAI), a measure of insulin sensitivity, was assessed in one trial of Qimai Jiangtang Yin (Li 2004). No significant differences were detected.

4.8.6 Lipids

Cholesterol outcomes were measured in seven trials (Fan GJ 2004; Hao 2004; Tang 2007; Wei 2001; Yang B 2004; Zeng 2006; Zhou 2003). Triglycerides were also measured in these seven trials. High density lipoprotein (HDL) cholesterol was measured in two trials (Tang 2007; Zhou 2003).

One trial that measured all three outcomes, Jian Pi Zhi Shen Huo Xue (Tang 2007) showed a significant improvement in reducing total cholesterol (MD -0.73 mmol/L; 95% CI -1.15 to -0.31), HDL-cholesterol (MD 0.30 mmol/L; 95% CI 0.10 to 0.50) and triglycerides (MD -0.31 mmol/L; 95% CI -0.52 to -0.10) for the combined intervention of Chinese herbal medicines with lifestyle interventions.
Jiangtang bushen tang (Fan GJ 2004), Tang Kang Yin (Yang B 2004), Liu Wei Di Huang Tang (Zeng 2006), and Xiaoke Huayu Pian (Wei 2001) also all showed a significant improvement compared to the control in reducing total cholesterol and triglycerides.

4.8.7 Body mass index (BMI)

Five trials comparing herbal medicine with lifestyle modification with lifestyle modification alone measured BMI. Xiaoke Yuye decoction (Wei 2001), Tang Kang Yin decoction (Yang 2004), and Liu Wei Di Huang capsule (Zeng 2006) all demonstrated a significant improvement in BMI. There was no significant improvement in BMI in those taking Jinqi Jiang Tang pian (Zhou 2003) and Jiangtang bushen tang (Fan GJ 2004).

4.8.8 Blood pressure

Two trials (Zeng 2006; Zhou 2003) in this comparison group examined blood pressure. Liu wei di huang capsules were statistically significantly more effective than the control group in reducing diastolic (MD -3 mm Hg; 95% CI -4 to -1) and systolic (MD -4 mm Hg; CI 95% -7 to -1) blood pressure. The diastolic blood pressure data for Jinqi Jiangtang pian were unusual in favour of lifestyle intervention alone (MD 20 mm Hg; 95% CI 19 to 21) and we were unable to contact the author to clarify any reporting anomaly. There were no significant differences in the systolic blood pressure (MD -0.4 mm Hg; 95% CI -3 to 2).

4.8.9 Subgroup analysis: Astragalus membranecus and FBG

Astragalus membranecus was present as a main ingredient in five of the trials and it was analysed in a subgroup analysis. In three of these trials with Astragalus membranecus there was a significant difference of combined herbal medicine with lifestyle interventions in FBG compared to the control (Wang 2005; Zhou 2003). However, the remaining three trials did not detect a significant difference (Fan GJ 2004; Li 2004; Tang 2007).

*Herbal medicine plus lifestyle modification versus placebo plus lifestyle modification*
Two trials compared a Chinese herbal medicine with placebo with the co-intervention of lifestyle modification.

Danzhi jiangtang jiao capsules (Fang 2007) combined with lifestyle modification were significantly better than a placebo and lifestyle modification in improving 2hr-oGTT blood glucose (MD -1.44 mmol/L; 95% CI -2.01 to -0.87). But there was no significant difference between the groups in reducing fasting blood glucose (MD -0.40 mmol/L; 95% CI -0.83 to -0.03). Triglycerides and insulin levels also showed significant reductions.

Bofu-Tsusho-San (Hioki C 2004) significantly improved fasting blood glucose (MD -0.28 mmol/L; 95% CI -0.46 to -0.10) but not 2hr-oGTT blood glucose (MD -0.12 mmol/L; 95% CI -0.60 to 0.36). There was no significant difference in the HbA1c between those taking Bofu-Tsusho-San and the control group. There was no significant difference in cholesterol levels found in the trial of Bofu-Tsusho-San, and while Bofu-Tsusho-San did not show an improvement in total cholesterol outcomes it demonstrated a significant difference in increasing HDL-cholesterol (MD 0.25 mmol/L; 95% CI 0.12 to 0.38).

Herbal medicine plus lifestyle modification versus metformin plus lifestyle modification

There was no significant difference in the 2-hr glucose tolerance test levels between Tangping san plus lifestyle modification and metformin plus lifestyle modification at the end of the three months intervention. No other outcomes were reported for Tangping San (Qu 2002).

Herbal medicine versus placebo

Compared with placebo, those taking Qi wei tang ping capsules (Wang 2008) showed significantly better results for fasting blood glucose and 2hr-oGTT blood glucose. There was a significant higher level of normalisation of fasting blood glucose compared to placebo (RR 2.94, 95% CI 1.47 to 5.87). There was no significant difference in BMI or waist-to-hip ratio in the herbal medicine group compared to those taking placebo.

Herbal medicine versus metformin
Chapter 4 Chinese Herbal Medicines for People with Impaired Glucose Tolerance or Impaired Fasting Blood Glucose - A Systematic Review

There was no significant difference between Fufang cangzhu decoction and metformin in reducing fasting blood glucose, cholesterol, triglycerides, insulin, weight, or waist-to-hip ratio (Shi J 2005). We were unable to ascertain if this comparison was constructed as a non-inferiority trial.

**Herbal medicine plus lifestyle modification versus acarbose plus lifestyle modification**

There was no significant difference between the Jian Pi Zhi Shen Huo Xue (Tang 2007) and acarbose in any of the outcome measures (FBG, 2hr-oGTT blood glucose, insulin, lipids or HbA1c). There was also no significant difference between Jian Pi Zhi Shen Huo Xue and acarbose regarding the normalisation of fasting blood glucose (Tang 2007).

**Herbal medicine plus antihypertensive medication versus antihypertensive medication alone**

The Chinese herbal medicine, Yi Qi Yang Yin Huo Xue combined with antihypertensive medication was significantly better than the antihypertensive medication alone in reducing fasting blood glucose (one trial, MD -0.96 mmol/L, 95% CI -1.55 to -0.37). Yi Qi Yang Yin Huo Xue was also significantly better than the control in reducing cholesterol, triglycerides and increasing HDL-cholesterol. There was no significant difference between Yi Qi Yang Yin Huo Xue and the control in regard to systolic or diastolic blood pressure. This trial also evaluated quality of life using an instrument comprised of eight scales designed for hypertension based on a study of an American hypertensive population (Testa 1989) and validated for a Chinese population (Du 1994). The trial found that on the five of the eight scales: physical symptoms distress scale, sexual symptoms distress scale, sleep dysfunction scale, positive symptom scale and working performance, there was a significant difference in favour of the herbal medicine group (Lu X 2005). There was no significant difference in the measures of life satisfaction scale, social participation scale and general well-being adjustment scale. However, it was difficult to disentangle the effects of the various compound on quality of life. This study reported that there were no adverse renal or liver findings and in ECG tests.

**Herbal medicine plus basic education versus basic education alone**
In this comparison one study compared Jinqi Jiang Tang tablets with a control with a co-intervention of basic education about IGT (Wang 2005). This did not involve diet or exercise instruction. Normalisation of blood glucose was significant (RR 10.80; 95% CI 3.47 to 33.66) as was the incidence of diabetes (RR 0.44; 95% 0.22 to 0.87) and reduction of fasting blood glucose (MD -0.88; 95% CI -1.14 to -0.62) and 2-hr oGTT. There was a significant reduction in triglycerides but not total cholesterol in the intervention group compared to the control.

Adverse events

Five of 17 trials reported outcomes for adverse events. In the trial of Bufo-Tsusho-San there were four withdrawals; three from the treatment group for non-compliance because of loose bowels. In Wang there were two instances of abdominal discomfort, one participant from each group (Wang 2008). In the two other studies recording outcomes for adverse events none were reported (Wei 2001; Lu X 2005). In the trial of Jinqi Jiangtang (Wang 2005) three cases in the intervention group developed mild gastro-intestinal symptoms in the early stage of taking the Chinese herbal medicine. These resolved after one to two weeks.

4.9 Discussion

4.9.1 Summary of main results

Sixteen randomised trials were included in this review. There was considerable clinical heterogeneity in the interventions of the included studies. In the 16 studies lasting four weeks to two years there were eight different comparisons, with 15 unique herbal formulations investigated.

In this systematic review we found evidence from eight trials that Chinese herbal medicines combined with lifestyle modification were significantly better at normalising blood glucose levels then lifestyle modification alone (RR 2.07; 95% CI 1.52 to 2.82). In a meta-analysis of eight trials, those receiving Chinese herbs were also more likely to have a reduced incidence of diabetes (RR 0.33; 95% CI 0.19 to 0.58). In the pooling of the results for the meta-analyses of the two measures of normalising blood glucose and incidence of diabetes there was no considerable statistical heterogeneity among the comparisons ($I^2 = 66\%$ and $I^2 = 0\%$,
respectively). It is important to note that there is a clinical difference in the herbal composition of these interventions and likely a difference in the active components. But these Chinese herbal medicines are not completely dissimilar. They form part of a 'group' of herbal medicines with hypoglycaemic effects designed to normalised elevated blood glucose and prevent diabetes. The population groups according to age, gender and ethnicity were similar. However, any pooled effect size should be interpreted only as a crude indicator of the overall direction of the findings. Further, all of these trials had a high risk of bias. Specifically, none of these trials were blinded and three of the trials reported unclear randomisation procedures. Nevertheless, these findings indicate that participants receiving Chinese herbs were less likely to develop diabetes and more likely to have normal blood glucose than those in the control group. The result therefore provides guidance for future research not for specific clinical practice.

Xiaoke huayu tablets (Hao 2004), Xiaoke Yuye decoction (Wei 2001) and Jian Pi Zhi Shen Huo Xue (Tang 2007) combined with lifestyle modification were all statistically significant in reducing glycosylated haemoglobin A1c (HbA1c) compared to the control of lifestyle modification alone.

Compared with placebo and lifestyle modification, Danzhi jiangtang jiao capsules (Fang ZH 2007) with lifestyle modification were significantly better at reducing 2hr blood glucose after oral glucose tolerance testing (oGTT). Bofu-Tsusho-San (Hioki C 2004) combined with lifestyle modification was significantly better at reducing fasting blood glucose (FBG).

Compared with placebo alone, Qiweitang ping (Wang 2008) was significantly better at normalising blood glucose, reducing FBG and 2hr-oGTT blood glucose.

Three trials compared Chinese herbal medicines with a pharmaceutical control. However, these were not clearly specified as non-inferiority or equivalence trials. Compared with metformin, Fufang cangzhu (Shi J 2005) showed no significant difference in reducing FBG. Compared to metformin combined with lifestyle modification, Tangping san (Qu LX 2002) combined with lifestyle modification showed no significant differences in reducing 2hr-oGTT blood glucose.
There was no significant difference between Jian Pi Zhi Shen Huo Xue (Tang 2007) compared to acarbose, with both groups receiving lifestyle modification, on any of the outcome measures.

In a trial of an antihypertensive pharmaceutical the combination of Yi Qi Yang Yin Huo Xue (Lu X 2005) with the antihypertensive drug was significantly better at reducing FBG, cholesterol, triglycerides and HDL-cholesterol than the antihypertensive drug alone.

Some of the Chinese herbal medicines showed potential for improving cholesterol and triglycerides along with normalising FBG. Jian Pi Zhi Shen Huo Xue, Jiangtang bushen tang, Tang Kang Yin, Liu Wei Di Huang Tang, and Xiaoke huayu pian all showed a significant improvement compared to the control in reducing total cholesterol and triglycerides.

4.9.2 Overall completeness and applicability of evidence

The age and gender of participants in the included trials was representative of the general global population showing IGT (IDF 2008). All but one trial were conducted in a Chinese population. Ethnic differences exist with regard to BMI, diabetic control as reflected by HbA1c levels and these may impact on the applicability of interventions (Hong 2004).

4.9.3 Quality of the evidence

Thirteen of the 16 trials included in this review demonstrated a risk of bias in at least two of several key criteria: random sequence generation; allocation concealment; blinding of participants, outcome assessors and intervention providers; incomplete outcome data; selective outcome reporting; and other sources of bias (see Figure 4-2).

Details of sequence generation and concealment allocation were only reported in one of the published papers. Trial authors were contacted to clarify details. We found that nine trials had used adequate sequence generation methods (Fan GJ 2004; Fang ZH 2007; Hioki C 2004; Lu X 2005; Wang 2008; Wei 2001; Yang B 2004; Zeng 2006; Zhou 2003). Allocation concealment was less frequently understood or adequately
performed, with only five of the trial authors providing satisfactory details when questioned (Fang ZH 2007; Hioki C 2004; Wang 2008; Wei 2001; Zeng 2006). Empirical evidence suggests that failure to meet these criteria, such as adequate allocation concealment, is associated with overestimates of effect.

In clarifying risk of bias with authors it was apparent that the concept of randomisation was not always fully understood. Of the 83 full papers retrieved, 34 claimed to be randomised but after contacting authors only 17 of these were truly randomised (50%). This is lower than the findings of a Cochrane review of Chinese herbal medicines for the treatment of common cold which found more than 95% of the authors misunderstood the concept of randomisation (Wu 2007).

Overall only three of the 16 included trials were well designed and had a fairly low risk of bias (Fang ZH 2007; Hioki C 2004; Wang 2008). The insufficient number of trials prohibited us from performing meaningful sensitivity analyses to clarify robustness of the review results to the exclusion of trials with inadequate methodology.

The double-blind, placebo controlled trial of Dan zhi jiang tang jiao (Fang ZH 2007) reported a significant improvement in 2 hr-oGTT blood glucose, insulin and triglycerides but there was no significant difference in fasting blood glucose. The method of sequence generation and allocation concealment was not reported in the trial but deemed adequate after an interview with one of the authors.

A second double-blind trial compared Bofu-Tsusho-San plus lifestyle modification versus placebo plus lifestyle modification in 81 people over six months. People randomised to Bofu-Tsusho-San plus lifestyle modification demonstrated a significantly improved fasting blood glucose but not 2hr-oGTT blood glucose (Hioki C 2004). There was no significant difference in glycosylated haemoglobin A1c (HbA1c) between those taking Bofu-Tsusho-San and the control group.

The third double-blind trial, comparing Qi wei jiangtang yin with placebo, demonstrated a significant improvement in the rate of normalisation of fasting blood glucose, reduction of fasting blood glucose, and 2hr-oGTT (Wang 2008) in those randomised to the placebo group. This trial had a duration of 24 months and a low risk of bias as well as an adequately powered sample. However, as there are no other
trials of this herbal medicine in this population group, these results cannot be seen as definitive.

There were few trials (n = 4) that collected HbA1c data. This will be an important outcome measure to collect in future trials. According to the American Diabetes Association Expert Committee on the Diagnosis of Diabetes, the European Association for the Study of Diabetes, and the International Diabetes Federation, the HbA1c will become the preferred diagnostic test for diabetes (ADA 2009).

In many of the trials it is possible that the statistical power may not have been adequate. Several studies have reported rates of natural reversion to normal glucose levels of one third to one half for participants identified with IGT (Forrest 1988; Riccardi 1985). Moreover, rates of reversion to normal glucose levels appeared independent of the duration of follow-up, with a range of two months to 10 years (Rambod 2009). The rate of reversion needs to be built into statistical calculations of the power required to detect a difference in blood glucose and other outcomes.

Twelve of the 16 trials had lifestyle modifications as a co-intervention, all but two trials failed to provide any details on the nature of this intervention. Without thorough details, replication of the trials to build evidence for these interventions is not possible. Further this operates as a potentially confounding factor and calls into question the veracity of the results.

Overall the positive evidence in favour of Chinese herbal medicines for the treatment of impaired glucose tolerance is constrained by the following factors: a lack of trials that tested the same medicine, lack of details on co-interventions, unclear methods of randomisation, poor reporting and other risks of bias.

4.9.4 Potential biases in the review process

We have tried to reduce bias by contacting all trial authors to clarify the methods of randomisation. In this way we were able to eliminate trials that were only quasi-randomised. Nonetheless we were unable to contact the authors of five of the included trials to clarify the methods of randomisation (Hao 2004; Li 2004; Qu LX 2002; Wang 2005).
4.9.5 Agreements and disagreements with other studies or reviews

As far as we are aware of, no systematic review has been done with a focus on Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting glucose.

4.10 Conclusions

4.10.1 Implications for practice

The available evidence suggests that some Chinese herbal medicines could be considered as a potential treatment in people with impaired glucose tolerance and reduce the incidence of diabetes. Given the sources of potential bias further evidence is required to confirm these trends. A separate systematic review on the efficacy of lifestyle education concluded that lifestyle education was clearly effective for reducing two-hour plasma glucose after an oral glucose tolerance test and the incidence of type 2 diabetes over one year (Yamaoka 2005). Our review adds to this growing body of evidence, in 80% of the included trials lifestyle modification was used as a co-intervention.

4.10.2 Implications for research

Further trials are required before any conclusions can confidently be reached about the effects of Chinese herbal medicines for the treatment of impaired glucose tolerance and the delay of diabetes onset.

Future trials need to be designed in such a way as to address the risk of bias identified in the trials reviewed here. It is essential that such trials have adequate methods of randomisation and allocation concealment and that these methods are clearly reported. Ideally, future trials will involve a control of a pharmacological nature or be placebo-controlled. The Chinese herbal medicines and the control intervention need to be manufactured in such a way that participants and intervention providers can be blinded. If a lifestyle modification is to be used as a co-intervention or control this should be described in detail. The rate of reversion to normal blood glucose needs to be built into statistical calculations of the power of the trial required
to detect a difference in blood glucose and other outcomes. Along with fasting blood glucose outcomes, other measurements of efficacy and safety should include glycosylated haemoglobin A1c (HbA1c), health-related quality of life, death from any cause, diabetic complications, economic outcomes and adverse events.

All future Chinese herbal medicines trials should be reported according to the elaborated CONSORT statement for reporting randomised controlled trials of herbal medicines (Gagnier 2006).
CHAPTER 5

Individual Herbs for Prediabetes and the Herbal Composition of the Clinical Trial Formulation – Jiangtang Xiaozhi

An estimated 800-1200 medicinal plants have been reported to have anti-diabetic activity (Evans, 2009; Leach, 2007). Most commercially manufactured drugs were initially developed from medicinal plants (World Health Organisation, 2005). Of note, metformin, the current first line treatment for IGT and type 2 diabetes mellitus (diabetes), is derived from Galega officinalis (French lilac). Use of French lilac for diabetes-type symptoms has been recorded since medieval times (Witters, 2001).

Recognising the rich heritage of traditional medicine systems for treating diabetes, the World Health Organisation Study Group on diabetes recommended at its meetings of 1980, 1985 and 1994 that traditional treatments, including herbal treatments, be investigated further (World Health Organisation, 1985, 1999). While the WHO has yet to report on such further investigation there have been efforts made to review the safety and efficacy in humans of Chinese herbal treatments for diabetes and IGT (Yeh, Eisenberg et al. 2003; Liu, Zhang et al. 2004).

One of the aims of this thesis was to evaluate the effectiveness and safety of a Chinese herbal medicine, Jiangtang Xiaozhi. This chapter provides the scientific background and rationale for the clinical trial formula. Firstly, the context is set by introducing the research approaches to developing TCM formulations together with an explanation of the nomenclature and structural principles applied in this chapter. Then, the individual herbs that were prevalent in the herbal formulas in the clinical trials reviewed in Chapter 3 and Chapter 4, are examined together with the herbs not otherwise mentioned but which are part of the Jiangtang Xiaozhi formula. The evidence from mechanistic studies, traditional uses, phytochemical constituents and available toxicity information of these individual herbs is presented. Greater detail is provided on the herbal components of Jiangtang Xiaozhi. The final section presents the preclinical and unpublished clinical trial data for Jiangtang Xiaozhi. The chapter
concludes with a summary of the pharmacological rationale for the clinical trial formula.

### 5.1 Approach

The development of new treatments for disease revolves around the randomised controlled trial. As discussed in Chapter 3, this methodology has multiple limitations when investigating the efficacy of TCM. At the time the present research on Jiangtang Xiaozhi was conceived, other available research designs for investigating the efficacy of TCM had not achieved adequate peer consensus nor were they in common usage. Whole systems research was at an early stage of development and expensive to undertake, and the rigor and robustness of pragmatic trial design was lacking (Ritenbaugh 2003; Verhoef, Lewith et al. 2005; Zwarenstein, Treweek et al. 2008).

Typically in the development of a pharmaceutical drug, research commences \textit{invivo} and \textit{invitro}, examining toxicology and determining the mechanism of action. These stages of development are outlined in Figure 5-1. This type of research seeks to identify the active substances of herbal treatments and investigate the mechanism of action (Tang, Wei, Chen, & Liu, 2006) and has become a common approach to the investigation of Chinese herbs. The decade since 2000 has witnessed an explosion of growth in numbers of \textit{invivo} and \textit{invitro} studies of herbs with hypoglycaemic properties (see for example Arun & Nalini, 2002; Babu & Srinivasan, 1997; Bebrevska et al., 2010; Chen, Feng, Guo, Sun, & Jiang, 2001; Chen et al., 2001; Chen, Li, & Yu, 2008). Mechanistic studies relevant to the development of Jiangtang Xiaozhi are summarised in the next section.

Traditional Chinese medicines are, almost by definition, already in use, and in some cases have been used for hundreds of years (Unschuld, 2003). Undertaking expensive \textit{invivo} and \textit{invitro} studies is not therefore necessarily a useful approach. In the absence of alternative appropriate research designs, the most common approach is to show efficacy in humans through randomised controlled trials. An efficacy based approach is outlined in Figure 5 1. Efficacy refers to the capacity of a drug to bring about more good than harm in human subjects (Tang, 2006). The development of
our clinical trial formula, Jiangtang Xiaozi, has been guided by the conceptual principles of an efficacy based approach though without the distinctly linear fashion presented below.

**Figure 5-1.** Comparison of approaches to research on novel and traditional treatments. Source: Tang, 2006

It is important to appreciate that most Chinese medicinal herbs contain between 11 and 50 reported compounds which in turn represent only a fraction of the total constituents of each herb, and some of which are found in more than one herb (Ehrman, Barlow, & Hylands, 2007). Ehrman and colleagues have mapped and categorised traditional Chinese herbs into a comprehensive database of over 9000 compounds from 240 of the most commonly used and adequately documented Chinese herbs. According to Ehrman and colleagues there are 10 major phytochemical classes with distinct TCM profiles. These classes are:

1. Aliphatics (including acetylenes) (574 compounds)
2. Alkaloids (861 compounds)

3. Simple phenolics (phenols, phenylpropanoids, coumarins and other small phenolics (1203 compounds)

4. Quinones (and related classes such as anthracenes) (276 compounds)

5. Lignans (327 compounds)

6. Polyphenols (flavonoids and tannins) (1162 compounds)

7. Monoterpenes (801 compounds)

8. Sesquiterpenes (881 compounds)

9. Diterpenes (388 compounds)

10. Triterpenes (including sterols) (1644 compounds)

This chapter uses the classification structure of Ehrman and colleagues, as far as possible, so as to bring consistency to documenting the rationale for the Jiangtang Xiaozhi formulation.

Nomenclature used in the English language literature for traditional herbs is at times inconsistent. For example the interchangeable common naming of three herbs of the genus Curcuma - Jiang huang, Yujin, and Ezhu – as turmeric has been described by Wiseman (2001). In this chapter, as throughout the thesis, the Latin binomial (Genus species) is given in italics together with the Chinese pinyin name in its first citation, and the pinyin name thereafter (with capitalized first letters). Where there are two or more pinyin names, the most common name found in Bensky (1993), this is a widely used English reference source on the Chinese material medica. An exception is made for Ren Shen (Panax quinquefolium & Panax ginseng) where the widely used generic “ginseng” is used except when species-specific differentiations are needed.
Chapter 5 Individual Herbs for Prediabetes and the Herbal Composition of the Clinical Trial Formulation – Jiangtang Xiaozhi

5.2 Individual Herbs

Chapter 3 described the results of 36 published controlled trials of Chinese herbal medicines for people with IGT. The herbs used in those trials are referenced in Table 5-1. Three of the 36 trials did not report the composition of their herbal formulae and therefore cannot be included in this analysis. Huang Qi appears in 22 of the 33 RCTs for which the information was available. Typically this herb was included in a large dosage. Shu Di Huang and Sheng Di Huang also appear frequently. Ge Gen, Shan Yao, Fu Ling, Tian Hua Fen and Huang Lian feature in over a third of the formulas. The six herbs used in the unpublished clinical trial of Jiangtang Xiaozhi are also included in Table 5.1. Of those herbs, three have not been previously reported in the treatment of IGT (Jiang Huang, Kun Bu and Li Zhi He). Table 5.1 provides a count of the frequency that each herb has been reported in the published trials. While a simple count of frequency of occurrence in controlled trials does not indicate efficacy of a herb it does direct attention to dominant rationale among contemporary researchers in the field.
Table 5-1. *Chinese herbs used in complex formulas in 33 controlled trials and one unpublished trial involving people with IGT*

<table>
<thead>
<tr>
<th>Herb</th>
<th>Reference to studies</th>
<th>Frequency$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai Zhu (<em>Atractylodis macrocephalae</em>)</td>
<td>(An SH, 2007; Li, Xu, Ling, &amp; Hu, 2002; Luo HX, 2008; Wei, Hong, &amp; Ye, 2008; Xin XX, 2007)</td>
<td>5</td>
</tr>
<tr>
<td>Ban Xia (<em>Pinelliae ternatae</em>)</td>
<td>(An SH, 2007; Li, et al., 2002; Luo HX, 2008; Xu YJ, 2008; Yuan WL, 2008)</td>
<td>6</td>
</tr>
<tr>
<td>Dang Shen (<em>Codonopsis pilulosa</em>)</td>
<td>(An SH, 2007; Li, et al., 2002; Wang, Jiao, &amp; Chen, 2008; Wei, et al., 2008; Xin XX, 2007)</td>
<td>5</td>
</tr>
<tr>
<td>Fu Ling (<em>Poria cocos</em>)</td>
<td>(An SH, 2007; Fang, 2007; Huang JX, 2003; Li &amp; Zhang, 2007; Li, et al., 2002; Tang et al., 2007; Wang YF, 2008; Xin XX, 2007; Xue LH, 2008; Yuan WL, 2008)</td>
<td>12</td>
</tr>
<tr>
<td>Huang Jing (<em>Polygonatum sibiricum</em>)</td>
<td>(Dai FF, 2005; Ding P, 2007; Fang, 2007; Liu, Wang, Kan, &amp; Zheng, 2007; Wei, Sun, &amp; Long, 2001)</td>
<td>5</td>
</tr>
<tr>
<td>Herb</td>
<td>Source</td>
<td>Trials</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Huang Lian (Coptis chinensis)</td>
<td>(Dai FF, 2005; Fan, et al., 2004; Liu, et al., 2007; Luo GB, 2005; Luo HX, 2008; Wei, et al., 2008; Xu YJ, 2008; Xue LH, 2008; Yang et al., 2004; Zhou ZN, 2001)</td>
<td>10 trials</td>
</tr>
<tr>
<td>Ge Gen (Pueraria lobata)</td>
<td>(An SH, 2007; Fan, et al., 2004; C. P. Li, et al., 2004; Li, et al., 2002; Luo HX, 2008; Wei, et al., 2008; Xu et al., 2008; Xue LH, 2008; Zhou ZN, 2001)</td>
<td>14</td>
</tr>
<tr>
<td>Jiang Huang</td>
<td>Unpublished trial of Jiangtang Xiaozhi only</td>
<td>0</td>
</tr>
<tr>
<td>Kun Bu (Ecklonia thallus)</td>
<td>Unpublished trial of Jiangtang Xiaozhi only</td>
<td>0</td>
</tr>
<tr>
<td>Li Zhi He (Litchi semen)</td>
<td>Unpublished trial of Jiangtang Xiaozhi only</td>
<td>0</td>
</tr>
<tr>
<td>Nu Zhen Zi (Ligustrum lucidum)</td>
<td>(Fan, Luo et al. 2004; Li CP 2004; Yang B 2004; Luo GB 2005)</td>
<td>4</td>
</tr>
<tr>
<td>Ren Shen (Panax ginseng)</td>
<td>(An SH, 2007; Liu, et al., 2007; Wang YF, 2008; Yang, et al., 2004)</td>
<td>4</td>
</tr>
</tbody>
</table>
### Notes.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
</table>

- **a** “Frequency” is a count of the number of times the herb has been reported as an ingredient in the controlled trials for people with IGT that were reported in chapter 3.
- **b** As an addition in Liu et al., 2007 and Luo HX 2008.
- **c** Sheng is the dried root, Shu is the steamed root.
- **d** As an addition Xue (2008)
The next section examines the individual herbs used in the published clinical trials of Chinese herbal medicines to treat people with IGT, as well as those components of the unpublished clinical trial formula, Jiangtang Xiaozhi. Table 5-2 provides a summary of major constituents and pharmacologic activities of those herbs. There was inadequate relevant data to report for six herbs: Bai Zhu, Ban Xia, Cang Zhu, Dang Shen, Shan Zha and Ze Xie. The six herbs that are part of the Jiangtang Xiaozhi formula are described in greater detail than the other herbs.

5.2.1 Shan Yao (*Dioscorea opposita*)

Shan Yao, a well-known edible and traditional medicinal plant available throughout most of China, is a variety of Chinese yam. There is little animal or clinical research into the action of Shan Yao in the treatment of impaired glucose tolerance or diabetes. The traditional functions of Shan Yao are to tonify the qi and to tonify the yin of the Lungs and the Kidneys (Bensky, 1993). Deficiency of both qi and yin are commonly seen in impaired glucose tolerance.

In an animal study to determine which of the six herbs in Liu Wei Di Huang Wan accounts for its beneficial effect on insulin resistance, Shan Yao was found to be the key herb (Hsu, Wu, Liu, & Cheng, 2007). Oral administration of Shan Yao into streptozotocin-induced diabetic rats for 10 days increased the response to exogenous insulin. This may mean the herb has potential for subjects who need to increase insulin sensitivity.
Table 5-2: Summary of major constituents and pharmacologic activities of Chinese single herbs prescribed for IGT with hypoglycaemic effects

<table>
<thead>
<tr>
<th>Herb: Pinyin (English/Latin Genus species)</th>
<th>No. of compounds&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Phytochemical constituents by major class&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Other key constituents</th>
<th>Relevant pharmacologic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang Qi (Astragalus membranaceus)</td>
<td>53</td>
<td>Triterpenes – saponins (a triterpene glycoside) esp astragalosides Flavonoids (polyphenol) Coumarin (simple phenolic)</td>
<td>Polysaccharides</td>
<td>Immune potentiating activity and wide range of other effects but little documented of glycemic or insulin related effects.</td>
</tr>
<tr>
<td>Jiang Huang (Curcuma longa)</td>
<td>49</td>
<td>Sesquiterpenes</td>
<td>Curcuminoides, volatile oil</td>
<td>Activates PPAR-y within cells; activates AMPK; anti-oxidant and anti-inflammatory</td>
</tr>
<tr>
<td>Huang Lian (Coptidis chinensis)</td>
<td>26</td>
<td>Alkaloids</td>
<td></td>
<td>Berberine is a much investigated quaternary ammonium salt from Huang Lian with multiple effects including anti-inflammatory properties.</td>
</tr>
<tr>
<td>Shan Yao (Dioscoreae opposita)</td>
<td>14</td>
<td>Triterpenes – saponins (a triterpene glycoside)</td>
<td>Choline, d-abscisin II, vitamin C, mannan, phytic acid, allantoin</td>
<td>Improves insulin sensitivity - limited research</td>
</tr>
<tr>
<td>Herb: Pinyin (English/Latin Genus species)</td>
<td>No. of compounds*</td>
<td>Phytochemical constituents by major class</td>
<td>Other key constituents</td>
<td>Relevant pharmacologic activity</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------------------</td>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Ren Shen (<em>Panax quinquefolium</em> &amp; <em>Panax ginseng</em>)</td>
<td>126</td>
<td>Triterpenes – saponins (a triterpene glycoside); ginsenoside (also a triterpene glycoside)</td>
<td>Polysaccharides</td>
<td>Activates fatty acid oxidation pathways by increased AMPK; enhances mitochondrial function by upregulation of mitochondrial biogenesis; augments GLUT4-mediated glucose utilization in skeletal muscle.</td>
</tr>
<tr>
<td>Huang Jing (<em>Polygonatum sibiricum</em>)</td>
<td></td>
<td>Triterpenes - steroidal saponins</td>
<td>Azetidine-2-carboxylic acid, aspartic acid, homoserine, diaminobutyric acid, digitalis glycoside</td>
<td>Inhibits activity of α-glucosidase in digestive canal; improves metabolism of glucose and triglyceride; increases insulin secretion from beta-cells; may restore damaged islets</td>
</tr>
<tr>
<td>Fu Ling (<em>Poria cocos</em>)</td>
<td>21</td>
<td>Triterpenes incl sterols</td>
<td>polynsaccharides, several organic acids such as tumulosic acid, eubricoic acid, pinicolic acid, and pachymic acid, lecithin, gum, choline</td>
<td>Inhibits BBMV glucose uptake and stimulates GLUT4 glucose uptake</td>
</tr>
<tr>
<td>Ge Gen (<em>Puerariae lobata</em>)</td>
<td>49</td>
<td>Flavonoids (polyphenol)</td>
<td></td>
<td>Stimulates antioxidant enzymes; potentiates insulin-induced preadipocyte differentiation; promotes glucose-uptake of adipocytes; promotes PPARγ expression</td>
</tr>
<tr>
<td>Herb: Pinyin (English/Latin Genus species)</td>
<td>Phytochemical constituents by major class&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Other key constituents</td>
<td>Relevant pharmacologic activity</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------</td>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>Nu Zhen Zi (Ligustrum lucidum)</td>
<td>Flavonoids (polyphenol)</td>
<td>Glycosides and volatile oil.</td>
<td>May stimulate secretory ability of the islet cells of rats with STZ-induced diabetes; may promote the replenishment of b-cell mass.</td>
<td></td>
</tr>
<tr>
<td>Di Huang (Rehmanniae glutinosa)</td>
<td>Monoterpenes - iridoids esp iridoid monosaccharide glycoside (esp catalpol) Flavonoid</td>
<td>Polysaccharides; oligosaccharides; ionone glucosides, narcarotenoids</td>
<td>Stimulates insulin secretion and reduces liver glycogen content</td>
<td></td>
</tr>
<tr>
<td>Tian Hua Fen (Trichosanthis kirilowii)</td>
<td>Triterpenes – saponins (a triterpene glycoside)</td>
<td>Glycans: trichosans A, B, C, D and E</td>
<td>anti-hypoglycemic</td>
<td></td>
</tr>
<tr>
<td>Jiang Huang</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kun Bu (Ecklonia thallus)</td>
<td>Triterpene - Sterols</td>
<td>Polysaccharides esp fucoidans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li Zhi He (Litchi semen)</td>
<td>saponins</td>
<td>Essential oils contain alcohols, aldehydes, ketons, fatty acids, aliphatic esters and terpenes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes.

<sup>a</sup> from Bensky (1993) and the *Dictionary of Natural Products*;
<sup>b</sup> from Ehrman, Barlow & Hylands (2007); <sup>d</sup> from Yu et al. (2010)
5.2.2 Ren Shen (Panax quinquefolium and Panax ginseng)

Two types of ginseng have been studied in patients with diabetes and in animal models: Panax quinquefolium (American ginseng) and Panax ginseng (Korean, Chinese or Siberian ginseng). Each type of ginseng differs in the potency of the multiple biologically active components. Further, researchers have noted that different ginseng batches of the same type have variable pharmacologic efficacies (Sievenpiper, Arnason, Leiter, & Vuksan, 2003).

Ginseng extracts from all parts of the plant – berry, root and leaf – have been found to exert an anti-hyperglycaemic effect (Li, Zheng, Bukuru, & De Kimpe, 2004). The active constituents of ginseng include the phytochemicals saponin ginsenoside and the polysaccharides.

While the saponin ginsenoside is thought to be key to ginseng’s clinical efficacy in diabetes, it is likely mediated by multiple chemical constituents (Vogler, Pittler, & Ernst, 1999). The component panaxans (panaxans A to E) elicit hypoglycemia in both normal and diabetic mice (Ng & Yeung, 1985); the component adenosine inhibits catecholamine-induced lipolysis; and a component of ginseng, DPG-3-2, promotes insulin secretion in diabetic and glucose-loaded normal mice (Waki, Kyo, Yasuda, & Kimura, 1982). This is probably by enhancing insulin sensitivity, and directly or indirectly regulating the enzymes involved in glucose metabolism (Suzuki & Hikino, 1989).

Polysaccharides in Panax quinquefolius have also been shown to markedly increase insulin production and reduce the death of pancreatic β-cells (Wu, Luo, & Luo, 2007).

Panax ginseng improved insulin sensitivity and attenuated the development of diabetes in an obese diabetes animal model. This was thought to be due to: (a) increased energy expenditure with loss of adipose tissue; (b) activation of the fatty acid oxidation pathways by increased AMPK (adenosine monophosphate–activated protein kinase) activity, (c) enhanced mitochondrial function by upregulation of mitochondrial biogenesis, and (d) augmented GLUT4-mediated glucose utilization in skeletal muscle (Lee et al., 2009).
There have been a number of clinical trials conducted on the efficacy of ginseng in cardiovascular disease and a small number in diabetes. In a systematic review of RCTs of ginseng for cardiovascular risk factors, reductions in postprandial blood glucose levels in patients with and without diabetes were found. However, the total sample size and trial number were too small to conduct a meta-analysis (Buettner, Yeh, Phillips, Mittleman, & Kaptchuk, 2006).

The few controlled clinical trials of the use of ginseng in people with diabetes frequently used small samples (Xie, 2005). A small 12 week trial found no change in the primary endpoint of HbA1c but post prandial glucose regulation and serum insulin were improved (Vuksan et al., 2008). Another double blind, RCT conducted over 8 weeks did report a positive effect of ginseng on HbA1c levels as well as a reduction in plasma glucose in diabetes patients (Sotaniemi, 1995).

In a 2 year study, 14 out of 133 participants consuming higher than normal doses of ginseng (15 g per day) reported side effects that included hypertension, gastrointestinal disturbances, insomnia and nervousness. The validity of these observations is difficult to evaluate because of the absence of a placebo treatment in the study (Kitts & Hu, 2000). Ginseng may contain an estrogenic effect and an endocrine active substance which can affect neonate development.

### 5.2.3 Fu Ling (Poria cocos)

Fu Ling is a saprophytic fungus that grows on the roots of old, dead pine trees. Fu Ling has been used in traditional Chinese medicine to treat a wide variety of diseases, diabetes, dysentery, chronic fatigue syndrome, diarrhoea, dizziness, oedema, insomnia, kidney problems, nervousness, urination problems, and weakness (Lu, Cheng, Lin, & Chang). It commonly features in herbal formulations for treating diabetes and prediabetes.

For an agent to be antidiabetic, inhibitory effects on the brush border membrane vesicles (BBMV) glucose uptake are thought to be desirable. In an in vitro study, Fu Ling
significantly inhibited BBMV glucose uptake and stimulated Glut-4 glucose uptake (Lau et al., 2008).

Dehydrotrametenolic acid from Poria was found to promote adipocyte differentiation in vitro and improve oral glucose tolerance in db/db mice (Sato et al., 2002).

We did not locate any clinical studies of Poria as a single herb in the treatment of diabetes.

### 5.2.4 Huang Jiang (Polygonati Rhizoma)

Huang Jiang grows wild and is cultivated in most areas of China. It has been used traditionally for hundreds of years to treat many diseases, especially tuberculosis and diabetes.

Huang Jiang may influence hyperglycaemia in diabetic animals by inhibiting the activity of α-glucosidase in digestive canal, and improving the metabolism of glucose and triglyceride (Chen, Feng, Guo, Sun, & Jiang, 2001). In another animal study using the flavonoids extracted from *Polygonati rhizome* it was also found that insulin secretion increased from the β-cells of the islets of Langerhans (Shu et al., 2009). It has also been proposed that Huang Jiang may restore damaged islets (Chen, Feng, Guo, Sun, & Jiang, 2001).

In a study of a new herbal formula (NHF) consisting of Huang Jiang, Di Huang, Huang Qi, Ge Gen, Wu Wei Zi, and Gan Cao, diabetic rats administered NHF for 4 weeks showed significant decreases in blood glucose, significant increases in plasma insulin and the number and size of insulin-immunoreactive cells in the pancreas of diabetic rats (Kim, Kim, Lee, & Kwon, 2009). There was no attempt in this study to isolate the effects of each component herb.

Some clinical studies have shown that an extract from Huang Jiang reduced serum cholesterol, triglyceride and blood glucose levels in hyperlipidemia patients (Miura and Kato 1995; Chen, Feng et al. 2001).
In an acute toxicity test, the dose of Huang Jiang in mice was 64.5 g/kg (crude drug, equal to 150x human dose). The dose did not induce any toxicity sign or death in mice. In the chronic toxicity test, the dose used in rats was 120 times that of the human dose and did not induce abnormalities in haemology, blood biochemistry, autopsy, histopathology, appearance, behaviour and body weight of rats except for loose stools (Chen, Feng, Guo, Sun, Zhou, et al., 2001).

### 5.2.5 Ge Gen (*Puerariae lobata*)

The roots as well as flowers of this plant are medicinally used. The genus Pueraria is a rich source of isoflavonoids. Investigations into the effect of Ge Gen on diabetes is rather limited, with the bulk of research into this herb focusing on its antidipsotropic properties (Sieveking et al., 2005). However, it is one of the most commonly cited herbs in the ancient texts for the treating “wasting and thirsting disease” or diabetes (Flaws, Kuchinski, & Casanas, 2002). It also appeared frequently in the herbal formulas analysed in Chapter 3.

An animal study using a flavonoid extract from Ge Gen, kakonein, showed it was effective in lowering the blood glucose of alloxan induced diabetic mice (W. L. Li, et al., 2004). An intravenous injection of puerarin, another extract of Ge Gen, decreased the plasma glucose concentrations in a dose-dependent manner in STZ-diabetic rats and in normal rats, (Hsu, 2003). Ge Gen significantly inhibited the apoptosis of pancreatic islets in hydrogen peroxide (H$_2$O$_2$)-induced rat pancreatic islets damage. The mechanism of action was possibly due the stimulation of antioxidant enzymes (Xiong, 2006). Ge Gen also seems to potentiate insulin-induced preadipocyte differentiation, promote glucose-uptake of adipocytes and promote PPARγ expression (Xu et al., 2005).

The oral administration of a daily dose of 500 mg/kg of Ge Gen root extract over 3 weeks, resulted in the reduction of malondialdehyde in plasma, a marker of oxidative damage to lipids (Bebrevska et al.). There have been no clinical studies on Ge Gen as a single herb for diabetes.
5.2.6 Tian Hua Fen (*Trichosanthis kirilowii*)

The roots of Tian Hua Fen feature in many prescriptions for diabetes therapy in China (Flaws, et al., 2002). Research *in vivo* and *in vitro* of this herb for diabetes is almost non-existent. What we do know is that the glycans (trichosans A, B, C, D and E) showed an anti-hypoglycemic effect in normoglycemic mice (Li, et al., 2004). The main glycan, trichosan A, also exhibited activity in alloxan-induced hyperglycemic mice (Hikino, Yoshizawa, Suzuki, Oshima, & Konno, 1989). There were no clinical trials of this herb for diabetes.

5.2.7 Di Huang (*Rehmanniae glutinosa*)

Di Huang is cultivated throughout China as a medicinal herb and is widely used in Chinese herbal formulas for diabetes and prediabetes. The main active ingredient is likely to oligosaccharide. The root of Di Huang is used for different purposes when dried (Sheng Di Huang) as opposed to steamed (Shu Di Huang).

*In vivo* studies of extracts of Di Huang show that the mechanism of the hypoglycaemic activity is through the stimulation of insulin secretion and the reduction of the glycogen content in the liver (Li, Zheng et al. 2004; Zhang, Li et al. 2008). Di Huang has demonstrated a significant hypoglycaemic effect in both normal and alloxan-induced diabetic rats (Zhang, Zhou, Jia, Zhang, & Gu, 2004).

In another study, Di Huang was effective in promoting diabetic foot ulcer healing in rats through the processes of tissue regeneration, angiogenesis and inflammation control, but not glycaemia control (Lau et al., 2009). Di Huang inhibited the progression of diabetic nephropathy in *in vitro* studies (Yokozawa, Hyun Young, & Yamabe, 2004).

A combination of the herbs *Galla rhois, Rehmanniae radix, Machilus bark, Ginseng radix, Polygonatum radix,* and *Scutellariae radix* improved IRS2 induction in rat islets, glucose-stimulated insulin secretion and β-cell survival. IRS2 in beta-cells plays an important role in potentiating beta-cell function and mass. *Rehmanniae radix, Ginseng radix* and
Scutellariae radix together significantly enhanced glucose-stimulated insulin secretion compared to control. The increased level of glucokinase could explain the enhancement of glucose-stimulated insulin secretion with these extracts (Park, Hong, Sung, Lee, & Kwon, 2008).

Herbal components of Jiangtang Xiaozhi

5.2.8 Nu Zhen Zi (*Ligustrum lucidum*)

Pharmaceutical name: Fructus Ligustri Lucidi

English: Privet fruit, ligustrum

Pharmacology

In an animal study of Nu Zhen Zi, a decoction of the herb (15.30 g/kg) given for 10 days significantly decreased the blood glucose level in normal mice (Hao, Hang, & Wang, 1992). A similar result was found in alloxan diabetic mice (Chen, 2004). It is thought that main active component is oleanic acid. In rats with streptozotocin-induced diabetes treated with oleanic acid (OA) from Nu Zhen Zi for 40 days, changes in blood glucose levels and in oral glucose tolerance tests were more pronounced than in the diabetic control rats. OA-treated rats also exhibited increased serum insulin levels (Gao et al., 2007). These findings are supported by other animal studies (Hao, et al., 1992). A more recent study showed that oleanic acid in Nu Zhen Zi could also protect the liver function avoiding alloxan-induced damage in the diabetic rats (Gao et al., 2009).

The mechanism of action is unclear but it has been proposed that oleanic acid treatment might stimulate insulin release and promote the replenishment of beta-cell mass and consequently, result in the modulation of glucose levels and regulation of lipid metabolism (Gao, et al., 2007).

Nu Zhen Zi also demonstrated a significant reduction in plasma cholesterol and triglycerides in an animal model (Chen, 2004). In another study, oleanic acid treated rats
had lower triglycerides, total cholesterol, and low-density lipoprotein cholesterol than those in the diabetic control rats (Gao, et al., 2007).

The ethanol extract of the fruits of Nu Zhen Zi exhibited strong antioxidant effect against hemolysis of red blood cells induced by free radicals (He & But, 2001). Other animal studies have found that Nu Zhen Zi is hepatoprotective (Yim & Wu, 2001), antiinflammatory (Dai & Hang, 1989) and immunomodulatory (Ruan & Lu, 1999). Clinical studies in the U.S and China suggest it helps raise white blood cell counts for leukopenia induced by chemotherapy and radiotherapy (Scheid, 2002). Other experimental studies have shown that the aqueous extract inhibits the growth of transplanted tumor cells in animals (Hsu, 1996).

The fruit of Nu Zhen Zi has been used in traditional Chinese medicine for over 1000 years for its anti-tumour, antimutagenic, antidiabetic, and hepatoprotective properties (Ma, 2001).

Traditional uses

Yin tonic. In traditional Chinese medicine, Nu Zhen Zi is bitter, sweet, and cool, it enters the Liver and Kidney channels. It is used for enriching and nourishing the liver & kidneys, to clear deficient heat and improve the vision. It is indicated for yin deficiency with symptoms such as dizziness, spots before the eyes, weakness of the lower back and legs, and premature graying of the hair, as well as nightsweats (Bensky, 1993).

Traditional contraindications: it should be used with herbs that protect the Stomach and Spleen, and combined with warming herbs, otherwise there is a concern it will cause abdominal pain and diarrhea.

Major chemical constituents

Organic acids: oleanolic acid, acetyl oleanolc acid, 2α-hydroxyoleanolic acid, nuezhenidic acid, ursolic acid, 19α-hydroxy-3acetylursolic acid, ligustrosidic acid.
Flavonoids, glycosides: cosmoslin, luteolin-7-glucoside, cyanide-3-glucoside, cyanide-3-rutinoside, maldiven-3-rutinoside-5-glucoside, nuezhenide, meonuezhenide, acteoside, oleuropein.

Volatile oil: acetaldehyde, hydrazine methyloxate, thiopropanone, 2-ethoxypropane, 1-methyl-1-propylhydrazine, 4-acetoxy-2-butanone, 1-ethoxybutane, 2-ethoxybutane, 2,3-dimethylpentane, 3-methyl-hexane, ethylacetate, 2-acetyloxy-1-phenylethanone, 1-phenyl-1,2-butanediol, 1,2-diphenyl-1,2-ethanediol.

Other constituents: hydroxyphenlethanol, fatty acids, phospholipids, polysaccharides, amino acids (Bensky, 1993).

Toxicity studies

Toxicity is considered very low (Chen, 2004; Duke, 2002). No side effects were observed following one-time ingestion of 75g of Nu Zhen Zi by rabbits (Chen, 2004).

5.2.9 Huang Qi (Astragalus membranaceus)

Pharmaceutical name: Radix astragali

English: astragalus, milkvetch root

Pharmacology

Huang Qi is indigenous to China, Mongolia, Korea and Siberia and is commercially cultivated for its medicinal properties. It features in many anti-diabetic and hypoglycaemic formulas.

As shown in Tables 5-1 and 5-2 Huang Qi appears in most herbal medicine formulas for diabetes. It has a known effect on insulin, and has a protective effect on beta-cells. Huang Qi contains abundant polysaccharides. Studies suggest that these polysaccharides act two-dimensionally to regulate the level of blood glucose: increasing the blood glucose of hypoglycaemic animals or humans to normal level, and significantly lowering the level of blood glucose in diabetic rats & mice (Li, et al., 2004). Results from several in vivo and in
vitro studies support the understanding that the polysaccharides in Huang Qi not only restore glucose homeostasis but also improve insulin sensitivity and reduce endoplasmic reticulum stress (Mao, Wu et al. 2007; Wang, Zhang et al. 2009). This activity may in part be by decreasing the elevated expression and activity of PTP1B (an insulin signaling gene) in the skeletal muscles of diabetic rats (Wu et al., 2005). PTP1B is a well-established drug target in the treatment of diabetes and obesity.

Astragaloside IV (AGS-IV), a new glycoside of cycloartane-type triterpene isolated from the root of Huang Qi, has been used experimentally for its potent immune-stimulating, anti-inflammatory, and antioxidative actions. The protective mechanism of AGS-IV involved a decrease in declining blood glucose concentration and HbA1C levels, and an increase in plasma insulin levels (Mankil et al., 2006).

Of note is the common combination of Huang Qi and Nu Zhen Zi in traditional diabetes formulas. This combination has been shown to inhibit growth of murine renal cell carcinoma in vivo (Lau, 1994). Sanhuang (Astragalus membranaceus, Coptis chinensis, Scutellaria baicalensis) inhibits platelet aggregation in patients as well as aspirin 50 mg/day (Huang, 1995).

Huang Qi may also exert its effect through selectively increase adiponectin secretion in primary adipocytes. Adiponectin is an adipocyte-derived insulin-sensitizing hormone with antidiabetic properties. In animal models, these changes were associated with an alleviation of hyperglycaemia, glucose intolerance, and insulin resistance (Xu et al., 2009).

Other animal studies have shown Huang Qi to be useful in reversing early diabetic nephropathy (Zhang, Xie et al. 2009; Li, Zheng et al. 2004).

There have been no clinical trials of Huang Qi, as a single herb, for the prevention or treatment of diabetes.

Traditional uses
Tonifies the qi and blood; tonifies Spleen & raises yang; augments protective qi and stabilize the exterior; promotes urination reduces edema; also used for wasting & thirsting disorder.

Traditional contraindications: should not be used for pathogenic excess in the exterior. It tonifies yang so if yang is overabundant and yin is deficient, or the upper burner heat is excessive and lower burner deficient and cold, it should not be used. The concern is that it will raise qi to the exterior, leaving the interior even more deficient (Bensky, 2004).

**Major chemical constituents**


**Flavonoids:** formononetin, formonononetin

**Other constituents:** amino acids (>19), choline, betaine, folic acid, palmitic acid, n-hexadecanol, β-sitosterol, daucosterol, coumarin, polysaccharides (Bensky, 1993).

**Toxicity studies**

Huang Qi has very low toxicity. The LD$_{50}$ in mice for intraperitoneal injection is approximately 40g/kg (Chen, 2004). No adverse effects were observed in mice after oral administration of up to 100g/kg, a dose several hundred times as high as the effective oral dose in humans (World Health Organisation, 1999). Allergic reactions have also been reported, including skin eruptions, pruritis, and anaphylactic shock. For this reason, the herb should be used with caution in treating patients with allergies (Bensky, 1993).

No adverse effects were observed in mice after oral administration of up 100g/kg of Huang Qi, a dose several hundred times as high as the effective oral dose in humans (World Health Organisation, 1999)

**5.2.10 Huang Lian (Coptis chinensis)**

Pharmaceutical name: Rhizoma Coptidis
**Pharmacology**

Huang Lian grows throughout China. Berberine constitutes the most abundant alkaloid in the dried herb. Berberine has shown convincing antidiabetic effects (Xiao, 2002). In alloxan induced-diabetic rats, Huang Lian extract significantly lowered blood glucose at all experimented doses, with the highest reduction at the highest dose (0.125, 0.25 and 0.5 g/kg.day) (Yuan, Tu, Ye, & Wu, 2006). The mechanism of action appears to be through free radical scavenging, beta-cell regeneration and decreasing lipid peroxidation (Kong et al., 2009; Tang, et al., 2006; Zhou et al., 2009). *In vivo* administration of berberine in both diabetic induced mice and high-fat-fed rats resulted in increased AMP-activated protein kinase (AMPK) activity, reduced lipid accumulation, reduced body weight and sensitised insulin (Lee et al., 2006). Activation of AMPK pathways in multiple tissues by berberine is similar to the action of metformin.

Berberine also enhances the hypoglycemic action of insulin in diabetic animal models (Huang et al., 2006).

Huang Lian appears to exert a protective affect on beta-cells. Rat islets pretreated with Huang Lian extract retained the insulin-secretion capacity. These results suggest that Huang Lian may be a candidate for a therapeutic agent for type 2 diabetes prevention. The research also indicated that it was compounds in Huang Lian other than berberine that exerted this effect (Kwon, 2005).

Berberine reduces serum cholesterol, triglycerides, and LDL-cholesterol of hypercholesterolemic patients and high fat diet fed animals, and increases hepatic LDLR mRNA and protein levels through a post-transcriptional mechanism.

Other known pharmacological effects include antibiotic, anti-inflammatory, antipyretic, anti-ulcer and hypotensive.
Huang Lian also exhibits cholesterol lowering properties, with serum cholesterol decreasing in a dose dependent manner (Tang, et al., 2006; Yuan, et al., 2006).

Clinical studies

Several clinical trials of berberine in the treatment of diabetes have been reported in Chinese. In one of the first clinical trials, 60 patients received 0.3-0.5g of berberine, three times daily. Fasting plasma glucose concentrations were reduced from 11.6 to 6.6 mmol/L for 1–3 months (Ni, 1988). There were similar findings in another trial of 40 people with diabetes who received 0.3 or 0.5g (3x/daily) for 2 months, without change in their previous therapy. Fasting and postprandial plasma glucose concentrations were reduced by 21% and 27%, respectively (Xie, 2005). Wei et al. (2004) reported that treatment with berberine (0.5 g, three times daily) for 2 months in 30 patients with diabetes and fatty liver decreased fasting plasma glucose, triglyceride, and total cholesterol concentrations (Wei, 2004). There was a good tolerance of berberine with only one adverse effect reported - mild gastrointestinal discomfort. All these clinical studies had a high risk of bias as none were randomised or placebo-controlled.

Two further clinical trials which were randomised have recently been conducted with positive results. Both were 3 month trials examining berberine. In the first study, 36 adults with newly diagnosed diabetes were randomly assigned to berberine or metformin (0.5 g 3 times a day) for 3 months. The hypoglycaemic effect of berberine was similar to that of metformin (Yin J, 2008). HbA1c, fasting plasma insulin and homeostasis model assessment (HOMA) of insulin resistance index were reduced. Total cholesterol and low-density lipoprotein cholesterol decreased significantly as well. In the second RCT, 116 patients with diabetes were randomised to receive berberine (1.0 g daily) or a placebo (Zhang et al., 2008). Berberine significantly reduced fasting and postprandial plasma glucose by 1.4 and 3.1 mmol, respectively, at 3 months and HbA1c by 0.9% from the initial levels of 7.5%. The HOMA values, serum fasting and postprandial insulin concentrations were not significantly different between the berberine and placebo groups at 3 months. Serum cholesterol, triglycerides and LDL levels all reduced.
Chapter 5 Individual Herbs for Prediabetes and the Herbal Composition of the Clinical Trial Formulation – Jiangtang Xiaozhi

Traditional uses

Huang Lian is very bitter and very cold. It enters the Heart, Liver, Stomach and Large Intestine channels. Major therapeutic actions in traditional Chinese medicine include: Clears heat & dries Dampness; drains Fire and resolves Toxicity. It is indicated for diarrhea or dysentery; acid regurgitation. Its strong bitter, cold and drying properties mean that it should be used in caution in those with Cold, and yin or yang deficiency (Murugan & Pari, 2006).

Major chemical constituents

Alkaloids: berberine (4-8%), coptisine (0.8-2%), epiberberine, beberrubine, palmatine (1-4%), columbamine, jatrorrhizine, worenine, magnoflorine, berberastine, groenlandicine;

Phenolic compounds: 3,4-dihydroxyphenethylalcoholglucoside, 3-carboxy-4-hydroxyphenoxyglucoside, ferulic acid;

Flavonoids: quercetin

Other compounds: lumicaeruleic acid, obakunone, obakulactone {Bensky D, 2004 #11} and (World Health Organisation, 1999).

Toxicity studies

The LD50 for berberine in mice is 24.3 mg/kg via intraperitoneal injection, with respiratory depression the main cause of death (Chen, 2004). Berberine was reported to be well tolerated in therapeutic doses of 500mg, and no serious intoxication was reported in humans (World Health Organisation, 1999). During one clinical trial, 20 (34.5%) patients experienced transient gastrointestinal adverse effects. Liver or kidney functions were normal for all patients (Yin J, 2008). Mild to moderate constipation was observed in five participants in the berberine group (Zhang, et al., 2008).

5.2.11 Li Zhi He (Litchi semen)

Pharmaceutical name: Semen Litchi
Chapter 5 Individual Herbs for Prediabetes and the Herbal Composition of the Clinical Trial Formulation – Jiangtang Xiaozhi

English: litchi seed, lychee seed

Pharmacology

The aqueous extract of Li Zhi He lowered blood glucose in normal and alloxan-induced diabetic mice, the hypoglycaemic effect was found to be similar to glibenclamide and phenformin (Li, Zhang et al., 2004). It is used as medicinal tablet to treat gestational diabetes in China. Administration of Li Zhi He to mice via subcutaneous injection lowered blood glucose levels (Chen, 2004). In another study, Li Zhi He reduced levels of TNF-alpha, hyper-leptinemia and hyperinsulinemia, antagonized insulin resistance, fortified insulin sensitivity, and improve functions of liver and kidney in type 2 diabetic rats (Guo, 2004).

Traditional uses

Li Zhi He is sweet, astringent and warm. It travels through the Liver and Stomach channels. In traditional Chinese medicine, Li Zhi He is used to move Qi, relieve pain, disperse Cold, and regulate Qi. It is indicated for hernial pain, chronic epigastric pain and pre-menstrual or post-partum abdominal pain. It is traditionally contraindicated in patients who do not exhibit cold and damp accumulation.

Major chemical constituents

Fixed oil: palmitic acid, oleic acid, linoleic acid, dihyrosterculic acid, cis-5,6-nethlenetetra-decanoic acid, cis-3,4-methylenetetradecanoic acid, cis-vaccenoic acid

Anthocyanes: cyaniding-3-rutinoside, cyaniding-3-glucoside, malvidin-3-acetylglucoside

Amino acids: α-(methylenecyclopropyl)glycine, asparagine, tyrosine, alanine, threonine, valine

Volatile oil: 2,3-butanediol, 3-acetoin, copaene, cis-caryophyllene, allo-aromadendrene, humulene, δ-cadinene, α-curcumene, calamenene, ledol, guaiazulene, xanthorrhizol

Other constituents: saponins, tannins (Bensky, 1993).
Toxicity studies

Li Zhi He is very well tolerated. There were no fatalities following administration of 20 g/kg in mice via oral ingestion (Chen, 2004).

5.2.12 Kun Bu (Eckloniae thallus)

Pharmaceutical name: Thallus Laminariae seu Eckloniae

English: laminaria, kelp, tangle

Pharmacology

In a clinical trial of a composite formula including Kun Bu and four other herbs in people with impaired glucose tolerance total cholesterol and triglycerides were reduced (Ling X, 2000).

Kun Bu has a known hypoglycaemic effect; and in vitro can reduce blood pressure. There is also some evidence that it can reduce serum cholesterol and triglycerides (Chen, 2004).

Traditional uses

Kun Bu is salty and cold, it enters the Kidney, Liver and Stomach channel. Its main actions in traditional Chinese medicine are to reduce Phlegm and soften nodules; promote urination and reduce swelling. The main indications are for hyperthyroidism and hypothyroidism (in different dosages), scrofula or goiter; and leg edema.

Major chemical constituents

Polysaccharides: alginic acid, alginates, fucansulfate B-I, B-II, C-I, C-II

Other constituents: eckol, 6,6-bieckol, dieckol, phlorofucoeckol A, 2-0-phloroeckol, 2-0-phloro-6,6-bieckol, histamine dihydroiodate (Bensky D, 2004).
Toxicity studies

Anecdotally Kun Bu is a very safe herb being consumed as kelp. However, no toxicity studies are available.

5.2.13 Jiang Huang (*Curcumae longae*)

Pharmaceutical name: Rhizoma Curcumae Longae

English: tumeric rhizome

Pharmacology

Jiang Huang, commonly known as turmeric, is native to southern Asia and cultivated extensively in India and China. More than 30 Curcuma species (Zingiberaceae) are found in Asia, where the tuber and the rhizomes of these plants are used as both food and medicine. Curcumin and tetrahydrocurcumin have been isolated as key active ingredients in Jiang Huang.

Jiang Huang is thought to regulate diabetes in several ways: reduction of inflammation, reduction of blood glucose levels, modulation of lipid profiles, prevention of pancreatic β-cell death and by increasing insulin (Aggarwal & Harikumar, 2009).

Jiang Huang’s capacity to reduce blood glucose levels in streptozotocin (STZ)-induced diabetic rats (Maiti, Mukherjee, Gantait, Saha, & Mukherjee, 2007) is thought to be derived from its powerful antioxidant activity in pancreatic β-cells, and enhancement of the activation of peroxisome proliferator-activated receptors (PPAR-γ) within cells (Nishiyama et al., 2005). Anti-diabetic drugs, thiazolidinediones (TZDs), act by binding to PPAR-γ. By activating PPARγ insulin resistance is decreased. Curcumin treatment reduces blood glucose in STZ-induced diabetic rats (Pari & Murugan, 2007; Thirunavukarasu, Murali Manoharan Sri, & Venugopal Padmanabhan, 2004). Curcumin ameliorated diabetes in high-fat diet-induced obese and leptin-deficient ob/ob mice (Weisberg, Leibel, & Tortoriello, 2008).
Chapter 5 Individual Herbs for Prediabetes and the Herbal Composition of the Clinical Trial Formulation – Jiangtang Xiaozhi

Jiang Huang’s hypoglycaemic effects are also in part due to a reduction in hepatic glucose production caused by activation of 5’ adenosine monophosphate-activated protein kinase (AMPK). AMPK inhibits of G6Pase activity and PEPCK activity, over-expression of the enzyme PEPCK can result in diabetes (Fujiwara et al., 2008). The net effect of AMPK activation is stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and the modulation of insulin secretion by pancreatic beta-cells.

Several studies have explored the anti-oxidative properties of curcumin. Mice given curcumin then exposed to STZ (which normally causes diabetes) had retarded islet reactive oxygen species (ROS) generation and apoptosis was inhibited. This indicated that the use of curcumin may rescue pancreatic islets from damage without affecting the normal function of these cellular structures. Curcumin was effective in preventing glucose-induced oxidative stress in the endothelial cells and in the heart of diabetic animals. In diabetic rats, curcumin prevented diabetes-induced decreased antioxidant enzyme levels, prevented oxidative stress on the endothelial cells, and prevented kidney dysfunction (Sharma, Kulkarni et al. 2006; Meghana, Sanjeev et al. 2007).

Jiang Huang has been found to be effective in animal models in attenuating diabetes mellitus-related microvascular and macrovascular changes (Arun and Nalini 2002; Sharma, Kulkarni et al. 2006; Aggarwal and Harikumar 2009). Curcumin has been shown to prevent the advanced glycated endproducts (AGE)-induced complications of diabetes (Sajithlal, Chithra, & Chandrakasan, 1998). Several animal studies have demonstrated the hypolipidemic activity of curcumin in rats with STZ-induced diabetes (Babu & Srinivasan, 1997; Murugan & Pari, 2006; L. Pari & Murugan, 2005).

The use of curcumin is also recommended for prevention of AGE accumulation and the associated complications of diabetes (Murugan & Pari, 2006). The effect of tetrahydrocurcumin (THC), one of the active metabolites of Jiang Huang was examined on the antidiabetic and antioxidant status in streptozotocin–nicotinamide induced diabetic rats. Oral administration of THC at 80 mg/kg body weight of diabetic rats for 45 days resulted in
significant reduction in blood glucose and significant increase in plasma insulin levels (Murugan & Pari, 2006)

In another study Jiang Huang’s EtOH extract significantly suppressed an increase in blood glucose level in type 2 diabetic KK-A(y) mice (Kuroda, 2005).

No clinical studies of the use of Jiang Huang, or the extract curcumin, have been conducted to ascertain it’s effectiveness in the treatment of people with diabetes or IGT.

*Traditional uses*

In traditional Chinese medicine, Jiang Huang is considered acrid, bitter and warm. It enters the Spleen, Stomach and Liver. Its main actions are to invigorate the Blood and unblock menstruation; promote the movement of Qi and alleviate pain; and expel wind and promote the movement of Blood. It is indicated for hypochondriac pain, epigastric pain, dysmenorrhea, and hepatitis with hypochondriac pain (Bensky D, 2004).

*Major chemical constituents*

**Curcuminoides:** curcumin, demethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin  
**Sesquiterpenes:** curlone, turmeronol, A, B, germacrone-13-al, 4-hydroxybisabola-2,10-diene-9-one, 4-methoxy-5-hydroxybisabola

**Volatile oil:** tumeron, ar-tumerone, germacrone, curcumene, arcurcumene, terpinene, curdione, curcumol, turmerone, cineole, caryophyllene, limonene, linalool, α-pinene, β-pinene, camphene, isoborneol

*Toxicity studies*

Jiang Huang has been demonstrated to be safe in six human trials and has demonstrated anti-inflammatory activity (Chainani-Wu, 2003). Administration of Jiang Huang 40-100 grams per day for 3 days did not lead to any fatalities in mice. Furthermore, administration of Jiang Huang to rats at dosages up to 50 times the normal dose range for humans for 30 days did not demonstrate any significant change in body weight, dietary habits, physical activities, or functioning of internal organs (Chen JP, 2004).
5.3 Clinical trial formulation – Jiangtang Xiaozhi

Jiangtang Xiaozhi has been used clinically for over a decade by the Xiyuan Hospital, Beijing to treat people with diabetes. The formula is constructed on the basis of both traditional principles, modern research and clinical experience. In part it tonifies the Spleen qi (Huang Qi), dries damp and clears heat (Huang Lian), while support yin (Nu Zhen Zi). There is also good evidence in animal studies for the effectiveness of these herbs in the treatment of impaired glucose tolerance. The inclusion of Li Zhi He, Kun Bu and Jiang Huang is based on evidence from animal studies and clinical experience while still addressing some classic actions such as regulating qi and blood.

5.3.1 Composition of Jiangtang Xiaozhi

Jiangtang Xiaozhi capsules are composed of six active herbs and one excipient (potato starch). The chemistry and production process of Jiangtang Xiaozhi are provided in Appendix B-1.

1. Nu Zhen Zi (Fructus ligustri Lucidi, *Ligustrum lucidum Ait.*), 12g
2. Huang Qi (Radix astragali, Astragalus membranaceus (Fisch.), Bge.var.mongholicus(Bge.) Hsiao Astraglus membranaceus(Fisch.)Bge.) , 9g
3. Huang Lian (Rhizoma coptidis, Coptis chinensis Franch. Coptis deltoidea C.Y.Cheng et Hsiao, Coptis teeta Wall.) , 3g
4. Li Zhi He (Semen Litchi, Litchi chinensis Sonn.) , 6g
5. Kun Bu (Thallus Laminariae seu Eckloniae, *Ecklonia kurome Okam.*), 4.5g
6. Jiang Huang (Rhizoma curcumae Longae, *Curcuma longa L.*), 4.5g

5.4 Preclinical Studies

Results from three preclinical animal studies indicate Jiangtang Xiaozhi is effective in treating elevated blood glucose and lipids (see Appendix B-2 for details).
In the first animal study, STZ-diabetic rats on a high sugar and fat diet were administered Jiangtang Xiaozi for two consecutive months. Blood glucose in Jiangtang Xiaozi capsule large dose group (group 5) decreased 31.23% (p<0.001) compared to that in the control group (type 2 diabetes established, no treatment). Blood lipids in Jiangtang Xiaozi capsule large (8g/kg) and medium (4g/kg) dose groups decreased (p<0.05~0.001) compared to the control group.

In the second study of immediate STZ diabetic rat model, different doses of Jiangtang Xiaozi were administered for 8 weeks. Blood glucose decreased significantly in the medium (4g/kg) and large (8g/kg) dose groups treated with Jiangtang Xiaozi. The third study was in a diabetic mice model (established by Alloxan). After one month of Jiangtang Xiaozi, significant reductions in blood glucose were seen in the medium (5g/kg) and large (10g/kg) dose and no change at the small dose (2.5g/kg).

5.5 Clinical Study

A randomised clinical trial (commercial-in-confidence) was conducted in XiYuan Hospital, Beijing to determine the effects of a Jiangtang Xiaozi formula on glycemic control, obesity, lipids and insulin sensitivity in 60 people with type 2 diabetes compared with Jin Qi Melbine.

Jin Qi Melbine (“Jin-Qi Traditional Chinese Tablet”) is a herbal formula approved by the Chinese Government for use in the treatment of type 2 diabetes. In a double-blind, placebo controlled trial with 216 people with type 2 diabetes for 3 months, Jin Qi decreased fasting blood glucose (Vray & Attali, 1995). The mechanism for action were not well reported but may include digestive carbohydrate absorption (Yeh, Eisenberg, Kaptchuk, & Phillips, 2003). The formula comprises Astragalus membranecus, Lonicera japonica and Coptis chinensis.

In the XiYuan trial the Jiangtang Xiaozi group received an 8 week treatment course. There was a significant 14% reduction in fasting glucose and an 8% reduction in HbA1C. This reduction was similar to the Jin Qi Melbine control group (Table 5-3). In subjects receiving
only the Jiangtang Xiaozhi and taking no other blood sugar lowering medication \((n=13)\), all glucose metabolic parameters decreased significantly \((P<0.01)\) after treatment. HDL and LDL cholesterol also improved significantly compared to pre-treatment.

**Table 5-3** Comparison of outcome measures before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Jiangtang Xiaozhi Group</th>
<th>Melbine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>BMI</td>
<td>27.26 ±2.65</td>
<td>26.70 ±2.55**</td>
</tr>
<tr>
<td>Fasting glucose ((\text{mmol/L}))</td>
<td>9.15 ±2.32</td>
<td>7.85 ±1.87*</td>
</tr>
<tr>
<td>2-h plasma glucose ((\text{mmol/L}))</td>
<td>11.41 ±2.63</td>
<td>9.91 ±1.93**</td>
</tr>
<tr>
<td>HbA(_1C) ((%))</td>
<td>7.35 ±1.12</td>
<td>6.73 ±1.02*</td>
</tr>
<tr>
<td>Total cholesterol ((\text{mmol/L}))</td>
<td>4.99 ±0.98</td>
<td>4.85 ±0.82</td>
</tr>
<tr>
<td>HDL cholesterol ((\text{mmol/L}))</td>
<td>1.29 ±0.55</td>
<td>1.35 ±0.51*</td>
</tr>
<tr>
<td>LDL cholesterol ((\text{mmol/L}))</td>
<td>2.60 ±1.11</td>
<td>2.33 ±0.89*</td>
</tr>
<tr>
<td>Triglycerides ((\text{mmol/L}))</td>
<td>2.54 ±1.77</td>
<td>2.18 ±1.30</td>
</tr>
<tr>
<td>Insulin Sensitivity ((\text{IS}))</td>
<td>0.42 ±0.38</td>
<td>0.13 ±0.59</td>
</tr>
<tr>
<td>Insulin Action Index ((\text{IAI}))</td>
<td>-4.81 ±0.30</td>
<td>-4.14 ±0.50**</td>
</tr>
</tbody>
</table>

*Note.*

Data are means ±SE. *\(P<0.05\) vs pretreatment; **\(P<0.01\) vs pretreatment.

Missing data \(n\)(treatment/control) \(n = 20\) (9/11). Data was not collected due to economic reasons. Insulin was measured by ELISA. HOMA function was used to calculate the IS and IAI.

The effect on inflammatory markers was only assessed in the treatment group. As shown in Table 5-4, concentrations of TNF\(\alpha\), CRP and IL-6 were all significantly reduced.
Table 5-4. Effect of Jiangtang Xiaozhi Treatment (n=30) on Inflammation Markers

<table>
<thead>
<tr>
<th>Inflammation markers</th>
<th>Baseline</th>
<th>After Treatment with Jiangtang Xiaozhi</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα (ng/ml)</td>
<td>1.25 ±0.45</td>
<td>0.81 ±0.26** (t=5.345)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>4.50 ±4.33</td>
<td>1.87 ±1.32** (t=4.176)</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>542.58 ±123.37</td>
<td>442.19 ±97.23** (t=3.530)</td>
</tr>
</tbody>
</table>

Data are means ±SE. **P<0.01 vs pretreatment.

Jiangtang Xiaozhi was as effective as Jin Qi Melbine in lowering blood sugar, BMI, WHR and improving insulin sensitivity. However, it has a more favourable effect on inflammatory markers and liver function than this treatment. The significant reduction of the inflammatory marker TNFα suggests that this mechanism is closely associated with how the Jiangtang Xiaozhi treatment exerts its effect. The performance of the formula in these preliminary studies is comparable to other Chinese herbal formulas used in the treatment of diabetes and prediabetes. However testing in a more rigorous fashion and in a lengthier trial is required.

5.6 Conclusion

There is strong evidence for the anti-diabetic effect of some composite Chinese formulas and individual herbs. A number of clinical trials have been conducted using individual Chinese herbs to treat people with prediabetes. The majority of these trials have been of poor quality; thus the antihyperglycaemic efficacy of the individual herbs remains inconclusive. The systematic reviews of Chinese herbs for diabetes and Chinese herbs for IGT concluded that, although the herbs have been shown to be safe, there is insufficient evidence to make conclusions about their efficacy (Grant et al., 2009; Liu, Zhang, Wang, &
This was despite the direction of the evidence for a positive effect being strong: 76% of studies showed improved indices of glycaemic control. The trials have been under-powered or the samples otherwise too small, lacked randomization and blinding, and drop-outs have been poorly reported.

Complex herbal formulae may have a synergistic effect targeting various sites within the whole body which are affected by the pattern of disease. For example, they may combine to lower blood glucose but also treat the “Blood stasis” associated with peripheral neuropathy. In a review of Chinese natural products for the treatment of diabetes, Tao, Wang and Jia (2007) gave priority to the potential for synergistic effects:

> Combination herbal formulae and combination phytochemical compounds derived from traditional formulae with a holistic therapeutic approach may hold the potential to become the therapeutics of choice in the future, due to the synergistic effect and dynamic adjustment achieved by the multiple ingredients that inhibit causative factors at different stages (p. 984).

The individual herbs in the formula, Jiangtang Xiaozhi have exhibited good hypoglycaemic and anti-diabetic effects in animal studies and in some cases human trials. The randomised clinical trial of Jiangtang Xiaozhi conducted in China has shown that the combination of herbs is effective in treating people with diabetes. To conclusively determine whether the herbal formula is effective in diabetes prevention would require a lengthy and resource intensive trial. In the first instance, it is more feasible to establish the effectiveness of the trial formula in a rigorous clinical trial in a western population with prediabetes.
A Randomised Controlled Clinical Trial -

Method

The animal and human studies of the individual herbs in the Chinese herbal formula, *Jiangtang Xiaozhi* and a small clinical trial conducted in China have produced encouraging results warranting further investigation.

There is no known cure or prevention for the escalating disease of diabetes. The investigation of a herbal medicine that may reduce the risk of overt diabetes in subjects with prediabetes or slow the progression of the disease is warranted given the physical, social and economic costs of diabetes and the limitations of current treatment regimes as discussed in Chapter 2. Potential outcomes of this trial are to produce an assessment of the effectiveness and safety of *Jiangtang Xiaozhi*, and to contribute to the growth of rigorous herbal medicine trials in this field.

The methodology for the clinical trial of Jiangtang Xiaozhi in people with prediabetes is reported according to the CONSORT statement (Altman et al., 2001). Approval for the study was obtained from the Human Research Ethics Committee at the University of Western Sydney.

6.1 Research objectives

The aim of this randomised controlled trial was to assess the effectiveness of a Chinese herbal formula, *Jiangtang Xiaozhi*, in treating impaired glucose control and insulin resistance in persons with prediabetes and early diabetes.

The specific objectives of this research were to investigate the effectiveness of *Jiangtang Xiaozhi* in treating elevated blood glucose levels, as measured by changes in fasting blood glucose (FBG), post-prandial plasma glucose and glycosylated haemoglobin (HbA1c). Secondary outcomes measured were insulin, C-reactive
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

protein, obesity and waist girth, lipids, blood pressure and health-related quality of life.

The null hypothesis is that the Chinese herbal formula, Jiangtang Xiaozhi, has no added value in treating impaired glucose tolerance or insulin resistance in persons with prediabetes and early diabetes compared to placebo.

6.2 Research design

The trial was a randomised, subject and assessor blind of 16 weeks duration with follow-up 8 weeks later. Subjects were randomly allocated to receive either Chinese herbal medicine or a placebo. Subjects did not know the group to which they were randomised until the completion of the study. The trial design and participant flow are summarised in Figure 6-1.

6.3 Setting

The clinical trial was initially conducted in two locations: Bankstown Campus (University of Western Sydney), and the Invitation to Health Medical Centre, Gosford. Slow recruitment led to the opening of an additional venue in January 2008 at Parramatta Campus of University of Western Sydney (UWS). The Parramatta Campus venue recruited the most participants ($n = 30$). Equipment and procedures were identical at each venue.

6.4 Participants

6.4.1 Principles guiding selection of criteria

Selection criteria was designed to ensure that outcomes could be measured accurately and efficiently in the setting of a clinical trial that included heterogeneous populations; and to exclude individuals with conditions or treatments that would interfere with participation or completion of the protocol, or that had a confounding effect on the measurement of the outcomes of the study.
6.4.2 Inclusion criteria

To participate in this study, persons had to be at least 18 years of age. The study was open to both men and women from all ethnic groups.

The initial criteria for inclusion was diagnosis with impaired glucose tolerance according to World Health Organisation criteria: fasting plasma glucose (FPG) level of <7.0 AND 2 hr plasma glucose load level ≥ 7.8 <11.1). The criteria were expanded in June 2008 due to slow recruitment to include persons with ‘mild’ type 2 diabetes. ‘Mild’ diabetes is not a diagnosis and was defined for the purpose of this study as people diagnosed within the last five years and whose diabetes was diet and
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

Exercise controlled and were not on any medication to control their blood glucose levels.

6.4.3 Exclusion criteria

The exclusion criteria were designed to ensure that those participants who had serious concurrent medical problems and those who were taking medications that may affect glucose or lipid profiles were excluded. Participants were excluded from the trial if they had an underlying disease likely to limit life span and/or increase the risk of interventions. These conditions included cancer requiring treatment in the past 5 years with the exception of cancers which have been cured, or in the opinion of the investigator, carry a good prognosis; an infectious diseases: self-reported HIV or active tuberculosis; cardiovascular disease with hospitalisation in prior 6 months, uncontrolled hypertension, stroke or transient ischemic attack in the prior 6 months, left bundle branch block on ECG; gastrointestinal disease such as inflammatory bowel disease requiring treatment in the past 6 months; and renal disease (serum creatinine >160mmol/L) or anaemia.

Participants were also excluded if they had conditions or behaviours likely to affect the conduct of the trial, such as unwilling or unable to give informed consent; weight loss of more than 10% in past 6 months for any reason except post-partum weight loss; pregnant or breast feeding; major psychiatric disorder which, in the opinion of clinic staff would impede conduct of trial; or major surgery in the past month or were to have surgery during the trial.

Participants were excluded if they had a disease related to metabolism or were taking medication known to have an effect on blood sugar such as Cushing’s syndrome, acromegaly, chronic pancreatitis, thyroid disease, were taking some antihypertensives such as beta-blockers, some lipid lowering agents, prescribed weight loss drugs.
6.4.4 Recruitment

Participants were recruited by media (radio, television, newspapers) as organised by the media department of UWS and by approaching general practitioners through the Central Coast Divisions of General Practice.

A formidable recruitment challenge was that prediabetes is asymptomatic and not recognised as a potentially serious condition. The “hidden” nature of this condition required that potential participants be sensitized to their risk and to the benefits of taking part in this study.

Cost of recruitment was another challenge. The Diabetes Prevention Program, a large multicentre randomised controlled trial designed to test whether diet and exercise or medication can prevent or delay type 2 diabetes, spent an average of US$1075 per randomised participant excluding staff cost (DPP Research Group, 2002). Their most successful strategies were direct mail followed by print media. The cost of direct mail was high but mainly due to the cost of printing of colour brochures. Recruitment through community screenings was considered high-cost with a low yield. These strategies were considered for this trial within the constraints of a limited budget.

Recruitment strategies for this clinical trial were as follows:

- Media launch coordinated by UWS Media Unit, a summary of media coverage from the launch is provided in Table 6-1;
- Advertising in local papers and Coffee News (a newsletter placed in coffee shops in north west Sydney and the Central Coast);
- Direct mail out to Diabetes NSW prediabetes cohort;
- Presentations to Diabetes educators at three locations (City, Central Coast and Liverpool);
- Websites:
  - CompleMED, University of Western Sydney
Chapter 6: Randomised controlled trial of Jiangtang Xiaozi for the treatment of prediabetes and mild diabetes: Method

- Diabetes NSW
- Invitation to Health Medical Centre (a Central Coast medical centre)
- Clinical Trials database(s)
- Presentation to ITH Medical Centre GPs and distribution of health professional information sheets;
- Email all patients on the ITH Medical Centre database (over 1000 patients); and
- Posters on UWS campuses.
Table 6-1 *Summary of recruitment media coverage*

<table>
<thead>
<tr>
<th>Type of media</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Television</td>
<td>Channel 10 News (2 time slots)</td>
</tr>
<tr>
<td>Newspapers</td>
<td>SMH (Sydney): 2 articles</td>
</tr>
<tr>
<td></td>
<td>Daily Telegraph (Sydney)</td>
</tr>
<tr>
<td></td>
<td>Sun Herald</td>
</tr>
<tr>
<td></td>
<td>Weekend Australian</td>
</tr>
<tr>
<td></td>
<td>MX (Sydney)</td>
</tr>
<tr>
<td></td>
<td>Launceston Examiner (TAS)</td>
</tr>
<tr>
<td></td>
<td>Central Coast Express Advocate</td>
</tr>
<tr>
<td></td>
<td>Bankstown Canterbury Torch</td>
</tr>
<tr>
<td></td>
<td>Parramatta Advertiser</td>
</tr>
<tr>
<td></td>
<td>Parramatta Sun</td>
</tr>
<tr>
<td></td>
<td>Peninsula News (Central Coast)</td>
</tr>
<tr>
<td></td>
<td>AAP Newswire</td>
</tr>
<tr>
<td></td>
<td>Diabetes NSW</td>
</tr>
<tr>
<td>Radio</td>
<td>ABC Local Newcastle Interview</td>
</tr>
<tr>
<td></td>
<td>ABC Local Darwin News</td>
</tr>
<tr>
<td></td>
<td>ABC Local Brisbane Interview</td>
</tr>
<tr>
<td></td>
<td>ABC Perth News</td>
</tr>
<tr>
<td></td>
<td>2GO FM (Gosford) News</td>
</tr>
</tbody>
</table>
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

A central phone number and/or email address was provided for potential participants to call in all advertising, presentations and print media. The most phone calls and email contacts were stimulated by local advertising and from the direct mail out to Diabetes NSW members. Over 600 phone calls and email contacts were recorded during the recruitment period June 2007 – July 2008. However, a large number of people misunderstood the initial diagnostic criteria, often thinking the trial was for people with diabetes not prediabetes. Others were unable to attend one of the locations.

An additional challenge for recruitment was the technique required for determining the presence of prediabetes and eligibility for the trial. IGT is not routinely determined in clinical settings. The diagnostic procedure of a 2 hour oral glucose tolerance test is required. Potential participants needed to be encouraged to attend their doctor for a pathology request to undertake an OGTT to determine their eligibility. In some cases a pathology request form was provided to the potential participant by UWS. The oral glucose tolerance test may cause discomfort and nausea, and requires careful preparation on the part of the individual. Participants were required to undertake three oral glucose tolerance tests throughout the trial.

6.4.5 Screening procedures and interview

Interested persons were screened by the principal investigator or research assistant over the phone to preliminarily assess eligibility and the method of entering the trial. A copy of the phone screening criteria is located at Appendix C-1.

To confirm eligibility a positive Oral Glucose Tolerance Test (OGTT) had to be conducted or have been conducted within the previous three months by the same laboratory being used in the clinical trial. An OGTT was administered after three days of carbohydrate loading according to specific guidelines and an overnight fast of 12 hours, during which only water was drunk (see Appendix C-2). A fasting blood glucose sample was collected then subjects drank 75 g of glucose over a course of 5 minutes. Blood samples were collected 2 hours after the test load.

The following results suggest different conditions:
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

- OGTT levels are considered normal up to 7.8 mmol/l (140 mg/dl).
- Levels between 7.8–11.0 mmol/l (140–199 mg/dl) are referred to as impaired glucose tolerance or pre-diabetes.
- Diabetes is diagnosed when OGTT levels are 11.0 mmol/l (200 mg/dl) or higher.

Potential participants attended one of three locations: the Invitation to Health Integrated Medical Centre, Wyoming (on the Central Coast of NSW), Parramatta UWS campus or Bankstown UWS campus (both in western Sydney).

During an initial appointment participants gave informed consent and were enrolled in the study. Baseline measures were collected and medication was dispensed. In cases where the potential participant had not had an OGTT they were given a pathology request to attend Symbion Laverty Pathology for testing. Once their results were received by the principal investigator they were advised whether their eligibility had been confirmed and whether they were then able to commence medication.

Informed consent involved detailed provision at the appropriate level of comprehension for each person, about the purpose, methods, demands, risks, inconveniences, discomforts, benefits and possible outcomes of the research. If asked, participants were advised that their results could be provided but not their allocated intervention, until the data analysis was complete and the results were written up. The informed consent form can be found at Appendix C-3 and participant information sheet is located in Appendix C-4.

6.5 Interventions

Details of the interventions are provided in accordance with the elaborated CONSORT statement for herbal medicines (Gagnier et al., 2006).

Both the Jiangtang Xiaozhi Capsule and the placebo were manufactured in China by Tianjin Zhongxin Pharmaceutical Group Corporation Ltd, a pharmaceutical manufacturer in China with an Australian Good Manufacturing Practice (GMP)
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

license issued by the Therapeutic Goods Administration (TGA). The protocols for the manufacture, packaging and labelling of the treatments are described below.

6.5.1 Jiangtang Xiaozhi tablets

The Jiangtang Xiaozhi tablets consists of six herbs and two excipients as listed in Composition of Jiangtang Xiaozhi tablets in Table 6-2.

Table 6-2 Composition of Jiangtang Xiaozhi tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Individual tablet</th>
<th>Dosage of 3 tablets</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nu Zhen Zi (Ligustrum lucidum Ait.; Oleaceae; privet fruit)</td>
<td>1.33</td>
<td>4.00</td>
<td>35%</td>
</tr>
<tr>
<td>Huang Qi (Astragalus membranaceus (Fisch.) BGE; Fabaceae; milk vetch root)</td>
<td>0.67</td>
<td>2.00</td>
<td>18%</td>
</tr>
<tr>
<td>Huang Lian (Coptis chinensis Franch.; Ranunculaceae; coptis rhizome)</td>
<td>0.33</td>
<td>1.00</td>
<td>9%</td>
</tr>
<tr>
<td>Li Zhi He (Litchi chinensis SONN.; Sapindaceae; lychee nut)</td>
<td>0.67</td>
<td>2.00</td>
<td>18%</td>
</tr>
<tr>
<td>Kun Bu (Ecklonia kurome OKAM.; Alariaceae; kelp)</td>
<td>0.06</td>
<td>0.17</td>
<td>1%</td>
</tr>
<tr>
<td>Jiang Huang (Curcuma longa L.; Zingiberaceae; tumeric rhizome)</td>
<td>0.50</td>
<td>1.50</td>
<td>13%</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.02</td>
<td>0.05</td>
<td>1%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.21</td>
<td>0.64</td>
<td>6%</td>
</tr>
<tr>
<td>Total</td>
<td>3.79g</td>
<td>11.36g</td>
<td>100%</td>
</tr>
</tbody>
</table>
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

6.5.2 Jiangtang Xiaozhi tablets manufacturing process

Nu Zhen Zi (*Ligustrum lucidum* Ait.; Oleaceae; privet fruit): Heating, refluxing, extracting Nu Zhen Zi (fruit of the plant used) 3 times with 6 folds of 75% ethanol, 2 hours each time. Combining the ethanol extracting solutions; Reclaiming ethanol; Drying.

Jiang Huang (*Curcuma longa* L.; Zingiberaceae; tumeric rhizome): Adding 10 folds of water into crushed Jiang huang; Distilling with water vapour for 8 hours. Collecting naphtha; Water solution and dregs of decoction standby; naphtha with 8 folds of β-cyclodextrin and 80 folds of water; Stirring for 1 hour at 50°C; Refrigerating overnight; filtrating; Drying at 40°C; crushing into a fine powder.

Li Zhi He (*Litchi chinensis* SONN; Sapindaceae; leechee nut) and Kun Bu (*Ecklonia kurome* OKAM.; Alariaceae; kelp): Adding 10 folds of water into pit of Li Zhi and Kun Bu; Decocting 3 times, 0.5 hour each time; Combining decoctions; filtrating; Combining the filtration with the water solution of jiang huang; Condensing to relative density of 1.10-1.15 (measured at 50°C); Adding ethanol till 60%; Refrigerating overnight; filtrating; solution standby.

Huang Lian (*Coptis chinensis* Franch. Ranunculaceae; coptis rhizome), Huang Qi (*Astragalus membranaceus* (Fisch.) BGE; Fabaceae; milk vetch root) and Jiang Huang (*Curcuma longa* L.; Zingiberaceae; tumeric rhizome): Heating, refluxing, extracting huang lian (rhizome and root), huang qi and dregs of jiang huang with 6 times of 50% ethanol 3 times, 2 hours each time; Combining the ethanol extracting solutions; Combining the above. Standby solution, Condensing till relative density of 1.15-1.20 (measured at 50°C); Drying; Blending with the above nu zhen zi extractive, β-cyclodextrin, suitable amount of lactose, 3% crosslinking polyvinyl pyrrolidon evenly to make tablets; Drying; Again adding 3% crosslinking polyvinyl pyrrolidon and 0.5% magnesium stearate to press into 1,000 tablets.

Packaging: packed with polyvinyl chloride solid plates. Ten pills per packet.

Dosing schedule: 3 tablets 3 times a day (34g of the formula).
6.5.3 Placebo tablets

Composition of the placebo tablets is set out in Table 6-3.

Table 6-3 Composition of Jiangtang Xiaozhi allotype tablet (placebo)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>31.13%</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>31.13%</td>
</tr>
<tr>
<td>Dextrin</td>
<td>31.13%</td>
</tr>
<tr>
<td>Denatonium Benzoate</td>
<td>0.37%</td>
</tr>
<tr>
<td>Burnt sugar</td>
<td>6.23%</td>
</tr>
</tbody>
</table>

*Mixed with fresh carrot juice*

Total 100.00%

6.5.4 Placebo tablets manufacturing process

Mixing lactose, microcrystalline cellulose and dextrin evenly; Condensing fresh carrot juice suitably; Adding burnt and Denatonium Benzoate; mixing evenly; Pressing into tablets.

Packaging: packed with polyvinyl chloride solid plates. Ten pills per plate.

Dosing schedule: 3 tablets 3 times a day.

6.5.5 Labelling

Labelling was as per the TGA requirements and therefore each packet of pills stated:

- Name of sponsor
- Pharmaceutical dosage form
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

- Batch/code number to identify contents and packaging operation (may be encoded for blinding purposes)
- Directions for use (take 3 capsules 3 times per day)
- Statement “for clinical trial only”
- The name of the Principal Investigator
- A trial reference code
- Storage conditions
- Use-by or expiry date
- Statement “keep out of reach of children”
- And any other items required to be consistent with TG048 (Therapeutic Goods Order TG048).

6.5.6 Medication compliance

Participants were asked if they had missed any medication at each of their monthly visits. Returned medication was counted and subtracted from the total number of tablets dispensed so as to arrive at the amount taken.

6.6 Sample size

Sample size for the study aimed to be large enough to detect a statistically and clinically significant difference between the Chinese herbal medicine and placebo in the improvement of fasting plasma glucose (2-hour HPG) and HbA1c.

For a two arm trial, a sample of 50 participants in each group will detect changes in fasting glycaemia of 1.00 mmol/L, with a standard deviation (SD) of 1.6mmol/L. This estimate allows for a 10% withdrawal or non-compliance rate. This sample size has 80% power and a level of significance of p<0.05 (two tailed test).
To have 80% power to detect a 1% difference in HbA1C with a SD of 1.4%, a total sample of 74 is required. This estimate allows for a 10% withdrawal or non-compliance rate.

### 6.7 Randomisation and blinding

Proper randomisation eliminates selection bias (Altman, et al., 2001). Selection bias means treatment comparisons may be prejudiced, whether consciously or not. Proper randomisation involves two crucial steps: (a) the generation of an unpredictable allocation sequence, and (b) concealment or blinding of this sequence from the investigators and participants (Moher, Jones, & Lepage, 2001).

Randomisation in this study was “simple”. Simple randomisation means that each participant has a known probability of receiving each treatment, but the treatment is assigned by chance, in a way that cannot be predicted.

#### 6.7.1 Generation of allocation sequence

A random sequence in a simple block was computer-generated by the UWS trial coordinator who was external to the trial. The medication was sealed in sequentially numbered identical packets according to the allocation sequence.

Each individual was assigned a unique three digit participant identifier number that matched the labelled packets. This number was used on all electronic and paper based data collection items. Data was entered directly onto computer or onto a survey form (depending on the item) using this number as the only participant identifier.

#### 6.7.2 Allocation concealment and blinding

Participants and investigators were blind to the treatment allocated. Placebo and intervention were identical in appearance, taste and smell. The UWS trail coordinator supplied labelled packets of the interventions as required. The data analysis was conducted with the interventions known simply as ‘A’ and ‘B’.
To assess the effectiveness of the blinding, participants were asked at each encounter: ‘do you think you are taking the herbal medicine or the placebo?’

The code was revealed to investigators only when recruitment, data collection, laboratory analyses and data analyses were complete.

Data was collected on a database constructed by Australian Survey Research. The database was kept secure according to their rigorous protocols. Data was then transferred to Excel and then to SPSS v17 for analysis.

6.8 Primary outcome measure: glycaemic control

The clinical trial’s primary outcomes were the change in fasting blood glucose (FBG), post-prandial plasma glucose and glycosylated haemoglobin (HbA1c) in the Chinese herbal medicine group from baseline to the conclusion of the trial compared to a placebo. These primary outcome measures were chosen for two main reasons. Firstly, prediabetes and diabetes are the result of the body’s insulin not working effectively manifesting in poor glycaemic control. It is the poor glycaemic control that can lead to the diabetic retinopathy, neuropathy and other manifestations of diabetes. Glycaemic control can be assessed by fasting plasma glucose, post-prandial plasma glucose and HbA1c. Secondly, fasting plasma glucose with a 2hr post prandial plasma glucose (following an OGTT) is the main diagnostic criteria for prediabetes and diabetes (World Health Organisation, 1999). Impaired glucose tolerance is defined as fasting blood glucose ≤ 7.0 mmol/L and 2hr post-prandial (following an oral glucose tolerance test or OGTT) levels between 7.8–11.0 mmol/l. Diabetes is diagnosed when fasting blood glucose levels are ≥ 7.0 mmol/L and/or OGTT levels are 11.0 mmol/l (200 mg/dl) or higher.

The diagnostic criteria for impaired glucose tolerance are not without limitations. Time of day and stress has been shown to alter glucose concentration. Biological variations such as age also affect glucose levels (Santaguida et al., 2005). Further, the test is inconvenient for participants involving an overnight fast and a two hour
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

testing period. It is nonetheless the recommended diagnostic criteria for prediabetes and diabetes.

Testing for HbA1c is a simple way to obtain an estimation of the average blood sugar during the past two months. Glycation of haemoglobin occurs over the 120 day lifespan of the red blood cell. Theoretical models and clinical studies suggest that a patient with stable control will have 50% of their HbA1c formed in the month prior to sampling, 25% the month before that and the remaining 25% in months 2-4 (Kilpatrick, 2008). However, no data exists to define the utility of HbA1c in monitoring prediabetes (Twigg, Kamp, Davis, Neylon, & Flack, 2007).

HbA1c is also not without its limitation and can be affected by several factors. Iron deficiency anaemia can lead to rises in HbA1c of up to 2% (Coban, Ozdogan, & Timuragaoglu, 2004; El-Aguouza, Abu Shahla, & Sirdah, 2002). Menopausal status (Koga, Saito, Mukai, Matsumoto, & Kasayama, 2009) and high doses of aspirin (4g/day) can lead to rises in HbA1c. Uncommonly, high-dose salicylates, more than 1g Vitamin C (Davie, Gould, & Yudkin, 1992), and Vitamin E (Ceriello et al., 1991), have been reported as interfering substances (Saudek, Derr, & Kalyani, 2006). HbA1c also increases with age. Further there is global variation in laboratory method used for determining HbA1c (Collier, Ghosh, Davidson & Kilpatrick, 2009).

Normal ranges vary depending on pathology but it is desirable to keep levels between 4.3-6.3%; even at ‘stable’ or ‘on target’ HbA1c levels and prediabetic levels, microvascular and macrovascular damage can still be occurring. HbA1c levels below 7% have been shown to have unexpected hyperglycaemic excursions, marked glucose variability and higher-than-recommended glucose levels after a standard meal (Kohnert et al., 2007). Nonetheless an International Expert Committee, recommended that the HbA1C level of 6.5% be set as the diagnosis for diabetes (International Expert Committee on Diabetes, 2009). They recommended that use of the categorical clinical states of IGT, IFG and prediabetes be phased out, and that HbA1c measurements replace glucose measurements. At the time of our research this recommendation was yet to be implemented in Australia.
Chapter 6: Randomised controlled trial of Jiangtang Xiaozi for the treatment of prediabetes and mild diabetes: Method

6.9 Secondary outcomes

The secondary outcomes were established with a view to helping explain the primary outcome results, and shedding light on how the intervention might affect other risk factors for diabetes. These are at least as clinically meaningful as the primary outcomes. The secondary outcomes included in this study are insulin, C-reactive protein, obesity and waist girth, lipids, blood pressure and health-related quality of life.

6.9.1 Insulin

Prediabetes is a result of the body’s insulin not working effectively. This is known as insulin resistance.

The gold standard for measuring insulin resistance is the euglycaemic clamp test (DeFronzo, 1979). The disadvantages of the clamp test are its requirements - two intravenous lines, calibrated pumps and online plasma glucose level determination and trained personnel. At the end of a clamp study, particularly with a high insulin dose, the subject’s plasma glucose level must be monitored for some time (Ferrannini & Mari, 1998). Such requirements make the test expensive and laborious.

Over the past two decades other methods have been developed that are easier to use. These have then been validated against the ‘gold standard’ - the euglycaemic clamp test. Model assessments of insulin resistance include the Homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI) and the continuous infusion of glucose with model assessment (CIGMA).

The Homeostatic model assessment (HOMA) was used to assess beta-cell dysfunction and insulin resistance (Levy, Matthews, & Hermans, 1998). HOMA%S is a measure of insulin sensitivity, HOMA%B is a measure of beta-cell function, and HOMA-IR is a measure of insulin resistance. The results of all three measures need to be reported together for proper interpretation.

QUICKI is an equation that is similar to HOMA with similar limitations but has been less widely used (Antuna-Puente et al., 2008; Katz, 2000; Monzillo & Hamdy, 2003).
CIGMA requires 3 samples of insulin taken at 50, 55 and 60 min. It has not been widely used or validated, although one study found that it has a coefficient of covariance of 21% (Matthews et al., 1985). HOMA is the most robust and commonly used of all these tools (Wallace & Matthews, 2002).

HOMA was developed around 1990 as a method for measuring insulin sensitivity (Bonora et al., 2000). It uses a mathematical model, now computerised, to estimate insulin sensitivity and beta-cell function from fasting plasma glucose and insulin. Although three samples at 5 minute intervals is recommended, one sample is often and reliably used for assessing longitudinal changes within an individual (Wallace & Matthews, 2002).

HOMA was selected as the model to use in this trial for two reasons. Firstly, it has been widely used and validated in a number of studies (Fukushima M, 1999; Fukushima et al., 1999; Hanson et al., 2000; Lansang, Williams, & Carroll, 2001). It has found to correlate well with the euglycaemic clamp method. In recent studies, the coefficient of variation has been shown to be between 7.8% (Bonora, et al., 2000) and 11.7% (Emoto, 1999). Secondly, the sampling is simple, inexpensive and non-intrusive.

The underlying physiological basis of the HOMA model is the feedback loop between the hepatic glucose output and the beta-cells. Plasma glucose in the basal state is regulated by the hepatic glucose output, which is insulin dependent (Wallace, Levy, & Matthews, 2004).

A normal weight, healthy person < 35 years has a HOMA-IR of 1, HOMA%B of 100% and HOMA%S of 100%. However, HOMA values need careful interpretation and should not be considered in isolation. For example, an increase in insulin sensitivity will show as movement toward 100% but may be accompanied by a decrease in HOMAβ-cell %. This may represent a decrease in beta-cell activity not necessarily a decline in beta cell health.

The HOMA calculations in this research were derived from the HOMAV2.2 computer package which estimates steady state beta cell function (HOMA%B) and
insulin sensitivity (HOMA%S), as percentages of a normal reference population. The computer program for the HOMA Calculator v2.2.2, released 12 December 2007, was downloaded from the Diabetes Trial Unit, University of Oxford website http://www.dtu.ox.ac.uk/.

As HOMA is a steady state model, only clinically realistic values that would be seen in a fasting subject should be used (Barr et al., 2009). These are: (a) plasma glucose 3.5 to 25.0 mmol/L, and (b) plasma insulin 2.9 to 57.6 mmol/L (20 to 400 pmol/L).

Outcome measures:
- Changes in serum insulin
- Changes in HOMA.

6.9.2 C-reactive protein

C-reactive protein (CRP) is an inflammatory marker. It has been found to predict the development of type 2 diabetes independent of any other risk factors and individuals with IGT have been found to have higher than normal CRP levels (Festa et al., 2004; Hung et al., 2006).

The inflammatory response in cases such as stress have a known effect on glycaemic levels (Collier, Dossett, May, & Diaz, 2008). Indeed, elevated CRP concentration have been found to be a significant predictor of diabetes, independent of obesity and insulin resistance (Doi et al., 2005; Tan, 2003). Similarly, elevated levels of both CRP and another inflammatory marker, interleukin-6, predict the development of type 2 diabetes. These data support a possible role for inflammation in diabetogenesis (Pradhan, Manson, Rifai, Buring, & Ridker, 2001).

Outcome Measure
- Changes in C-reactive protein.
6.9.3 Obesity and waist girth

People who are overweight are at higher risk of developing diabetes (Engberg et al., 2009; Lindstrom & Tuomilehto, 2003; Pan et al., 1997). The definitions of overweight (BMI>25) and obesity (BMI>30) reflect the relationship between BMI with morbidity and mortality outcomes (WHO, 1998). Furthermore, obesity affects insulin sensitivity (Dixon, Dixon, & O'Brien, 2003).

Risk of developing diabetes is increased for men with a waist girth of more than 94cm and women with a waist girth of more than 80cm (Dalton et al., 2003; Edelstein et al., 1997; Lindstrom & Tuomilehto, 2003). Obesity defined by waist-hip ratio carries the highest risk for each of type 2 diabetes, hypertension and dyslipidaemia in both men and women (Dalton, et al., 2003)

Outcome measures

- Changes in weight, BMI, waist and hip girth (waist-hip ratio).

6.9.4 Lipids

People with high triglycerides and low level of high density lipid (HDL) cholesterol and/or high total cholesterol are at a higher risk of developing diabetes.

Hypertriglyceridaemia is an important predictor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes (Fontbonne et al., 1989). Both diabetes and IGT are known to be associated with several adverse cardiovascular risk factors, including hypertension, obesity, central obesity, hyperinsulinemia and serum lipid and lipoprotein abnormalities, characterized mainly by elevated serum total triglycerides and low HDL cholesterol (Laakso & Lehto, 1998; Zhang et al., 2008).

Outcome measures

- Changes in triglycerides, high-density lipoprotein-cholesterol and total cholesterol.
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

6.9.5 Blood pressure

People at risk of diabetes often have high blood pressure. Studies have shown that changes in glucose metabolism affect an upward shift in blood pressure. It has been posited that the higher blood pressure in IGT and diabetes may be due to vascular endothelial cell resistance to insulin action (Falkner, Sherif, Sumner, & Kushner, 1999; Morales et al., 1993).

Outcome measures

- Diastolic and systolic blood pressure.

6.9.6 Health-related quality of life (HRQoL)

While the HRQoL of people with diabetes has been widely studied (Manuel, 2004; UKPDS, 1999), it is only recently that research has begun to examine the health-related quality of life (HRQoL) in those with prediabetes also (Hakkinen et al., 2009; Tapp et al., 2006). This research has shown that people with prediabetes have reduced functioning in physical and social dimensions (Tapp, et al., 2006) and general health and body pain dimensions (Chittleborough, 2006; Hakkinen, et al., 2009).

HRQoL was used in this study to determine if the herbal medicine conferred any benefit and to assess how this cohort of people with prediabetes and mild diabetes compared with the Australian general population.

The instrument selected to assess HRQoL was the 36-item short-form health survey Version 2 (SF-36v2). The SF-36 is a well validated and reliable tool for assessing eight dimensions of health and well-being (Ware, 2000). The support for the selection of this instrument was further strengthened by the existence of Australian normative data for the general population (Hawthorne, Osborne, Taylor, & Sansoni, 2007) and Australian research on HRQoL in people with prediabetes and diabetes using the SF-36 (Chittleborough, 2006; Tapp, et al., 2006).

The eight dimensions of health and well-being assessed by the SF-36 are set out below (Ware, 2000).
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

1. Physical functioning (PF): indicates the extent to which, on a typical day, a person is limited by their health in performing a range of physical activities, including bathing and dressing.

2. Role—physical (RF): indicates the effects of physical health on a person’s performance of their work or other daily activities; that is, whether limited in the kinds of work or other activities they were able to do, or reduced the time spent on these activities, or had difficulty performing these activities due to physical health.

3. Bodily pain (BP): indicates the severity of pain experienced and the extent to which it had interfered with their normal activities.

4. General health (GH): combines self-assessed health status with indicators of current expectations and perceptions of health relative to the health of others.

5. Vitality (VT): indicates a person’s energy level and level of fatigue.

6. Social functioning (SF): indicates the impact of health or emotional problems on the quality and quantity of a person’s social activities with others.

7. Role—emotional (RE): indicates the effects of physical health on a person’s performance of their work or other daily activities; that is, whether limited in the kinds of work or other activities they were able to do, or reduced the time spent on these activities, or had difficulty performing these activities due to emotional problems.

8. Mental health (MH): indicates the amount of time a person experienced feelings of nervousness, anxiety, depression and happiness.

Except for PF and GH, the dimensions focus on aspects of health and well-being during the four weeks prior to the interview.

Version 2 was developed between 1996 and 2000 to address the cross-cultural shortcomings of Version 1 (Sansoni, 2001; Ware, 2000). This study uses the Australian SF-36 Version 2 which differs from the US version in its use of metric rather than imperial units (Sansoni, 2001). The Australian general population norms,
weighted for age and gender, were used as the reference for the study group (Hawthorne, et al., 2007).

Version 2 uses norm-based scoring of scale scores to arrive at a T-score. Our research uses Australian normative data based on Australian weights derived from similar analysis to that used to determine the US norms (Hawthorne, et al., 2007). Norm-based transformation follows the steps set out by Ware et al (Ware, 2000).

Outcome measure

- Completed Australian SF-36 Version 2.0 questionnaire (copy at Appendix C-5).

### 6.9.7 Adverse effects and safety tests

In addition to the efficacy parameters which provided information of systemic effects of the interventions, the further safety parameters are:

- full blood cell count;
- pregnancy test;
- liver function test; and
- Renal function test.

### 6.10 Treatment and assessment procedure

The duration of the study was 24 weeks. Participants were required to take the medication for 16 weeks and attend a follow up appointment at 24 weeks. The duration of the time for taking the medication was based on the minimum time required to identify a change in the HbA1c measure. The follow-up period allowed for an analysis of any of the intervention’s sustained treatment effects.

The participants were required to attend appointments to have blood samples taken by a qualified venapuncturist and other outcome items measured. As shown in Table 6-4 participants attended a monthly appointment where certain data were routinely collected depending on the stage of the trial.
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

Table 6-4 Timing of Outcome Measures

<table>
<thead>
<tr>
<th>Exam</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
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</thead>
<tbody>
<tr>
<td>Primary</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Waist girth</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip girth</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Weight</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>C-RP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lipid profile</td>
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<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SF36</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.11 Outcome measure protocols

All outcome measure results were recorded either directly onto an electronic data collection form or on paper form. Case Report Forms are detailed in Appendix C-7.
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

The physical examination protocol followed the WHO recommended model for diabetes and other non-communicable disease field surveys.

6.11.1 Interview protocol

Participants moved through the interviews and physical examination procedures in the following manner.

1. Initial Enrolment Questions: General Demographics, Family History, Women’s Health, Current Medication & Supplements & Health History: interview with data entered directly onto the database.

2. Nutrition and Physical Activity Survey: interview with data entered directly onto the database

3. SF-36: participant to fill out questionnaire (Initial, Wk16 & Wk 24 visits)

4. Physical measurements: data entered directly onto database

5. Traditional Chinese Medicine Diagnosis: interview with data entered directly onto the database (Initial visit only)

6. Attend Pathology for blood sampling & OGTT: data to be entered directly onto database as soon as it is received.

Questionnaires were entered promptly into the Survey Manager database. The Survey Manager database was designed by AusSurveys to minimise errors by locking fields to receive only certain values and using drop down boxes where appropriate. Open ended questions were kept to a minimum.

6.11.2 Initial enrolment questions

General Demographics

These questions were designed to capture unique identifying data and variables that might influence outcome measures such as ethnicity, age and gender. Education and employment has been found to influence compliance and were collected to provide useful analysis had compliance emerge as an issue in the trial.
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

Family History

Family history is a strong predictor of developing diabetes. It was collected to provide data about a possible confounding factor in response to treatment.

Health History

These questions were designed to elicit any health factors that might impact on the participant’s outcomes and might have needed to be monitored.

Women’s’ Health

A history of gestational diabetes is a predictor for developing diabetes. Menopause is also known to impact on glucose tolerance.

Polycystic Ovary Syndrome (PCOS) is a condition where a woman of childbearing age does not ovulate, that is, the eggs or ova are not released from the ovary. This causes cysts in the ovaries to develop and the level of male hormones, such as testosterone, to become elevated in the bloodstream. Most women with polycystic ovary are overweight and have insulin resistance, which is the association with type 2 diabetes. It is estimated that 30-50% of women with PCOS will have impaired glucose tolerance or diabetes by the age of 30. These questions were designed by a Clinical Endocrinologist on the Central Coast and used in the 2006 Central Coast Community Survey to identify women at risk of PCOS. It was possible that the trial sample might recruit sufficient PCOS participants to enable separate analysis.

Current Medications and Supplements

These questions are designed to ensure that medications and supplements have been stable for more than 3 months; and that any changes in dosage or medication are identified. Changes may affect the clinical outcome measures.

6.11.3 Blood sampling procedures

Blood samples were collected by venipuncture at a Symbion Laverty Pathology. Post prandial glucose was collected after an overnight fast of at least 10-12 hours and 3 days of carbohydrate loading (see Appendix C-2). A standard 75-g oral glucose
tolerance test was performed. Other blood specimens were collected according to the order outlined in Table 6-5.

Table 6-5 Pathology order of collection and normal values

<table>
<thead>
<tr>
<th>Order of collection</th>
<th>Tube</th>
<th>Normal values (Symbion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glucose</td>
<td>SST</td>
<td>3.4 - 7.7 mmol/L</td>
</tr>
<tr>
<td>2. Insulin</td>
<td>SST</td>
<td>0 – 9 mU/L</td>
</tr>
<tr>
<td>3. Total cholesterol, HDL-cholesterol, and triglycerides</td>
<td>SST</td>
<td>Total 3.5 - 5.4 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL &gt; 1.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triglycerides 0.1 - 2.0 mmol/L</td>
</tr>
<tr>
<td>4. HbA1c</td>
<td>EDTA</td>
<td>4.3 - 6.3 %</td>
</tr>
<tr>
<td>5. C-RP</td>
<td>SST</td>
<td>0 – 6 mg/L</td>
</tr>
<tr>
<td>6. Liver function</td>
<td>SST</td>
<td></td>
</tr>
<tr>
<td>7. FBC</td>
<td>EDTA</td>
<td></td>
</tr>
<tr>
<td>8. Renal function</td>
<td>SST</td>
<td></td>
</tr>
</tbody>
</table>

6.11.4 Height and weight

Height was measured without shoes using a stadiometer, which had been mounted onto a stable backing board on a flat surface. Each participant was positioned to be standing fully erect with heels, buttocks and shoulders resting lightly against the board and facing forwards so that the Frankfort plane (line passing horizontally from the ear canal to the lowest point of the eye orbit) was in the horizontal position.

Weight was measured after removal of shoes and when wearing light clothing only, using A&D Digital Scales (Model UC-321) and recorded to the nearest 0.1 kg.

Body Mass Index (BMI) was calculated by weight (measured to within 0.1kg) divided by height (measured to within 0.5cm) squared.
6.11.5 Waist and hip girth

Waist girth was measured using a measuring tape, with measurements made halfway between the lower border of the ribs, and the iliac crest in a horizontal plane (Davies, 2008).

Hip girth was measured at the widest point over the buttocks.

Men with a waist girth 94–101.9 cm and women with a waist girth 80–87.9 cm were classified as overweight, whilst men with a waist girth $\geq 102.0$ cm and women with a waist girth $\geq 88.0$ cm were classified as obese. Waist-hip ratio (WHR) was obtained by dividing the mean waist girth by the mean hip-girth. Men with a WHR 0.90–0.99 and women with a WHR 0.80–0.84 were classified as overweight, whilst men with a WHR $\geq 1.00$ and women with a WHR $\geq 0.85$ were classified as obese (Barr et al., 2006).

6.11.6 Blood pressure

Blood pressure was measured in a seated position after the participant had rested for at least 5 minutes. Two readings on the left arm were taken 1 minute apart. To obtain the final measure of blood pressure, the mean of the two readings was calculated and recorded. Blood pressure was measured using a Durashock DS66 hand held aneroid sphygmomanometer.

6.11.7 Physical activity and nutritional intake

Participants were asked to continue with their normal diet and exercise for the duration of the trial. Participants were all encouraged to eat 5-7 serves of fruit and vegetables a day and exercise for a minimum of 20 minutes on most days of the week. At each visit participants were asked to complete a Nutrition and Physical Activity Survey (copy at Appendix C-6).

The physical activity questions were designed to determine if the participant was participating in sufficient activity to confer a health benefit. Cholesterol, glucose, weight and other clinical outcome measures can be altered by physical activity alone.
The National Physical Activity Guidelines for Australians recommend that the ‘accumulation of 30 minutes of moderate physical activity on most days of the week’ is beneficial for health (DHAC, 1999). The method used to calculate physical activity was adopted from the New South Wales Population Health Survey (NSW Health, 2007). These in turn have been calculated from questions asked in the Active Australia Survey. Adequate physical activity is calculated as undertaking physical activity for a total of 150 minutes per week over 5 separate occasions. The total minutes are calculated by adding minutes in the last week spent walking continuously for at least 10 minutes, minutes doing moderate physical activity, plus minutes doing vigorous physical activity multiplied by 2.

Changes in nutrition alone may also change some clinical outcome measures (Kinmonth, Angus, Jenkins, Smith, & Baum, 1982; Meyer et al., 2000; Wolever & Jenkins, 1986). Adequate fruit and vegetable consumption is defined in the Australian Guide to Healthy Eating and the Dietary Guidelines for Australian Adults (NHMRC, 2003). The indicator includes those who met the recommended fruit consumption of at least 2 serves a day of fruit for people aged 16 and over. One serve is equivalent to 1 medium piece or 2 small pieces of fruit. The indicator also includes those who met the recommended consumption of vegetables. The recommended vegetable intake is at least 5 serves per day for persons aged 16 years and over. One serve is equivalent to 1/2 cup of cooked vegetables or 1 cup of salad vegetables.

6.12 Safety monitoring

The herbal formula has traditional and contemporary evidence for its safe use (see Chapter Four). Nonetheless safety parameters were collected according to the schedule outlined in Table 6-6. Details of the safety tests follow.

*Liver function test:* albumin, ALP, ALT (alanine aminotransferase), AST (aspartate aminotransferase), serum bilirubin, urine bilirubin, GGT (gamma...
glutamyltranspeptidase), LDH (lactate dehydrogenase), PT or prothrombin time, total protein.

Renal Function test: electrolytes, urea, creatinine, calcium, phosphate, uric acid, alkaline phosphate, globulin.

Full blood count: Hb g/L; Hct; RCC x 10 12/L; MCV fL; MCH pg; MCHC g/L; Plt x 10 9/L; WCC x 10 9/L; Neutrophils x 109/L; Lymphocytes x 109/L; Monocytes x 109/L; Eosinophils x 109/L; Basophils x 109/L.

Table 6-6 Timing of safety measures

<table>
<thead>
<tr>
<th>Test</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Liver function</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.12.1 Adverse events

The screening process was designed to find any previously unknown cause for exclusion, such that participants were assumed to have minimal risk of adverse events. The trial adhered to adverse event definitions, principles and guidelines from the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (Therapeutic Goods Administration (TGA), 2000) and ICH Harmonised Tripartite Guideline - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1994) and the CIOMS report Management of Safety Information from Clinical Trials (CIOMS Working Group VI, 2005).
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

During the trial, participants were asked about adverse events as part of the data collection and safety monitoring process. To avoid bias from leading open-ended questions, participants were asked “How have you felt since I saw you last?”

Adverse events were defined as follows.

**Adverse Event**

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An Adverse Event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal product.

**Mild Adverse Event**

The event causes minimal discomfort and does not significantly interfere with the patient’s normal activities.

**Moderate Adverse Event**

The event is sufficiently uncomfortable to cause some impairment to the patient’s normal activities.

**Severe Adverse Event**

The event is incapacitating and prevents the patient from participating in normal activities.

**Serious Adverse Event**

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (at the time)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

- Is a congenital anomaly/birth defect

Severe refers to the severity of the event at the time as opposed to the seriousness of the patient’s event outcome e.g. a headache might be severe and disabling but not serious. A mild heart attack though not disabling at the time has more serious health consequences.

6.13 Data analysis

6.13.1 Approach to analysis

In an ideal clinical trial, there would be no deviation from the treatment protocol and all participants would complete the trial. However, participants withdraw, and others fail to provide complete data sets for all visits. This may lead to non-comparability in characteristics across treatment groups and subject the trial to summary outcome measures that are more linked to retention than true outcome (Lewis, 1988; Nich, 2002; Wright & Sim, 2003).

The principle of intention to treat (ITT) analysis is used to describe the inclusion of all data from all participants that underwent randomization to treatment, regardless of their level of treatment received or protocol adherence (Nich, 2002). Data analysis is based on assignment of treatment regardless of receipt of treatment (Wright & Sim, 2003).

The primary efficacy analysis set for this study was predefined as an intention to treat analysis, which consisted of all randomised subjects who received at least one dose of the study herbal formula or placebo.

6.13.2 Missing data

The trial was designed to minimise missing data through careful data collection, monitoring and follow up. Nonetheless, the problem of missing data is common, and unless these values are missing completely at random there may be a loss of between-group comparability (Mallinckrodt et al., 2003; Nich, 2002).
Chapter 6: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Method

There is no consensus on estimating missing values and sophisticated models have been developed (Nich, 2002; Schafer, 2002). The most common method for dealing with missing data is to carry-forward the last piece of information available – also known as last observation carried forward.

For this study, last observation carried forward (LOCF) was used for missing observations. This is a conservative approach to missing data and enables a strict and robust intention to treat analysis. Finally, in the completed ITT database, all individuals included in the study (N = 71) had an imputed value in all variables at all points in time.

6.13.3 Statistical analysis

Descriptive statistics were used for the baseline variables for all participants. The data was raw and unadjusted. The primary endpoint for the analysis was the study end point – the last double blind visit. For those participants who completed the treatment, this was the visit at week 16. A double blind follow up visit was conducted 8 weeks after the completion of treatment. Unless otherwise indicated, data are reported as an intention-to-treat (ITT) population. The outcome measure of efficacy was mean percentage change in FBG and HbA1c from baseline to week 16.

Data were analysed using an analysis of each continuous (as distinguished from categorical) variable using a fixed-effects analysis of covariance (ANCOVA) of change of baseline to endpoint. Baseline referred to data collected before any treatment was received. The single-slope ANCOVA model included the outcome and the baseline values as the dependent variables, and the treatment or placebo groups as the dependent variables.

Statistical analyses were performed using SPSS v17. All data were visually inspected for normality of distribution.

Ninety-five per cent confidence intervals (CI) were calculated from the mean, SD, and the n of each group. The F-ratio statistic is used to determine the statistical significance. The F-ratio compares the variance between the groups (variance due to
treatment) divided by the variance within the groups (similar to combining the standard errors). A $p$ value of $<0.05$ was considered statistically significant.

Fasting insulin, HOMA-IR, HOMA insulin sensitivity and HOMA beta cell were non-normally distributed. These data were log transformed to improve kurtosis and skewness before applying parametric statistical tests. HOMA estimates are usually not normally distributed (Wallace, 2004). These variables were all transformed back for presentation in the tables.

Post-hoc testing using pairwise comparisons of the estimated marginal means was used for within group analysis across the trial phases.
CHAPTER 7

Randomised Controlled Trial

Results

This chapter reports on the results of the randomised controlled trial of the Chinese herbal medicine, Jiangtang Xiaozhi in people with prediabetes and mild diabetes. It summarises the recruitment, flow of participants, baseline characteristics of participants and the results of primary and secondary outcomes measures.

7.1 Recruitment

Participants were eligible for enrolment in the trial if they had a diagnosis of IGT or mild diabetes. To confirm eligibility, participants were required to complete a 2 hour oral glucose tolerance test or produce OGTT pathology results no older than three months. Eligible participants were formally enrolled in the study, informed consent was given and they were randomised into a treatment group. A sequence of randomisation numbers was generated using Microsoft Excel computer randomisation strategies. Randomisation was organised by a research officer who was not directly involved in the trial at the Centre of Complementary Medicine Research (CompleMED). Randomisation was conducted completely external and unknown to the research team members.

The study commenced recruitment in July 2007 and closed recruitment in August 2008. The last patient completed the study in February 2009. Participants were recruited from the Sydney and Gosford areas of NSW. Of the 485 participants screened, 382 were ineligible and 71 were randomised and included in the analysis (see Figure 7-1).

The two main reasons for ineligibility were fasting blood glucose levels being too high or too low to meet the trial inclusion criteria; or they were on medication for their blood glucose. Five people decided not to participate before they were randomised.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Figure 7-1 Participant flow through recruitment to trial completion

7.2 Participant discontinuation

Of the 63 participants who completed the study, 28 (88%) were in the placebo group and 35 (90%) were in the Chinese herbal medicine (CHM) group.

In the placebo group, four participants withdrew from the trial. Two weeks into the trial, one participant was given medication for Meniere’s disease. The medication has a known effect on blood glucose levels. Another participant, also in week 2, decided to take medication for her blood sugar rather than being involved in the trial.
A third participant did not notice any changes by week 12 and decided not to continue. One participant started a new job and could not continue with the trial after week 12.

In the CHM group, four participants withdrew. One participant experienced dizziness within 24 hours of starting the medication. The participant was withdrawn from the study. One participant was not contactable after collection of data and pathology at Week 4. Two participants withdrew from the study in Week 9 as they did not notice any therapeutic benefits from taking the medication and decided they did not have the time to continue.

All participants were included in the intention-to-treat analysis.

7.3 Baseline characteristics of participants

Randomisation ensures that baseline values in treatment groups of clinical trials are samples from the same population. Between-group *t*-tests were performed on continuous measures and chi-square tests on categorical values so as to identify any differences to be considered in the analysis. Baseline characteristics of the participants in each group are summarised and reported below.

7.3.1 Risk factors for diabetes

Risk factors for diabetes of the placebo and CHM group at baseline are shown in Table 7-1 along with other relevant medical history. Some of these risk factors were collected and considered for their potentially confounding effect on the trial outcomes and others were considered as outcome measures. Overall there was no significant variation between the CHM and placebo group on age, sex, ethnicity, family history of diabetes, history of hypertension, and smoking.

Age: The mean age for the two groups was similar, 59.8 (±9.0) years in the placebo group and 58.3 (±9.8) years in the CHM group (*p* = .5). The age range was also similar, 40-75 years and 36 – 83 years in the placebo and CHM groups, respectively.
Table 7-1 Between-group comparison of risk factors for diabetes at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 32)</th>
<th>CHM (n = 39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age and Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male — n</td>
<td>18</td>
<td>15</td>
<td>.14</td>
</tr>
<tr>
<td>Female — n</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age — mean (range) age (years)</td>
<td>59.9 (40-75)</td>
<td>58.3 (36-83)</td>
<td>.50</td>
</tr>
<tr>
<td><strong>Risk factors for diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity&lt;sup&gt;a&lt;/sup&gt; — n</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Born in Australia</td>
<td>21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Born in Asia (incl Indian sub-continent),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle East, North Africa, Southern Europe</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes&lt;sup&gt;b&lt;/sup&gt; — n</td>
<td>16</td>
<td>17</td>
<td>.60</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>Current smoker — n</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker — n</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong> — n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking medication for hypertension</td>
<td>17</td>
<td>19</td>
<td>.71</td>
</tr>
<tr>
<td>History of essential hypertension</td>
<td>17</td>
<td>22</td>
<td>.40</td>
</tr>
</tbody>
</table>
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

**Other medical history**

| Duration of IGT or diabetes — mean yrs (range) | 5.2 (0-16) | 3.3 (0-16) | .07 |
| Diagnosed with type 2 diabetes — n            | 21         | 18         | .09 |
| History of high lipids — n                    | 18         | 23         | .82 |
| Taking medication for cholesterol — n         | 14         | 15         | .65 |
| Currently taking prescription medication — n  | 30         | 29         | .06*|
| Currently taking vitamins, minerals or herbal supplements — n | 24 | 24 | .23 |

Note. The table presents raw, unadjusted data; SD — Standard deviation.

a Ethnicity was classified using country of birth, and Aboriginal and Torres Strait Islander heritage was ascertained by a separate question.

b Family history refers to those with a 1st degree relative with diagnosed type 2 diabetes. Duration of IGT or diabetes refers to time from actual diagnosis by pathology.

* indicates the test was significant at p<.05

**Sex:** The CHM group had a higher proportion of women than the placebo group; 24 (62%) versus 14 (44%) respectively. Men have a higher risk of developing diabetes than women. IGT, but IGT is more common in women (11.9 vs. 9.2%)(Dunstan et al., 2002). However there was no significant difference between the two groups (p = .14).

**Ethnicity:** In an examination of potential risk factors for the development of diabetes in the Australian population, the risk for people of southern European, Asian, Aboriginal and Torres Strait Islander and Pacific Islander background were similar and were combined into a single, high-risk ethnic group (Chen, Li, & Yu, 2008). A similar single, high-risk ethnic group was used for this analysis. There were no people of Aboriginal or Torres Islander, or Pacific Islander background in the
sample. The distribution of this high-risk group was similar in the placebo and the CHM group (9 and 13 in each group respectively). The proportion of people born in Australia was not significantly different between the two groups ($p = .45$).

**Family history:** There was a strong family history of diabetes. The two groups had a similar proportion of first degree relatives with diabetes; 44% ($n = 17$) in the CHM group and 50% ($n = 16$) in the placebo group ($p = .60$). There were 9 participants in the placebo group and 16 in the CHM group who did not report a first degree or a second degree relative.

**Use of antihypertensive medications:** Seventeen participants in the placebo group and 19 in the treatment group took concomitant antihypertensive agents representing 53% and 49% of the total participants in their respective cohort. There was no significant difference between the CHM and the placebo groups ($p = .71$).

**Smoking:** There were few current smokers in either group and no significant difference in smoking habits between the two groups ($p = .70$). Ten participants in the placebo group and 15 in the CHM group had previously had a regular smoking habit.

### 7.3.2 Other medical history

Lipid lowering medication was being taken by 14 people in the placebo group and 15 in the CHM group ($p = .65$).

The mean duration since diagnosis of IGT or diabetes was longer in the placebo group (5.2 years and 3.3 years respectively) but this was not statistically significant ($p = .07$). The range of time since diagnosis ranged from newly diagnosed to chronic (over 16 years) in both groups.

The majority of participants in both groups were taking prescription medication, 30 and 29 in the placebo and CHM group respectively.

There were 24 participants in each group taking vitamins, minerals and/or herbal medicines for a variety of ailments, ranging from depression to arthritis ($p = .23$).
Participants were asked to keep their supplement regime stable throughout the course of the trial and to notify the principal investigator of any changes.

### 7.3.3 Anthropometric measurements

Anthropometric and biochemical baseline levels are shown in Table 7-2.

**BMI**: There was no significant difference in BMI between the placebo (32.0±8.0) and the CHM (29.8 ±4.9) groups \( (p = .17) \).

**Body Weight**: Baseline body weight was significantly higher \( (p = .05) \) in the placebo group (92.0± 28.5 kg) compared to that in the CHM group (80.5±15.1 kg).

**Waist**: There was a significant difference \( (p = .01) \) in waist measurement between the placebo group (109.9±22.1 cm) and the CHM group (97.6±11.1 cm).

**Waist-hip-ratio**: Waist-hip-ratio measurements were significantly different \( (p = .012) \) between the placebo (.97 ±19) and CHM group (.88±.07) respectively.

Table 7-2 *Between-group comparison of anthropometric measures at baseline*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>CHM</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ( \text{kg/m}^2 )</td>
<td>32 (8.0)</td>
<td>29.8 (4.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Weight ( \text{kg} )</td>
<td>92.0 (28.5)</td>
<td>80.5 (15.1)</td>
<td>.05</td>
</tr>
<tr>
<td>Waist ( \text{cm} )</td>
<td>109.9 (22.1)</td>
<td>97.6 (11.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>.97 (.19)</td>
<td>.88 (.07)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note. Table presents raw, unadjusted data. SD — Standard deviation.

a Missing data for waist girth: placebo group n=1.

---

175
7.3.4 Biochemical measurements

Biochemical measures for participants in each group at baseline are shown in Table 7-3. There were no significant differences found on any of the primary outcome measures of glycaemic control at baseline.

*Fasting blood glucose:* Fasting blood glucose levels were not significantly different ($p = .17$) between the placebo (6.65 ±1.04 mmol/L) and CHM (6.34±.87 mmol/L) in groups at baseline.

*Post-prandial blood glucose:* Two hour post-prandial fasting blood glucose was only slightly higher in the placebo (1.98±2.90 mmol/L) group compared to the CHM (10.45±2.32 mmol/L) group at baseline, but this was not significant ($p = .40$).

*HbA1c:* Glycaemic control, as measured by HbA1c, exhibited no significant difference between groups ($= .50$), with mean levels of 6.37% (±67) in the placebo group and 6.26% (±53) in the CHM group.

*Insulin:* Insulin levels were higher (.72) in the placebo group (15.53±9.65) than the CHM group (11.79±6.93) at baseline but this was not statistically significant ($p = .07$).

*Total cholesterol:* Total cholesterol was higher in the CHM group (4.9±1.0 mmol/L) compared to the placebo group (4.5±.9 mmol/L) but this was not statistically significant ($p = .06$).

*Triglycerides:* Triglycerides were similar in both groups at baseline, 1.7±.9 mmol/L and 1.7±1.3 mmol/L in the placebo and CHM respectively ($p = 1.0$).

*HDL-Cholesterol:* HDL-cholesterol was slightly higher in the CHM group (1.45±.44 mmol/L) than the placebo group (1.28±.36 mmol/L) at baseline but not significantly ($p = .08$).

*C-reactive protein:* C-reactive protein was similar in both groups 6.7 mg/L (±5.3) in the placebo group and 6.7 mg/L (±7.6) in the CHM group ($p = 1.0$).
### Table 7-3 Between-group comparison of biochemical measures at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>CHM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 32 )</td>
<td>( n = 39 )</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma glucose — mmol/L (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>6.7 (1.0)</td>
<td>6.3 (.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Two hours after an oral glucose load</td>
<td>11.0 (2.9)</td>
<td>10.5 (2.3)</td>
<td>.40</td>
</tr>
<tr>
<td>Glycosylated haemoglobin — % (SD)</td>
<td>6.4 (.7)</td>
<td>6.3 (.6)</td>
<td>.50</td>
</tr>
<tr>
<td>Glycosylated haemoglobin — n ≥ 7%</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin — mmol/L (SD)</td>
<td>15.5 (9.7)</td>
<td>11.8 (6.9)</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Serum lipids — mmol/L (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.5 (.9)</td>
<td>4.9 (1.0)</td>
<td>.06</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.7 (.9)</td>
<td>1.7 (1.3)</td>
<td>.98</td>
</tr>
<tr>
<td>HDL cholesterol^</td>
<td>1.3 (.4)</td>
<td>1.5 (.4)</td>
<td>.08</td>
</tr>
<tr>
<td>C-reactive protein — mg/L (SD)^</td>
<td>6.7 (5.3)</td>
<td>6.7 (7.6)</td>
<td>.97</td>
</tr>
<tr>
<td>Systolic blood pressure — mmHg (SD)^</td>
<td>134.4 (14.0)</td>
<td>124.5 (13.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Diastolic blood pressure — mmHg (SD)^</td>
<td>81.7 (15.9)</td>
<td>76.4 (11.1)</td>
<td>.12</td>
</tr>
</tbody>
</table>

Note. ^Missing data: waist measurement placebo group 1; C-reactive protein Placebo group 1 and CHM 1; HDL CHM group 1; Systolic Blood Pressure CHM group 2; Diastolic BP CHM group 3.

**Blood pressure:** Systolic blood pressure was significantly higher \( (p = .004) \) in the placebo group \( (134.4 ±14.0 \text{ mmHg}) \) compared to the CHM group \( (124.5 ±13.3 \text{ mmHg}) \). There was no significant difference \( (p = .12) \) in diastolic blood pressure between the placebo group \( (81.7±15.9 \text{ mmHg}) \) and the CHM group \( (76.4±11.1 \text{ mmHg}) \).
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

7.3.5 Physical activity, fruit and vegetable intake

Physical activity is known to affect insulin and blood sugar levels (Hakkinen et al., 2009; Laaksonen, 2005). As shown in Table 7-4, the majority of participants in both groups were not undertaking adequate physical activity at baseline. Only 34% of participants in the placebo and 23% in the CHM group undertook over 150 minutes of exercise per week on five separate occasions.

Similar results were found in terms of vegetable intake: Only 25% participants in the placebo group and 36% in the CHM group were eating the recommended level of five serves of vegetables per day. Fruit consumption, however, seemed to be more adequate in both groups (63% and 57% in the placebo and the CHM group respectively).

There were no significant between-group differences at baseline on either physical activity or nutritional variables.

Table 7-4 Between-group comparison of number of participants with adequate physical activity, and fruit & vegetable intake at baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 32)</th>
<th>CHM (n = 39)</th>
<th>p-value+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activitya</td>
<td></td>
<td></td>
<td>.29</td>
</tr>
<tr>
<td>Adequate</td>
<td>11 (34%)</td>
<td>9 (23%)</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>19 (59%)</td>
<td>30 (77%)</td>
<td></td>
</tr>
<tr>
<td>Fruit and Vegetable intakeb</td>
<td></td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>Adequate fruit</td>
<td>20 (63%)</td>
<td>22 (57%)</td>
<td></td>
</tr>
<tr>
<td>Adequate vegetables</td>
<td>8 (25%)</td>
<td>14 (36%)</td>
<td></td>
</tr>
</tbody>
</table>

Note. Between group differences were assessed using chi-square.

a Adequate physical activity is defined as undertaking physical activity for a total of 150 minutes per week over 5 separate occasions. bAdequate fruit consumption was at least 2 serves of fruit a day. Adequate vegetable intake is at least 5 serves per day.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozi for the treatment of prediabetes and mild diabetes: Results

7.4 Primary outcomes

At completion of treatment (week 16), after accounting for baseline values of each of the outcome variables, there were no significant differences identified between the placebo group and the CHM group for any of the glycaemic measurements. Findings for each primary outcome glycaemic measure over time are reported below. Differences on each measure within-groups over time and between-groups at each time point were analysed by ANCOVA using the baseline measure as the covariant.

7.4.1 Fasting blood glucose levels

Baseline assessment

The baseline means for fasting blood glucose were 6.65 ±1.04 mmol/L in the placebo group and 6.34 ±0.87 mmol/L in the CHM group. There was no significant difference between these two groups at baseline (p = .17).

Week 4

At Week 4 of treatment, fasting blood glucose levels were 6.60±1.34 mmol/L and 6.17 ±.97 mmol/L in the placebo and CHM groups respectively, with no significant difference between groups (p = .45). Within groups, there was no significant change over time in the placebo (p = .73) or CHM (p = .14) group.

Week 8

At Week 8, fasting blood glucose levels were 6.56±1.21mmol/L and 6.19±1.01mmol/L in the placebo and CHM groups respectively, with no significant difference between groups (p = .58). Within each group there was no significant change in the placebo (p = .50) or CHM (p = .22) groups from their baseline level.

Week 12

At Week 12 of the trial, there was no significant difference between the CHM and the placebo group (p = .98). FBG levels were 6.48±1.12mmol/L and 6.22±1.04 mmol/L in the placebo and CHM groups respectively. Within group differences
showed no significant change since baseline in the placebo ($p = .16$) or CHM group ($p = .34$).

**Week 16**

After adjusting for pre-intervention values, Table 7-5 shows that fasting blood glucose was not significantly different ($p = .73$) at the completion of the treatment (Week 16) between the CHM group (6.5 ± 7 mmol/L) and the placebo group (6.5±7 mmol/L). No significant differences were detected between baseline and week 16 values within either the placebo or the CHM group (unadjusted data) for fasting blood glucose (placebo $p = .85$; CHM $p = .85$).

Table 7-5 *Outcome: Fasting Blood Glucose (mmol/L) at Baseline and Week 16*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>6.7 (1.0)</td>
<td>6.3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Week 16 (SD)</td>
<td>6.7 (1.3)</td>
<td>6.3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Mean change$^a$</td>
<td>.03</td>
<td>-.02</td>
<td></td>
</tr>
<tr>
<td>F-ratio</td>
<td>.12</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>$p$-value</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes

$^a$means derived from raw data;

$^b$ANCOVA analysis - each outcome was adjusted for baseline values

**Follow up (Week 24)**

At follow-up 8 weeks after the completion of treatment, there was no significant difference ($p = .82$) between the fasting blood glucose levels of the placebo (6.76±1.24 mmol/L) or the CHM group (6.49±1.56 mmol/L). There was no difference within the placebo ($p = .44$) or CHM ($p = .45$) from baseline levels to Week 24.
The changes in fasting blood glucose for each group over time are shown in Figure 7-2.

![Effect of intervention over time on Fasting Blood Glucose](image)

**Figure 7-2** Effect of intervention over time on Fasting Blood Glucose

### 7.4.2 2hr Post-prandial glucose

**Baseline assessment**

The baseline means for 2hr post prandial blood glucose were 10.98 ±2.90 mmol/L in the placebo group and 10.45 ±2.32 mmol/L in the CHM group. There was no significant difference between these two groups at baseline ($p = .40$).

**Week 16**

Table 7-6 shows that at completion of the treatment in Week 16, 2hr post prandial blood glucose levels were 10.60 ±2.90 mmol/L and 9.66±2.59 mmol/L in the placebo and CHM groups respectively, with no significant difference between groups ($p = .51$).
Table 7-6 *Outcome: 2hr Post prandial glucose (mmol/L) at Baseline and Week 16*

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>Week 16 (SD) Mean change</td>
<td>Baseline (SD) Week 16 (SD) Mean change</td>
</tr>
<tr>
<td>11.0 (2.9)</td>
<td>10.6 (3.4) -38</td>
<td>10.5 (2.3) 9.7 (2.6) -79</td>
</tr>
</tbody>
</table>

Notes.

Mean change computed from paired-samples t-test

Means derived from raw data;

^aANCOVA analysis - each outcome was adjusted for baseline values

Within groups, there was a significant change (p = .03) in 2hr post prandial glucose levels from baseline to Week 16 within the CHM group. There was no significant change in the placebo group (p = .34).

*Follow up (Week 24)*

At follow-up 8 weeks after the completion of treatment, there was no significant difference (p = .22) between the 2hr post prandial blood glucose levels of the placebo (10.71±3.39 mmol/L) and the CHM groups (10.15±3.67 mmol/L). There was no significant change within either the placebo (p = .53) or CHM (p = .22) groups from baseline to Week 24.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozi for the treatment of prediabetes and mild diabetes: Results

The changes in post-prandial glucose for each group over time are shown in Figure 7-3.

![Figure 7-3 Effect over time of Intervention on 2hr Post-prandial Glucose](image)

### 7.4.3 Glycosylated haemoglobin (HbA1c)

#### Baseline assessment

Baseline levels of HbA1c levels were 6.4% (±.67) in the placebo group and 6.3% (±.53) in the CHM group. There was no significant difference between the groups.

#### Week 16

As shown in Table 7-7, there was no significant difference between the placebo group and the CHM group for HbA1c levels at completion of treatment in Week 16 ($p = .62$), after accounting for baseline values. Mean HbA1c levels for the CHM group were 6.4% (±.61) versus placebo 6.5% (±.66).
Table 7-7 *Outcome: HbA1c% values at Baseline and Week 16*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Week 16 (SD) Mean change</td>
<td>Baseline (SD) Week 16 (SD) Mean change</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.4 (.7)</td>
<td>6.5 (.7) .15</td>
<td>6.3 (.6) 6.4 (.6) .13</td>
</tr>
</tbody>
</table>

Notes
Mean changes computed from paired-samples t-test. Means derived from raw data.

*ANCOVA analysis - each outcome was adjusted for baseline values

*Follow up (Week 24)*

At follow-up, there was no significant difference (*p* = .29) between the HbA1c levels of the placebo (6.42±.76%) or the CHM group (6.44±.66%). There was no difference within the placebo (*p* = .57) from baseline levels to Week 24.

### 7.5 Secondary outcomes

Findings for each secondary outcome measure over time are reported below. Differences on each measure within-group over time and between-groups at each time point were analysed by ANCOVA using the baseline measure as the covariant except for categorical variables. Differences on categorical variables were analysed by chi-square test for independence.
7.5.1 Insulin

For the ANCOVA analysis, insulin data was log transformed to improve kurtosis and skewness. Results were transformed back for meaningful presentation.

Baseline assessment

Mean insulin levels were higher in the placebo group (15.53±9.65) than in the CHM group (11.79±6.93) at baseline but this was not statistically significant (\(p = .07\)).

Week 4

There was no significant difference between the two groups at Week 4 (\(p = .60\)); unadjusted mean insulin levels were 15.6±12.3 mmol/L and 11.82±7.3 mmol/L in the placebo and CHM group respectively.

Within each group there was no significant change from baseline at Week 4; \(p = .97\) and \(p = .98\) in the placebo and CHM group respectively.

Week 8

In Week 8, there was no significant difference between the placebo and the CHM groups (\(p = .59\)); unadjusted mean insulin levels were 15.5±10.4 mmol/L and 11.64±6.2 mmol/L in the placebo and CHM group respectively.

There was no significant change from baseline to Week 8 within the placebo (\(p = .96\)) or the CHM (\(p = .83\)) group.

Week 12

From baseline to Week 12 there was no significant difference between the placebo and CHM groups (\(p = .47\)). Unadjusted mean insulin levels were 14.7±8.9 mmol/L in the placebo group and 11.7±6.9 mmol/L in the CHM group.

There was no significant change within the placebo (\(p = .44\)) or the CHM (\(p = .93\)) groups at Week 12 of the treatment period.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Week 16

At the completion of the treatment period, there was a significant difference between the placebo and the CHM group ($p = .04$). Unadjusted mean levels of insulin, shown in Table 7-8, were $22.1 \pm 25.9$ mmol/L in the placebo group and $11.6 \pm 5.5$ mmol/L in the CHM group.

Table 7-8 Outcome: Insulin values at baseline and week 16

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>Wk 16 (SD)</td>
<td>Mean change*</td>
</tr>
<tr>
<td>15.5 (9.7)</td>
<td>22.1 (25.9)</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Notes.

*a mean change computed from paired-samples t-test

*b ANCOVA analysis - each outcome was adjusted for baseline covariance

There was no significant difference from baseline to treatment completion within the placebo group ($p = .11$) or the CHM group ($p = .82$).
Follow up (Week 24)

At follow-up, there was no significant difference between the insulin levels of the two groups compared to baseline ($p = .92$). Mean levels of insulin were 19.3±25.2 mmol/L in the placebo group and 14.4±12.2 mmol/L in the CHM group. There was no significant difference within the placebo ($p = .33$) or the CHM group ($p = .21$).

Figure 7-4 Effect of treatment over time on Insulin

7.5.2 Insulin resistance (HOMA-IR)

Baseline assessment

Insulin resistance as calculated by HOMA-IR was not significantly different ($p = .37$) between groups at baseline; mean levels were 2.12±1.30 and 1.63±.91 in the placebo and CHM groups respectively.

Week 4

At week 4 of treatment, HOMA-IR was not significantly different between groups ($p = .56$); mean levels were 1.93±1.26 in the placebo group and 1.58±.98 in the CHM group.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

From baseline to Week 4, there was no significant difference within the placebo group ($p = .43$) or the CHM ($p = .43$).

**Week 8**

At week 8 of treatment, HOMA-IR was not significantly different between groups ($p = .51$); mean levels were $2.06 \pm 1.38$ in the placebo group and $1.55 \pm .82$ in the CHM group.

From baseline to Week 8, there was no significant difference within the placebo group ($p = .68$) or the CHM ($p = .46$).

**Week 12**

At week 12 of treatment, HOMA-IR approached being significantly different between groups ($p = .37$); mean levels were $1.99 \pm 1.20$ in the placebo group and $1.58 \pm .92$ in the CHM group.

From baseline to Week 12, there was no significant difference within the placebo group ($p = .81$) or the CHM group ($p = .47$).

**Week 16**

Table 7-9 shows that at week 16 of treatment, HOMA-IR approached being significantly different between groups ($p = .06$); mean levels were $2.43 \pm 1.59$ in the placebo group and $1.58 \pm .74$ in the CHM group.
Table 7-9 Outcome: Insulin Resistance (HOMA-IR)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>Mean changeb</td>
<td>Baseline (SD)</td>
</tr>
<tr>
<td>2.06 (1.28)</td>
<td>2.43 (.37)</td>
<td>1.63 (.91)</td>
</tr>
</tbody>
</table>

Notes

a p-value calculated from log transformed data using ANCOVA

b mean change calculated from log transformed data using paired-samples t-test

† HOMA values cannot be calculated when the insulin value is <2.9 or >57.6 as they cease to be meaningful. One participant from the placebo group was excluded from the Wk 16 analysis and ANCOVA as the insulin value was 148 mmol/L.

From baseline to Week 16, there was no significant difference within the placebo group (p = .12) or the CHM group (p = .95).

Follow up (Week 24)

Figure 7-5 shows that the levels of HOMA-IR remained fairly steady in both groups from baseline until Week 16 when an increase in levels was observed in the placebo group. Levels in the placebo group had returned to normal at follow up.
From baseline to Week 24, there was no significant difference between the two groups ($p = 1.0$); and there was no significant difference within the placebo group ($p = .97$) or the CHM groups ($p = .58$).

**Figure 7-5 Effect Over Time of Treatment on HOMA-IR$^a$**

### 7.5.3 Beta-cell function (HOMA%B)

HOMA%B is a measure of beta-cell function, it should not be interpreted in an isolated manner but should be seen in conjunction with results for insulin resistance (HOMA-IR) and insulin sensitivity (HOMA%S) for correct understanding. Nonetheless the results are presented here and all HOMA measures discussed in Chapter Six.

**Baseline assessment**

There was no significant difference between the two groups at baseline ($p = .62$).

The mean level of HOMA%B was 86.5±36.8 and 81.5±34.5 in the placebo group and CHM groups respectively.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Week 4

There was no significant difference between the groups by Week 4 ($p = .27$). The mean level of HOMA%B at Week 4 in the placebo group was $85.9 \pm 39.6$ and in the CHM group, $82.2 \pm 33.7$.

Week 8

There was no significant difference between the two groups by Week 8 ($p = .72$). The mean level of HOMA%B at Week 8 was $88.8 \pm 43.9$ and $86.2 \pm 42.3$ in the placebo and CHM groups respectively.

Week 12

There was no significant difference between the placebo group and the CHM group at Week 12 ($p = .49$). The mean level of the HOMA%B at Week 12 was $89.6 \pm 36.8$ in the placebo group and $87.2 \pm 48.6$ in the CHM group.

Week 16

Table 7-10 shows that there was no significant difference between the two groups at the completion of the treatment period ($p = .26$). The mean level of HOMA%B at Week 16 was $98.8 \pm 48.3$ in the placebo group and $83.5 \pm 38.1$ in the CHM group.

Table 7-10 Outcome: Beta-cell function (HOMA%B)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>86.51 (36.78)</td>
<td>98.83 (48.29)</td>
<td></td>
</tr>
<tr>
<td>Wk 16 (SD)</td>
<td></td>
<td>81.52 (34.5)</td>
<td>83.5 (38.1)</td>
</tr>
<tr>
<td>Mean change$^b$</td>
<td>12.31</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>F-ratio</td>
<td>1.32</td>
<td>p-value</td>
<td>.26</td>
</tr>
</tbody>
</table>

Notes

$a$ p-value calculated from log transformed data using ANCOVA

$b$ mean change calculated from log transformed data using paired-samples t-test
† HOMA values cannot be calculated when the insulin value is <2.9 or >57.6 as they cease to be meaningful. One participant from the placebo group was excluded from the Wk 16 analysis and ANCOVA as the insulin value was 148 mmol/L.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Follow up (Week 24)

Figure 7-6 shows unadjusted data over the treatment and follow-up period for HOMA%B. At follow up, eight weeks after the completion of treatment there was no significant difference between the beta-cell function as measured by HOMA%B in the two groups ($p = .66$). The mean level of HOMA%B in the placebo group was $83.1\pm34.4$ and in the CHM group it was $86.8\pm4.3$.

\figure{7-6}{Effect Over Time of Treatment on HOMA%B$^a$}{7.5.4 Insulin sensitivity (HOMA%S)}

$^a$Means derived from raw, unadjusted, ITT data

7.5.4 Insulin sensitivity (HOMA%S)

Baseline assessment

Insulin sensitivity as calculated by HOMA%S was not significantly different ($p = .18$) between groups at baseline; mean levels were $72.8\pm46.4$ and $81.8\pm48.1$ in the placebo and CHM groups respectively.

Week 4
At week 4 of treatment, HOMA%S was not significantly different between groups \( (p = .32) \); mean levels were 74.2±44.1 in the placebo group and 91.2±6.3 in the CHM group.

From baseline to Week 4, there was no significant difference within the placebo group

Week 8

At week 8 of treatment, HOMA%S was not significantly different between groups \( (p = .14) \); mean levels were 71.4±41.3 in the placebo group and 85.3±48.4 in the CHM group.

From baseline to Week 8, there was no significant difference within the placebo group \( (p = .74) \) or the CHM \( (p = .33) \).

Week 12

At week 12 of treatment, HOMA%S was not significantly different \( (p = .10) \) between groups, mean levels were 67.1±33.4 in the placebo group and 85.4±47.2 in the CHM group.

From baseline to Week 12, there was no significant difference within the placebo group \( (p = .87) \) or the CHM group \( (p = .33) \).

Week 16

Table 7-11 shows there was no significant difference between the two groups in insulin sensitivity, as determined by HOMA%S, from baseline to the completion of treatment \( (p = .34) \). Mean levels at trial completion were 62.7±38.5 and 79.7±44.1 in the placebo and CHM groups respectively.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Table 7-11 Outcome: Insulin sensitivity (HOMA%)$^S$

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Wk 16 (SD) Mean change*</td>
<td>Baseline (SD) Week 16 (SD) Mean change*</td>
</tr>
<tr>
<td>Baseline</td>
<td>72.78 (46.42)</td>
<td>62.67 (38.48) -1.10</td>
<td>81.84 (48.12) 79.72 (44.14) -2.12</td>
</tr>
</tbody>
</table>

Notes
*mean change calculated from log transformed data using paired-samples t-test
^p-value calculated from log transformed data using ANCOVA
† HOMA values cannot be calculated when the insulin value is <2.9 or >57.6 as they cease to be meaningful. One participant from the placebo group was excluded from the Wk 16 analysis and ANCOVA as the insulin value was 148 mmol/L.

Insulin sensitivity within the placebo group declined over the period of trial, although this failed to reach statistical significance ($p = .35$). Insulin sensitivity at the completion of the treatment period was similar to baseline levels ($p = .32$).

Follow up (Week 24)

There was no significant difference between the placebo and CHM group at follow up compared to their baseline levels ($p = .88$). Eight weeks after treatment was completed, there was no significant change within the placebo ($p = .35$) or the CHM group ($p = .59$) compared to their baseline values.
Figure 7-7 shows the levels of HOMA%S over the duration of the trial for the placebo and the CHM group.

![Figure 7-7 Effect Over Time of Treatment on HOMA%S](image)

*Means derived from raw, unadjusted, ITT data*

In the CHM group, insulin sensitivity improved moderately at the outset of the trial, remained stable and returned to similar pre-treatment levels at Week 24. The placebo group showed a slight decline in insulin sensitivity but returned to pretreatment levels by Week 24. Mean levels were 70.3±39.2 and 74.4±41.1 in the placebo and CHM groups respectively.

### 7.5.5 HOMA sensitivity analysis

The HOMA calculator does not take insulin values which are outside those normally seen clinically, either too low or too high. There were some participants that had insulin values too high or too low for inclusion in HOMA and were therefore excluded from the ANCOVA.

At baseline one participant in the CHM group was excluded from the HOMA as the insulin level was too low (2 mmol/L).
At week 16, one participant in the placebo group was excluded from the HOMA analysis as the insulin value was too high (148 mmol/L).

At week 24, three participants were excluded as follows, two from the CHM group (values were 1 mmol/L and 75 mmol/L) and one from the placebo group (148 mmol/L).

A sensitivity analysis was conducted including these participants by imputing the highest insulin value acceptable (57.5 mmol/L) for HOMA calculation where the insulin value of the participant exceeded the top of the range. Similarly the lowest insulin value acceptable (2.9 mmol/L) was imputed for a participant with an insulin value too low for HOMA calculations. HOMA values cannot be calculated when the insulin value is <2.9 or >57.6.

Table 7-12 Sensitivity analysis: HOMA-IR, HOMA%S and HOMA%B

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo*</th>
<th></th>
<th>Chinese medicine*</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Wk 16</td>
<td>Baseline</td>
<td>Week 16</td>
<td>F-ratio</td>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td>(SD)</td>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.12±1.30</td>
<td>2.59±1.79</td>
<td>1.60±.92</td>
<td>1.57±.73</td>
<td>4.09</td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA%S</td>
<td>71.31±46</td>
<td>61.14±38</td>
<td>86.18±54</td>
<td>8.38±43.7</td>
<td>4.34</td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>84</td>
<td>67</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA%B</td>
<td>87.95±37</td>
<td>102.20±51</td>
<td>8.31±34.9</td>
<td>82.99±37</td>
<td>2.10</td>
<td>.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>08</td>
<td>.21</td>
<td>1</td>
<td>68</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes *raw data, with high and low insulin values imputed for HOMA calculations

**calculated from log transformed data with imputed HOMA values
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

The baseline to week 16 ANCOVA with the additional two values imputed resulted in slightly strengthened results for insulin resistance as measured by HOMA-IR, \( p = .05 \) versus \( p = .06 \) in the previous analysis.

For insulin sensitivity (HOMA%S) results became statistically significant, \( p = .04 \) versus \( p = .34 \) in the previous analysis.

For the beta-cell function (HOMA%B) results there continued to be no statistically significant result, \( p = .15 \) versus \( p = .26 \).

No significant changes were noticed in the baseline to week 24 ANCOVA. HOMA-IR at week 24 there was no significant difference between groups (\( p = .74 \)). HOMA%B at week 24 there was no significant difference between groups (\( p = .58 \)). HOMA%S at week 24 there was no significant difference between groups (\( p = .77 \)).

7.5.6 C-reactive protein

C-reactive protein (CRP) is an inflammatory marker. It has been found to predict the development of Type 2 diabetes independent of any other risk factors.

Baseline assessment

C-reactive protein (CRP) was similar in both groups 6.7±5.3 mg/L in the placebo group and 6.7±7.6 mg/L in the CHM group (\( p = 1.0 \)).

Week 4

Between the placebo and the CHM group there was no significant difference in CRP at Week 4 compared to baseline (\( p = .84 \)).

Within the placebo and the CHM group there was no significant difference between baseline values and week 4. Mean values of CRP were slightly lower in both groups, 6.3±6.0 mg/L, \( p = .63 \) and 6.0±7.2 mg/L, \( p = .84 \) in the placebo and CHM respectively.

Week 8
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Between the placebo and the CHM group there was no significant difference in CRP at Week 8 compared to baseline ($p = .11$).

Within the placebo group levels were similar to baseline in the placebo group (6.7±6.3 mg/L; $p = 1.0$) and had reduced in the CHM group (4.9±2.9 mg/L, $p = .17$).

**Week 16**

Table 7-13 shows that at the completion of the treatment period there was no significant difference between the two groups in the C-reactive protein levels ($p = .32$). Within the CHM group mean values decreased from 6.7±7.5 mg/L to 4.7±1.8 mg/L but not significantly ($p = .09$). Within the placebo group, mean values were also less than baseline from 6.7±5.3 mg/L to 4.6±2.2 mg/L but not significantly ($p = .11$).

**Table 7-13 Outcome: C-reactive protein**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>Wk 16 Mean change*</td>
<td>Baseline (SD)</td>
</tr>
<tr>
<td>6.73 (5.25)</td>
<td>5.18 (3.00)</td>
<td>1.55</td>
</tr>
</tbody>
</table>

*Follow up (Week 24)*

At follow up CRP levels were not significantly different between the two groups compared to baseline levels ($p = .32$).

Within the CHM group there was no significant change identified between baseline and follow up CRP levels; mean levels at week 24 were 5.01±2.5 mg/L ($p = .16$). In the placebo group, mean levels were significantly lower than the baseline levels 4.6±2.2 mg/L ($p = .02$).
7.5.7 Cholesterol

Baseline assessment

At baseline mean levels of cholesterol were 4.5±.9 mmol/L in the placebo group and 4.9±1.0 mmol/L in the CHM group. The difference between groups was approaching statistical significance (p = .06).

Week 8

There was no significant change between baseline and Week 8 of treatment between the two groups (p = .23). Mean levels were 4.6±.8 mmol/L in the placebo group and 4.8±.1 mmol/L in the CHM group. There was no significant change within the placebo (p = .21) or the CHM group (p = .17).

Week 16

Table 7-14 shows that the mean levels of cholesterol were not significantly different between the two groups at the completion of the treatment phase of the trial (p = .46), levels were 4.6±.8 mmol/L and 5.0±1.0 mmol/L in the placebo and CHM group respectively. There was no significant change within the placebo (p = .51) or the CHM group (p = .70) from the start of treatment to completion.

Table 7-14 Outcome: Total cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Wk 16 (SD) Mean change*</td>
<td>Baseline (SD) Week 16 (SD) Mean change*</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.47 (.85)</td>
<td>4.56 (.81) .09</td>
<td>4.91 (1.03) 4.96 (.94) -.05</td>
</tr>
</tbody>
</table>
Follow up (Week 24)

At follow up there was no significant difference between the two groups in cholesterol levels ($p = .88$), mean levels were $4.7 \pm 0.9$ mmol/L and $5.0 \pm 1.0$ mmol/L in the placebo and CHM group respectively.

There was no significant difference within the placebo ($p = .12$) or CHM group ($p = .34$) from baseline values to eight weeks after treatment was completed.

Sensitivity analysis: Cholesterol Lowering Medication

A sensitivity analysis was done to examine the effect on those not taking any cholesterol lowering medication to determine if there was any change to the week 16 results. When those taking cholesterol lowering medication were excluded from the analysis ($n = 29$), there was no significant change from baseline to week 16 in cholesterol levels ($p = .54$).

7.5.8 Triglycerides

Baseline assessment

At baseline mean levels of triglycerides were $1.67 \pm 0.93$ mmol/L and $1.66 \pm 1.27$ mmol/L in the placebo and CHM groups respectively.

Week 8

Triglycerides changed little between groups from baseline to week 8 of treatment ($p = .94$), mean levels were $1.68 \pm 0.93$ mmol/L in the placebo group and $1.69 \pm 1.14$ mmol/L in the CHM group.

Within the placebo and CHM group there was no significant change from baseline to week 8, $p = .94$ and $p = .84$ respectively.

Week 16
Triglycerides showed no significant change from baseline to end of treatment between groups ($p = .92$). Within the placebo group, mean triglycerides were $1.59 \pm .86$ mmol/L and showed no significant change ($p = .35$). Within the CHM group, mean triglycerides were $1.60 \pm .76$ mmol/L with no significant change at the end of treatment ($p = .73$).

**Table 7-15 Outcome: Triglycerides**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Wk 16 (SD)</td>
<td>Mean change*</td>
</tr>
<tr>
<td></td>
<td>1.67 (.93)</td>
<td>1.59 (.86)</td>
<td>-.08</td>
</tr>
</tbody>
</table>

**Follow up (Week 24)**

At follow up there was no difference between the two groups ($p = .39$). Within groups, mean levels within the placebo group were similar to baseline, $1.65 \pm .86$ mmol/L ($p = .71$); and within the CHM group levels were slightly lower but not significantly, $1.52 \pm .73$ mmol/L ($p = .41$).

**Sensitivity analysis: Cholesterol Lowering Medication**

There was no significant difference in triglyceride levels detected between groups at week 16 compared to baseline when those taking medication for cholesterol lowering were excluded ($p = .52$).

**7.5.9 HDL cholesterol**

**Baseline assessment**
At baseline high-density lipoprotein (HDL) cholesterol, otherwise known as ‘good’ cholesterol, was slightly higher in the CHM group (1.45±.44 mmol/L) than the placebo group (1.28±.36 mmol/L) but not significantly (p = .08).

**Week 8**

From baseline to week 8 there no significant change between groups (p = .48). HDL levels in the placebo group were similar to baseline (1.28±.36 mmol/L; p = .55). In the CHM levels were fairly similar to baseline (1.47±.54 mmol/L; p = 70).

**Week 16**

As shown in Table 7-16 by the completion of treatment there was a significant difference between groups when controlling for the baseline variation through ANCOVA (p = .03). Mean levels in the placebo group had slightly worsened (1.24±.30 mmol/L) compared to baseline and slightly improved in the CHM group (1.54±.53 mmol/L). There were no significant changes when looking within each group at completion compared to baseline; p = .47 and p = .14 in the placebo and CHM group, respectively.

Table 7-16 **Outcome: HDL Cholesterol**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>Wk 16 (SD)</td>
<td>Mean change*</td>
</tr>
<tr>
<td>1.28 (.30)</td>
<td>1.24 (.30)</td>
<td>-.04</td>
</tr>
</tbody>
</table>

*Follow up (Week 24)*
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Figure 7-8 shows the levels of HDL cholesterol over the treatment period and at follow up. There was no longer a significant difference between the two groups at follow up ($p = .11$). Mean levels in the CHM group decreased to $1.45 \pm .42$ mmol/L and were not significantly different to baseline levels ($p = .94$). Mean levels in the placebo group were $1.24 \pm .28$ mmol/L, similar to baseline levels ($p = .46$).

![Figure 7-8 Effect Over Time of Treatment on HDL Cholesterol]

**Sensitivity analysis: Cholesterol Lowering Medication**

When those taking medication for cholesterol lowering were excluded from the week 16 ANCOVA there was no longer a significant effect detected in the CHM group ($p = .13$). However, there may not have been significant numbers to detect an effect (placebo $n = 18$ and CHM $n = 24$).

### 7.5.10 Blood pressure

**Baseline assessment**

Systolic blood pressure was significantly higher ($p = .004$) in the placebo group ($134.4 \pm 14.0$ mmHg) compared to the CHM group ($124.5 \pm 13.3$ mmHg).

Diastolic blood pressure was similar in the placebo group ($81.7 \pm 15.9$ mmHg) and the CHM group ($76.4 \pm 11.1$ mmHg); $p = .12$. 
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Week 8

There was no significant difference between groups in either diastolic blood pressure ($p = .90$) or systolic blood pressure ($p = .96$).

Diastolic blood pressure significantly decreased from a mean of 81.7±15.9 mmHg to 77.8±15.9 ($p = .002$) within the placebo group between baseline and week 8. Mean diastolic blood pressure in the CHM group was 74.6±8.1 mmHg with no significant change from baseline ($p = .17$).

Systolic blood pressure did not change significantly within the placebo ($p = .09$) or the CHM ($p = .88$) group; mean values were 131.4±14.0 mmHg and 125.2±12.0 mmHg in the placebo and CHM groups respectively.

Week 16

As shown in Table 7-17, at completion of the treatment period, there was no significant differences in systolic blood pressure ($p = .96$) or diastolic blood pressure ($p = .96$) between the two groups.

Within the placebo group, mean systolic blood pressure was 13.1±16.1 mmHg slightly lower than baseline levels ($p = .07$). In the CHM group, mean systolic blood pressure was 124.1±15.5 mmHg virtually unchanged from baseline levels of 124.5±13.3 mmHg ($p = .74$).

At completion of the trial, diastolic blood pressure was significantly different compared to baseline within both the placebo ($p = .02$) and the CHM group ($p = .01$), reducing slightly to 74.3±20.2 mmHg and 71.7±8.6 mmHg in the placebo and CHM group respectively. Although a reduction at these levels is not clinically meaningful.
## Table 7-17 Outcome: Blood pressure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16 (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Wk 16 (SD)</td>
<td>Mean change* (SD)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>81.7 (15.9)</td>
<td>74.3 (2.2)</td>
<td>7.4</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>134.4 (14.0)</td>
<td>130.1 (16.1)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Notes

* SD – Standard Deviation

*mean change computed from paired-samples t-test

**Follow up (Week 24)**

At the follow up eight weeks after completion of the treatment there was no significant difference between both systolic (p = .99) and diastolic blood pressure (p = .20).

There was no significant difference within the CHM group from baseline to follow up in diastolic (p = .12) or systolic (p = .06) blood pressure. Mean diastolic levels at follow up were 73.5±8.3 mmHg and systolic levels were 121.5±12.3 mmHg.
In the placebo group, there was a statistically significant drop in systolic blood pressure (128.2±17.2 mmHg; $p = .02$) but not in diastolic blood pressure (79.5±15.5 mmHg; $p = .19$).

**Blood pressure and Anti-hypertensive Medication**

Results for systolic and diastolic blood pressure were not significantly affected by anti-hypertensive medication. Systolic blood pressure at week 16 in those taking blood pressure medication ($n = 33$) was not significantly different to baseline ($p = .61$), or in those not taking medication ($p = .90$).

Diastolic blood pressure at week 16 in those taking blood pressure medication was not significantly different to baseline ($p = .48$), or in those not taking medication ($p = .14$).

### 7.5.11 Weight

**Baseline assessment**

Baseline body weight was significantly higher ($p = .05$) in the placebo group (92.0±28.5 kg) compared to that in the CHM group (8.5±15.1 kg).

**Week 4**

In the ANCOVA analysis, there was no difference between the groups ($p = .31$) at week 4; mean values were 92.7±28.2 in the placebo group and 8.6±15.0 in the CHM group.

There was no significant difference within the placebo ($p = .17$) or the CHM ($p = .80$) at week 4 compared to their baseline values.

**Week 8**

At week 8, there was no significant difference between groups compared to baseline ($p = .30$); mean values were 92.1±28.6 in the placebo group and 80.2±14.9 in the CHM group.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

There was no significant difference within the placebo ($p = .56$) or the CHM ($p = .41$) at week 8 compared to their baseline values.

**Week 12**

There was no significant difference between groups at Week 12 compared to baseline ($p = .62$); mean values were $92.0\pm28.6$ in the placebo group and $80.4\pm15.0$ in the CHM group. These values were not significantly different within the placebo ($p = .95$) or the CHM ($p = .51$) at week 12 when compared to baseline values.

**Week 16**

As shown in Table 7-18, there was no significant difference between the CHM and the placebo group in weight ($p = .84$); mean values were $91.8\pm28.6$ in the placebo group and $80.4\pm15.0$ in the CHM group.

Within the placebo group, the mean weight was similar to baseline mean weight ($p = .46$). Likewise within the CHM group, the mean weight did not significantly change compared to baseline ($p = .76$).

**Table 7-18 Outcome: Weight**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (SD)</th>
<th>CHM (SD)</th>
<th>Difference between groups at Wk16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Week 16 (SD)</td>
<td>Mean change</td>
</tr>
<tr>
<td>Weight</td>
<td>92.0 (28.5)</td>
<td>91.8 (28.6)</td>
<td>.23</td>
</tr>
</tbody>
</table>

— kg
Follow up (Week 24)

Figure 7-9 shows that mean body weight was stable in both groups over the duration of the trial and the follow up. At follow up there was no significant between groups (\( p = .72 \)) or within groups; mean value in the placebo group was 91.8±28.6 kg (\( p = .58 \)) and 80.2±14.7 kg in the CHM (\( p = .37 \)).

![Figure 7-9 Effect Over Time of Treatment on Weight](image)

### 7.5.12 BMI

**Baseline assessment**

At the start of the trial there was no significant difference in BMI between the placebo (32.0±8.0) and the CHM (29.8 ±4.9) groups (\( p = .17 \)).

**Week 4**

At week 4 the two groups showed no significant difference in BMI (\( p = .68 \)). Within groups, BMI did not change significantly; mean values were 32.2±7.8 (\( p = .15 \)) and 29.9±4.8 (\( p = .41 \)) in the placebo and CHM groups respectively.

**Week 8**
At week 8 there was no significant difference between the two groups ($p = .34$). BMI remained stable within both groups compared to baseline; mean values were $32.0 \pm 8.0$ ($p = .63$) and $29.0 \pm 6.8$ ($p = .30$) in the placebo and CHM groups respectively.

**Week 12**

At week 12 BMI in the two groups was not significantly different ($p = .51$). No significant change was detected within groups at Week 12 compared to baseline; mean values were $31.4 \pm 1.6$ ($p = .58$) and $29.9 \pm 4.9$ ($p = .53$) in the placebo and CHM groups respectively.

**Week 16**

Table 7-19 shows that body mass index (BMI) remained similar for both groups from trial commencement to completion between groups ($p = .64$). Within groups, BMI stayed similar to baseline values; $32.5 \pm 8.8$ ($p = .28$) and $3.0 \pm 4.8$ ($p = .30$).

**Table 7-19 Outcome: BMI**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (SD)</th>
<th>CHM (SD)</th>
<th>Difference between groups at Wk16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Week 16 (SD)</td>
<td>Mean change</td>
</tr>
<tr>
<td><strong>BMI kg/m²</strong></td>
<td>32.0 (8.0)</td>
<td>31.2 (1.8)</td>
<td>.47</td>
</tr>
</tbody>
</table>
Follow up (Week 24)

Figure 7-10 shows that BMI varied little over the duration of the trial and at follow up were not significantly different between groups \( (p = .17) \). Mean values at follow up were not significantly different to baseline, in the CHM group values were almost the same as baseline, \( 29.7\pm4.8 \) \( (p = .61) \), and in the placebo group values were just higher, \( 34.0\pm12.1 \) then baseline but certainly not significantly \( (p = .26) \).

\[ 
\begin{align*}
\text{Wk0} & \quad \text{WK4} & \quad \text{Wk8} & \quad \text{Wk12} & \quad \text{Wk16} & \quad \text{Follow up} \\
\text{BMI} & \\
\end{align*}
\]

Figure 7-10 Effect Over Time of Treatment on BMI

7.5.13 Waist

Baseline assessment

At baseline there was a significant difference \( (p = .01) \) in waist measurement between the placebo group \( (109.9\pm22.1 \text{ cm}) \) and the CHM group \( (97.6\pm11.1 \text{ cm}) \).

Week 4
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

There was no significant difference between the two groups at week 4 adjusting for covariance at baseline ($p = .65$). Within groups, there was no significant change in the first 4 weeks of the trial; mean values were 109.6±2.9 cm ($p = .72$) in the placebo group and 99.2±11.5 ($p = .16$) in the CHM group.

**Week 8**

There was no significant difference in waist measurement between groups at week 8 after adjusting for baseline variation ($p = .11$). Within the placebo group, mean values were similar to baseline, 109.0±21.9 cm ($p = .39$). Within the CHM group, mean values were significantly higher, 10.0±12.2 cm ($p = .03$).

**Week 12**

At week 12 there was a significant difference between the waist measurement of the two groups in favour of the placebo group after values were adjusted for baseline ($p = .03$). Within groups there was a significant difference compared to baseline values in the placebo group, with a slight decrease in waist measurement 107.0±18.8 ($p = .03$); and in the CHM group with a slight increase in waist measurement 10.1±12.3 cm ($p = .03$).

**Week 16**

As shown in Table 7-20, at completion of the treatment period, the difference in waist measurements between the CHM and the placebo groups was borderline statistically significant in favour of the placebo group ($p = .05$). However, the magnitude of the change was very small (mean between-group difference of 2.2cm which is equivalent to .13 of a standard deviation) and therefore not clinically significant.

Within-group changes at trial completion were significant in the placebo group, with a mean value of 106.3±19.0 ($p = .01$) but not within the CHM group where the mean value was 99.1±11.9 ($p = .16$).
Table 7-20 Outcome: Waist

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (SD)</th>
<th>CHM (SD)</th>
<th>Difference between groups at Wk16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Week 16 (SD)</td>
<td>Mean change</td>
</tr>
<tr>
<td>Waist cm</td>
<td>109.9 (22.1)</td>
<td>106.3 (18.6)</td>
<td>3.59</td>
</tr>
</tbody>
</table>

Follow up (Week 24)

Figure 7-11 shows that waist measurements were fairly stable throughout the duration of the trial with some small shifts some of which were statistically significant but not so clinically meaningful. At Week 24, the difference between the two groups approached statistical significance ($p = .06$).

Mean values within groups at week 24 compared to baseline were statistically significant in the placebo group ($106.1 \pm 18.9$ cm; $p = .003$) but not in the CHM group ($98.6 \pm 11.9$ cm; $p = .36$).
7.5.14 Waist-hip-ratio

Baseline assessment

Waist-hip-ratio measurements were significantly different ($p = .012$) between the placebo ($0.97 \pm 0.19$) and CHM group ($0.88 \pm 0.07$).

Week 4

There was no significant difference in WHR between the two groups at week 4 adjusting for covariance at baseline ($p = .44$).

Within groups, there was no significant change in WHR the first 4 weeks of the trial; mean values were $0.94 \pm 0.10$ ($p = .32$) in the placebo group and $0.89 \pm 0.07$ ($p = .07$) in the CHM group.

Week 8

There was no significant difference in WHR between groups at week 8 after adjusting for baseline variation ($p = .47$).
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Within the placebo group, mean values were $0.95 \pm 0.11$ ($p = 0.38$). Within the CHM group, mean values were statistically significantly different compared to baseline, $0.90 \pm 0.08$ ($p = 0.03$), representing a clinically small increase.

**Week 12**

At week 12 there was no significant difference between the WHR of the two groups after values were adjusted for baseline ($p = 0.79$).

Within groups there was a significant difference compared to baseline values in the placebo group, with a slight decrease in mean WHR $0.94 \pm 0.11$ ($p = 0.24$); and in the CHM mean WHR was $0.89 \pm 0.07$ ($p = 0.04$), although statistically significant it represents a clinically marginal change.

**Week 16**

As shown in Table 7-21, at completion of the treatment period, the difference in WHR between the CHM and the placebo groups was not significant ($p = 0.93$).

Within group changes in the placebo group were not significant ($p = 0.16$), mean value at trial completion was $0.92 \pm 1$. Within the CHM group WHR was slightly and statistically significantly higher compared to baseline, mean value was $0.89 \pm 0.08$ ($p = 0.04$). Weight and waist-hip ratio did not change significantly in any group ($p = 0.84$ and $p = 0.93$ respectively).
Table 7-21 Outcome: WHR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (SD)</th>
<th>CHM (SD)</th>
<th>Difference between groups at Wk16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>Week 16 (SD)</td>
<td>Mean change</td>
</tr>
<tr>
<td>WHR waist/hips</td>
<td>.97 (.19)</td>
<td>.91 (.1)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Follow up (Week 24)

Figure 7-12 shows the WHR of the two groups over the duration of the trial and at follow up. There was no significant difference between groups at the end of the follow up period compared to baseline (p = .73). Within groups, mean values were similar to treatment completion and compared to baseline not statistically significant, mean values were .92±10 (p = .20) and .89±07 (.18) in the placebo and CHM groups respectively.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Figure 7-12 Effect Over Time of Treatment on WHR

7.5.15 Health related quality of life

The health related quality of life between the two groups at baseline is shown in Table 7-22. A higher score is indicative of better quality of life on that dimension.
Table 7-22 Baseline Health Related Quality of Life

<table>
<thead>
<tr>
<th>SF-36 Dimension</th>
<th>Placebo Mean (SD)</th>
<th>Chinese herbal medicine (SD)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning (PF)</td>
<td>44.59 (11.44)</td>
<td>47.18 (8.98)</td>
<td>.30</td>
</tr>
<tr>
<td>Role physical (RP)</td>
<td>46.23 (9.68)</td>
<td>47.15 (9.23)</td>
<td>.70</td>
</tr>
<tr>
<td>Bodily pain (BP)</td>
<td>46.30 (9.84)</td>
<td>45.59 (10.23)</td>
<td>.77</td>
</tr>
<tr>
<td>General health (GH)</td>
<td>44.52 (8.25)</td>
<td>46.91 (10.32)*</td>
<td>.30</td>
</tr>
<tr>
<td>Vitality (VT)</td>
<td>45.69 (5.79)</td>
<td>46.16 (6.75)</td>
<td>.76</td>
</tr>
<tr>
<td>Social functioning (SF)</td>
<td>47.44 (11.01)</td>
<td>46.39 (10.65)</td>
<td>.69</td>
</tr>
<tr>
<td>Role emotional (RE)</td>
<td>43.20 (12.68)</td>
<td>43.03 (14.95)</td>
<td>.96</td>
</tr>
<tr>
<td>Mental health (MH)</td>
<td>37.05 (8.15)</td>
<td>36.68 (7.48)</td>
<td>.85</td>
</tr>
</tbody>
</table>

Notes

*missing data n = 3

**p-value between study groups according to an independent samples 2-tailed t-test
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

The quality of life of the participants with early diabetes and impaired glucose tolerance were compared with the quality of life of the general Australian population. Figure 7-13 shows the Australian population normed T-scores compared with the T-scores from the participants of the clinical trial for the eight dimensions of the SF-36V2 (Hawthorne, Osborne, Taylor, & Sansoni, 2007).

Figure 7-13 Comparison of Baseline Group with Australian normative data

The clinical trial cohort differed significantly from the Australian normative data for both the age relevant cohort (55-64 yrs) on the dimensions of vitality (p<.02), role emotional (p<.0001) and mental health (p<.0001)

Baseline results are compared with the SF-36 results at Week 16 in Table 7-23.

Physical functioning

The physical functioning dimension of the SF-36 indicates the extent to which, on a typical day, a person is limited by their health in performing a range of physical activities. There were no significant differences between the two groups at baseline (p = .30) or week 16 (p = .72).
Within groups, the mean T-score for the placebo group at baseline was 44.59±11.44 compared to 44.73±12.34 at week 16 \((p = .89)\). The mean T-score for the CHM group was slightly higher at baseline 47.18±8.98 compared to 46.42±11.83 at week 16 \((p = .62)\).

**Role — Physical**

There were no significant differences between the two groups at baseline on the SF 36 dimension of Physical Role \((p = .70)\). At week 16, there was still no significant difference between groups \((p = .92)\).

At week 16 the mean T-score for the placebo group of 45.71±1.60 was not significantly different \((p = .72)\) to the baseline mean of 46.23±9.68. The mean T-score for CHM group was 47.15±9.23 and at week 16 46.46±9.32 \((p = .66)\).

**Bodily pain**

There were no significant differences between the two groups at baseline on the SF 36 dimension of Bodily Pain \((p = .77)\). At week 16, there was still no significant difference between groups \((p = .28)\).

At week 16 the mean T-score for the placebo group of 45.33±11.23 was not significantly different \((p = .51)\) to the baseline mean of 46.30±9.84. The mean T-score for CHM group was 45.59±10.23 and at week 16, 47.16±10.16 \((p = .36)\).

**General Health**

There were no significant differences between the two groups at baseline on the SF 36 dimension of General Health \((p = .30)\). At week 16, there was still no significant difference between groups \((p = .31)\).

At week 16 the mean T-score for the placebo group of 45.18±8.86 was not significantly different \((p = .57)\) to the baseline mean of 46.23±9.68. The mean T-score for CHM group was 46.91±1.32 and at week 16 48.32±8.66 \((p = .24)\).
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Vitality

There were no significant differences between the two groups at baseline on the SF 36 dimension of Vitality ($p = .76$). At week 16, there was still no significant difference between groups ($p = .53$).

At week 16 the mean T-score for the placebo group of 47.56±10.85 was not significantly different ($p = .26$) to the baseline mean of 45.91±5.74. The mean T-score for CHM group was significantly better ($p = .03$) at week 16 (48.99±9.0) compared to the baseline mean value of 46.16±6.76.

Social functioning

There were no significant differences between the two groups at baseline on the SF 36 dimension of Social Functioning ($p = .69$). At week 16, there was still no significant difference between groups ($p = .21$).

At week 16 the mean T-score for the placebo group of 45.17±12.05 was not significantly different ($p = .09$) to the baseline mean of 47.16±11.07. The mean T-score for CHM group was similar ($p = .75$) at week 16 (46.85±10.95) compared to the baseline mean value of 46.39±10.65.

Role—emotional

There were no significant differences between the two groups at baseline on the SF 36 dimension of Role-Emotional ($p = .96$). At week 16, there was still no significant difference between groups ($p = .49$).

At week 16 the mean T-score for the placebo group of 42.60±12.91 was not significantly different ($p = .75$) to the baseline mean of 43.20±12.68. The mean T-score for CHM group was not significantly different ($p = .60$) at week 16 (44.49±13.40) compared to the baseline mean value of 43.03±14.95.
Mental health

There were no significant differences between the two groups at baseline on the SF 36 dimension of Mental Health ($p = .85$). At week 16, there was still no significant difference between groups ($p = 1.0$).

At week 16 the mean T-score for the placebo group of $36.79\pm7.97$ was not significantly different ($p = .89$) to the baseline mean of $36.64\pm7.97$. The mean T-score for CHM group was not significantly different ($p = .92$) at week 16 ($36.81\pm8.92$) compared to the baseline mean value of $36.68\pm7.48$. 


### Table 7-23 Health related quality of life: baseline – week 16

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (SD)*</th>
<th>CHM (SD)*</th>
<th>Difference between groups at Wk16^</th>
<th>F-ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 16</td>
<td>Mean change</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical funct</td>
<td>44.59 (11.44)</td>
<td>44.73 (12.34)</td>
<td>-.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>46.26 (9.66)</td>
<td>45.71 (10.60)</td>
<td>.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>46.30 (9.84)</td>
<td>45.33 (11.23)</td>
<td>.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>44.52 (8.25)</td>
<td>45.18 (8.86)</td>
<td>-.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>45.91 (5.74)</td>
<td>47.56 (10.85)</td>
<td>-1.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>47.16 (11.07)</td>
<td>45.17 (12.05)</td>
<td>1.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role emotional</td>
<td>43.20 (12.68)</td>
<td>42.60 (12.91)</td>
<td>.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>36.64 (7.95)</td>
<td>36.79 (7.97)</td>
<td>-.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes**

SD – Standard Deviation

*Unadjusted data
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

**ANCOVA analysis - each outcome was adjusted for baseline covariance.**

Figure 7-14 shows that the SF 36 T-scores for the placebo group and the CHM group at Week 16 were similar across all dimensions.

![Figure 7-14 SF-36 Dimension T-Scores at Week 16](image)

**7.5.16 Safety parameters**

The liver function of all participants was assessed at the baseline and throughout the trial to monitor for any possible adverse reactions. It is noted that the liver enzymes, ALT, AST and GGT, were slightly higher in the placebo group (32.8±23.0, 25.4±14.6, 48.9±61.4 respectively) than that in the CHM group (28.5±13.4, 22.2±6.7, 35.9±37.4 respectively). However these differences failed to reach statistically difference ($p = .34$, $p = .23$ and $p = .28$ respectively).
Table 7-24 *Liver function values at baseline*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>P value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 32</td>
<td>n = 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT — IU/L (SD)</td>
<td>32.78 (22.95)</td>
<td>28.78±13.45</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>AST — IU/L (SD)</td>
<td>25.44 (14.62)</td>
<td>22.27 (6.82)</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>GGT — IU/L (SD)</td>
<td>48.87 (61.42)</td>
<td>36.38±37.82</td>
<td>.28</td>
<td></td>
</tr>
</tbody>
</table>

Table 7-25 shows that at the completion of the trial, liver enzyme tests were not significantly different between groups.

Table 7-25 *Effect of Intervention over time on Liver Function*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk0</td>
<td>Wk16</td>
<td>Wk0</td>
</tr>
<tr>
<td>ALT</td>
<td>32.78±22.95</td>
<td>28.28±2.42</td>
<td>28.78±13.45</td>
</tr>
<tr>
<td>AST</td>
<td>25.44±14.62</td>
<td>24.84±12.71</td>
<td>22.27±6.82</td>
</tr>
<tr>
<td>GGT</td>
<td>48.87±61.42</td>
<td>46.23±45.55</td>
<td>36.38±37.82</td>
</tr>
</tbody>
</table>

7.5.17 Monitoring physical activity and nutritional intake

Behaviour change in physical and dietary habits was measured at different time intervals throughout the trial as it is known to affect blood glucose and insulin levels. As shown in Table 7-26, there was no significant change in any group on nutritional intake or physical activity from baseline to the completion of the trial.
Table 7-26 Physical activity and nutritional intake: baseline – week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 32</td>
<td>n = 39</td>
</tr>
<tr>
<td>Baseline</td>
<td>Wk 16</td>
<td>Baseline</td>
</tr>
<tr>
<td>Physical activity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Inadequate</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Fruit and Vegetable intake^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate fruit</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Adequate vegetables</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

7.6 Sub-group analysis

Two sub-group analyses were considered important and appropriate to conduct: the effect of the Chinese herbal medicine in people with diabetes versus prediabetes; and the effect of the Chinese herbal medicine in lean versus overweight people.

7.6.1 Diabetes and prediabetes

The Chinese herbal medicine was originally found to be effective in a cohort of people with diagnosed diabetes not prediabetes. It is possible that the CHM was effective or more effective in people at differing stages of the diabetes continuum. Hence a subgroup analysis people with diabetes and prediabetes was considered appropriate.

Prediabetes subgroup

As shown in Table 7-27, significant and borderline differences were found in the subgroup of people with prediabetes between those on placebo and those on the
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Chinese herbal medicine. At the completion of the treatment, insulin ($p = .02$), insulin resistance (HOMA-IR $p = .04$), insulin sensitivity (HOMA%B $p = .05$) and beta cell function (HOMA%S $p = .04$) were all significantly different compared to baseline. These are explored further below.

Table 7-27 Effect of CHM on primary outcomes and insulin in people with Prediabetes (ITT, ANCOVA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 15</td>
<td>n = 26</td>
<td></td>
</tr>
<tr>
<td>FBG</td>
<td>5.97 (.97)</td>
<td>6.16 (1.03)</td>
<td>.16</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.31±.60</td>
<td>6.27±.55</td>
<td>1.22</td>
</tr>
<tr>
<td>Insulin — mmol/L</td>
<td>25.95 (36.10)</td>
<td>1.85±4.55</td>
<td>6.25</td>
</tr>
<tr>
<td>HOMA†</td>
<td>2.26±1.70</td>
<td>1.45±.62</td>
<td>4.09</td>
</tr>
<tr>
<td>HOMA %B†</td>
<td>117.76±55.30</td>
<td>83.83±37.15</td>
<td>4.67</td>
</tr>
<tr>
<td>HOMA %S†</td>
<td>67.74±37.86</td>
<td>84.11±45.69</td>
<td>4.01</td>
</tr>
<tr>
<td>HDL — mmol/L</td>
<td>1.31±.32</td>
<td>1.65±.56</td>
<td>4.29</td>
</tr>
</tbody>
</table>

Notes
* presents raw, unadjusted mean values
** calculated from log transformed data
Fasting blood glucose

Figure 7-15 shows the effect over time of treatment on fasting blood glucose levels in people with prediabetes. In the prediabetes subgroup, there was no significant difference between baseline FBG levels, 6.05±0.88 mmol/L and 6.18±0.89 mmol/L in the placebo and CHM respectively, and week 16 ($p = .70$).

Within prediabetes subgroup, there was no significant difference from baseline FBG to week 16 in the placebo group ($p = .64$), or the CHM group ($p = .89$). At follow up there was no significant difference in FBG within the placebo ($p = .68$) or the CHM group ($p = .64$).

*Figure 7-15 Prediabetes subgroup: Fasting Blood Glucose*
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

HbA1c

At baseline there was no significant difference between groups, the mean levels 6.05±.50% and 6.13±.57% in the placebo and CHM groups respectively ($p = .67$).

Within the placebo group, there was a significant difference between baseline and week 16 ($p = .002$) but not between baseline and week 24 ($p = .09$). Within the CHM group there was a significant difference between baseline and week 16 ($p = .04$) and baseline and week 24 ($p = .01$). Both these statistical significant differences have little clinical significance.

At week 16 in the prediabetes subgroup, there was no significant difference between the placebo and CHM groups ($p = .28$). At follow up there was no significant difference between groups ($p = .89$).

Insulin

Figure 7-16 shows the unadjusted data for insulin levels over the period of the trial and at follow up in the prediabetes subgroup comparing the placebo and CHM groups. At baseline there was no significant difference between the two groups, $p = .62$.

![Figure 7-16 Prediabetes subgroup: Insulin](image)

$Figure 7-16$ Prediabetes subgroup: Insulin
In the prediabetes subgroup, at the completion of treatment there was a significant difference in insulin between the placebo group and the CHM group when adjusted for the baseline variations \((p = .02)\). Due to the high standard deviation at week 16 in the placebo group, data was examined for confounding factors such as outliers. None were identified. Data was log transformed for ANCOVA and \(t\)-test analysis to improve skewness and kurtosis and robustness of the results.

There was also a significant difference within the placebo group when Week 16 levels 25.95±36.01 were compared to baseline, 14.67±1.5 mmol/L \((p = .03)\). Within the CHM, mean levels had remained steady throughout the trial and there was no significant difference when week 16 levels 10.85±4.55 mmol/L were compared to baseline, 12.12±6.62 mmol/L \((p = .27)\).

At follow up levels were 22.69±35.60 in the placebo group and 10.50±4.70 in the CHM group \((p = .03)\).

**Insulin resistance (HOMA-IR)**

In the prediabetes subgroup, baseline levels of insulin resistance were 1.82±1.32 in the placebo group and 1.63±.88 in the CHM group \((p = .61)\).

Insulin resistance (HOMA-IR) was significantly different between groups at Week 16 \((p = .05)\), 2.26±1.70 and 1.45±.62 in the placebo and CHM group respectively.

At follow up, levels of IR between the placebo and CHM group were no longer significantly different to baseline; 1.78±1.11; \(p = .71\) and 1.47±.59, \(p = .24\) in the placebo and CHM groups respectively.

Within the placebo group, HOMA-IR was not significantly different from baseline levels at week 16 \((p = .22)\). Within the CHM group, HOMA-IR was not significantly different to baseline levels at week 16 \((p = .39)\).
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

*Insulin sensitivity (HOMA%S)*

There was no significant difference between groups at baseline ($p = .65$), HOMA%S levels were $83.36\pm49.15$ and $82.36\pm51.62$ in the placebo and CHM groups respectively.

At completion of the treatment period, there was a significant difference between groups, $67.74\pm37.86$ and $84.11\pm45.69$ in the placebo group and CHM group respectively ($p = .05$). At follow up, there was no longer a significant difference between groups ($p = .22$).

Within randomisation groups, there was no significant difference within the placebo group at week 16 ($p = .20$) or week 24 ($p = .66$) compared to baseline. Within the CHM group there was also no significant difference at week 16 ($p = .44$) or week 24 ($p = .19$).

*Beta cell function (HOMA%B)*

At baseline, there was no significant difference in beta-cell function (HOMA%B), $p = .46$, mean levels were $96.66\pm41.40$ and $86.32\pm35.16$ in the placebo and CHM groups respectively.

In the prediabetes subgroup at week 16, mean levels of HOMA%B were significantly different ($p = .04$), HOMA%B was $117.76\pm55.30$ and $83.83\pm37.15$ in the placebo and CHM groups respectively. At follow up there was no longer a significant difference between groups ($p = .64$), $96.09\pm37.45$ and $85.61\pm42.78$ in the placebo and CHM group respectively.

Within the groups, at week 16 there was no significant difference in placebo group ($p = .10$) or the CHM group .62. There was also no significant difference within groups at week 24, $p = .69$ and $p = .26$ in the placebo and CHM groups respectively.
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

HDL

In the prediabetes subgroup, there was no significant difference in HDL levels between groups at baseline 1.42±.44 mmol/L and 1.52±.46 mmol/L in the placebo and CHM groups respectively (p = .49).

At week 16, there was a significant difference between the two groups compared to baseline (p = .05), mean levels were 1.31±.32 and 1.65±.56 in the placebo and CHM group respectively. This statistically significant difference was still present at follow up (p = .05), mean levels were 1.31±.30 and 1.54±.44 in the placebo and CHM groups respectively.

Within the placebo group, there was no significant difference between baseline and week 16 (p = .28) or week 24 (p = .21). Within the CHM group, there was no significant difference between baseline and week 16 (p = .19) or week 24 (p = .79).

Diabetes subgroup

Table 7-28 shows no significant differences were found in the subgroup of people with diabetes between the placebo group and the CHM group on any of the outcome measures. It is likely this sub-group was too small to detect any differences.
Table 7-28 Effect of CHM on primary outcomes and insulin in people with Diabetes (ITT, ANCOVA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Chinese herbal medicine</th>
<th>Difference between groups at Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 17</td>
<td>Chinese herbal medicine n = 13</td>
<td></td>
</tr>
<tr>
<td>Wk 16 (SD)</td>
<td>Week 16 (SD)</td>
<td>F-ratio</td>
<td>p-value</td>
</tr>
<tr>
<td>FBG</td>
<td>7.31 (1.18)</td>
<td>6.64 (1.06)</td>
<td>.19</td>
</tr>
<tr>
<td>2hr-GTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.70±.66</td>
<td>6.64±.68</td>
<td>.14</td>
</tr>
<tr>
<td>Insulin — mmol/L</td>
<td>18.65±11.30</td>
<td>13.08±6.93</td>
<td>.00</td>
</tr>
<tr>
<td>HOMA†</td>
<td>2.58±1.53</td>
<td>1.87±.90</td>
<td>.00</td>
</tr>
<tr>
<td>HOMA %B†</td>
<td>83.24±36.28</td>
<td>82.74±41.63</td>
<td>.04</td>
</tr>
<tr>
<td>HOMA %S†</td>
<td>58.51±39.63</td>
<td>80.70±41.59</td>
<td>.29</td>
</tr>
<tr>
<td>HDL — mmol/L</td>
<td>1.18±.22</td>
<td>1.32±.36</td>
<td>.00</td>
</tr>
</tbody>
</table>

Notes

* presents raw, unadjusted mean values

** calculated from log transformed data
**Fasting blood glucose: Diabetes sub-group**

Figure 7-17 shows the effect of the treatment over time on fasting blood glucose the diabetes sub-group. There was no significant difference between baseline levels, 7.18±0.89 mmol/L and 6.66±0.75 mmol/L in the placebo and CHM groups respectively \((p = .66)\).

As shown in Table 7-28, at week 16 there was no significant difference in FBG between groups \((p = .67)\).

Within those taking placebo in the diabetes sub-group there was no significant change from baseline levels to week 16 \((p = .53)\) or at follow up \((p = .24)\).

Within the CHM group there was no statistically significant difference in from baseline levels to week 16 \((p = .90)\) or at follow-up \((p = .52)\).

*Figure 7-17 Diabetes subgroup: Fasting Blood Glucose*
**Chapter 7: Randomised controlled trial of Jiangtang Xiaozi for the treatment of prediabetes and mild diabetes: Results**

**HbA1c**

Baseline levels were 6.65±.72% and 6.54±.68% in the placebo and CHM groups respectively.

There was no significant difference between groups in HbA1c levels at week 16 ($p = .71$) or at follow up ($p = .21$).

Within the placebo group there was no significant difference in levels from baseline to week 16 ($p = .56$) or to follow up ($p = .71$).

Within the CHM group there was no significant difference in HBA1c levels from baseline to week 16 ($p = .12$) or to follow up ($p = .12$).

**Insulin**

At baseline there was no significant difference between the two groups ($p = .12$). Figure shows the effect of the treatment over time on insulin in the diabetes subgroup (raw, unadjusted data).

Table 7-28 shows mean insulin levels at week 16 and that there was no significant difference in between the two groups when compared to baseline ($p = .99$). Although at follow up there was a significant difference between groups in favour of the placebo ($p = .04$).

In the diabetes subgroup, within the placebo group there was no significant change in insulin levels from baseline levels (16.29±9.15 mmol/L) to week 16 (18.65±11.30 mmol/L; $p = .34$). Within the CHM group there was no significant difference from baseline insulin levels, 11.15±7.76 mmol/L compared to 13.08±6.93 mmol/L ($p = .44$).

At follow up there was no significant difference in insulin levels within the placebo group ($p = .89$) although in the CHM group levels were significantly higher ($p = .01$).
Chapter 7: Randomised controlled trial of Jiangtang Xiaozhi for the treatment of prediabetes and mild diabetes: Results

Figure 7-17 Diabetes subgroup: Effect of treatment over time on insulin

*Insulin resistance (HOMA-IR)*

At baseline HOMA-IR was 2.26±1.25 in the placebo group and 1.64±1.02 in the CHM group (p = .19).

In the diabetes subgroup, at week 16, there was no significant difference between the placebo and CHM group (p = .96); 2.58±1.53 and 1.87±.90 in the placebo group and CHM group respectively. There was no significant difference between groups at follow up (p = .10).

Within groups, there was no significant change within the placebo group or the CHM group (p = .18 and p = .23 respectively). At follow up, HOMA-IR was 2.29±1.43 in the placebo group with no significant change from baseline (p = .90) and in the CHM group 2.37±1.25 (p = .06).

*Insulin sensitivity (HOMA%S)*

In the diabetes subgroup, baseline levels of insulin sensitivity were not significantly different between groups, 64.06±43.57 and 8.70±41.59 in the placebo and CHM groups respectively (p = .65).
At week 16, there was no significant difference between placebo and CHM groups in the diabetes subgroup; 58.51±39.63 and 70.21±40.80 in the placebo and CHM groups respectively (p = .87). There was no significant difference between groups at week 24 (p = .10).

Within the placebo group no significant change (p = .34); within the CHM group there was a significant change (p = .01). At follow up, levels were 64.77±4.29 and 56.75±37.56 in the placebo and CHM groups respectively. No significant difference was found within the placebo group (p = .93) but the significant difference noted within the CHM group at week 16 continued (p = .04).

Beta cell function (HOMA%B)

Baseline HOMA%B levels were 78.65±31.60 and 71.13±32.08 in the placebo and CHM group respectively (p = .64).

At week 16, there was no significant difference between groups in HOMA%B (p = .85); 83.24±36.28 and 82.74±41.63 in the placebo and CHM groups respectively. At follow up there was no significant difference between the groups (p = .12), 72.30±28.52 and 89.46±35.71 in the placebo group and CHM groups respectively.

Within groups, at week 16 there was no significant difference within the placebo group (p = .49) or the CHM group (p = .10).

HDL

At baseline HDL cholesterol levels were not significantly different between groups (p = .14); 1.15±.22 mmol/L and 1.28±.35 in the placebo group and CHM groups respectively.

There was no significant difference between the two groups at week 16 (p = .99) or at follow up (p = .75).

Within the placebo group there was no significant difference in HDL levels at week 16 compared to baseline (p = .39) or at follow up (p = .52). Within the CHM group
there was no significant difference in HDL levels at week 16 compared to baseline ($p = .31$) or at follow up ($p = .71$).

### 7.6.2 Comparison of lean and overweight sub-groups

The impact of BMI on fasting blood glucose and insulin outcomes was considered as a sub-group analysis. It has also been argued that a lean phenotype of Type 2 diabetes mellitus in adults found in the Indian sub-continent may be very distinct from the more characteristic form of Type 2 found in Caucasians. Not enough information is available, however, to characterize such subjects separately (World Health Organisation, 1999).

A sub-group of lean (BMI<25 kg/m$^2$) and overweight (BMI$\geq$25 kg/m$^2$) were identified. However there were inadequate numbers in each of the cells to enable a meaningful sub-group analysis. The placebo group had 4 participants in the lean subgroup and 28 in the overweight category; and the CHM had 6 participants in the lean subgroup and 33 in the overweight group.

### 7.7 Additional analysis of covariance

When sex was included as a covariant, it did not have a significant impact on the outcomes of fasting blood glucose ($p = .30$) or insulin ($p = .61$) at week 16.

Weight, waist and waist-hip-ratio and systolic blood pressure were unevenly distributed between the two groups at baseline. The placebo group had slightly and significantly higher values on all these variables. Each of these variables was included as a covariant on the fasting blood glucose and insulin values at the end of treatment (week 16) to determine if any significant effect was being exerted. There was no significant impact on fasting blood glucose of waist ($p = .59$), WHR ($p = .54$) or weight ($p = .75$). Likewise for insulin there was no impact of waist ($p = .66$), WHR (.09) or weight (.66).
7.8 Adverse effects

No fatalities or major adverse events occurred during the trial. One participant in the CHM group developed moderate dizziness within 24 hours of taking the medication. The participant stopped the medication for 24 hours and the dizziness ceased. The participant then restarted the medication for a further 48 hours and the dizziness returned. On contacting the principal investigator the participant was withdrawn from the study. The dizziness ceased when the medication was stopped.

7.9 Compliance and blinding

Compliance of medication was adequate in both groups. The dosage of three capsules three times a day was challenging for some participants and often a dose was missed. Table 7-29 shows that in week 4, 51% of the placebo group and 62% of the CHM group had missed doses of medication in the previous four weeks. In week 16, 50% of the placebo group and 59% of the CHM group had missed a dose of medication in the previous four weeks.

<table>
<thead>
<tr>
<th>Missed doses</th>
<th>Placebo</th>
<th>CHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>14 (44%)</td>
<td>22 (56.4%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>14 (44%)</td>
<td>15 (39%)</td>
</tr>
<tr>
<td>Week 16</td>
<td>16 (50%)</td>
<td>23 (59%)</td>
</tr>
</tbody>
</table>

Only 43 participants returned their remaining medication at the final visit, 18 in the placebo group and 25 in the CHM group. A pill count of remaining medication returned showed good compliance in both groups, 89% in the placebo group, 97% in the CHM group and 92% overall (excluding discontinued participants).

Blinding was effective with only 25% of participants correctly identifying their group in the first four weeks and 27% in the final four weeks of the intervention.
CHAPTER 8

Randomised Controlled Trial

Discussion

This study represents one of the earliest attempts to evaluate the effectiveness of Chinese herbal medicine for the treatment of prediabetes in a double-blind, placebo-controlled randomised clinical trial. This chapter discusses the baseline characteristics of clinical trial participants, principle findings of the clinical trial including primary and secondary outcome measures of the intervention, and the strengths and limitations of the study. Possible mechanisms of action of the intervention and its clinical and research implications are also discussed.

8.1 Baseline characteristics

Independent samples t-tests were performed to compare the baseline characteristics of the two study groups (active treatment and placebo) at the commencement of the trial. There was no significant difference between the CHM and placebo groups on age, sex, ethnicity, family history of diabetes, history of hypertension, smoking or use of cholesterol lowering or anti-hypertensive medication. Measures of glycaemic control (fasting plasma glucose, two hour postprandial glucose and glycosylated haemoglobin level) were similar across groups at baseline. Some anthropometric measures were different between the groups at baseline. Waist girth and waist-hip-ratio measurements were significantly different between the placebo and CHM groups at baseline. Even with removal of outliers for waist girth, differences remained.

The clinical trial cohort was similar in age as the IGT cohort that was assessed in the National, Population-based AusDiab Study (Barr et al., 2007). The authors of the AusDiab study reported a mean age of 58.5 (±13.8) while our study had an overall
mean age of 58.9 years. The current study reflected the higher prevalence of IGT among women by including slightly more females.

Family history is a significant predictor of IGT and diabetes. In our clinical trial 44% in the CHM group and 50% in the placebo group had a first degree relative with diabetes. These figures are similar to other IGT and diabetes prevention trials, such as the ACT NOW trial (DeFronzo et al.) and the Diabetes Prevention Program (Diabetes Prevention Program Research Group, 2002a) where 48% and 63% of participants had first degree relatives with diabetes.

In considering these significant differences at baseline it is important to note that the usefulness of a statistical comparison of baseline characteristics in a RCT trial remains controversial. It has been suggested that a significance test should only be used if there is concern that the randomisation process was flawed (Burgess, 2003; Matthews, 2006; Pocock, Assmann, Enos, & Kasten, 2002). If randomisation is carried out appropriately, any anomaly could only occur by chance. The null hypothesis that the two groups come from the same population is by definition true; we could then expect that 5% of such comparisons may be significant at the 5% level (Altman & Doré, 1990). Burgess argues that if 20 baseline characteristics are presented there is a 64% likelihood - by chance alone - of finding at least one statistically significant difference using two-sided t-test ($p < .05$) (Burgess, 2003). Since successful randomisation does not guarantee a perfect balance between groups (due to chance), the best strategy for dealing with differences in baseline between the clinical trial groups is to ensure that the final analysis of efficacy parameters is adjusted for the potentially confounding factors.

An analysis of covariance (ANCOVA) is a robust statistical procedure (Tabachnick & Fidell, 2007) and has been widely used to address any imbalances in groups at baseline. In the current study, this strategy was utilised in the final analyses of the outcome measures. In order to address the differences in weight, waist girth and waist-to-hip ratio between the placebo group and the CHM group at baseline, these variables were all considered as covariants in the analysis of the outcome measures. When each of these variables was included as a covariant on the outcome measures
of fasting blood glucose and insulin values at the end of treatment (week 16), no significant impact was detected.

8.2 Primary outcome measures

Our primary objective was to assess the efficacy of Jiangtang Xiaozhi Tang in treating the elevated blood glucose levels of people with impaired glucose tolerance. In the present study, fasting plasma glucose, two hour postprandial glucose and glycosylated haemoglobin level were used as primary efficacy outcome measures. These measures are commonly used to assess glycaemic control.

Many studies in recent years have investigated the efficacy of pharmaceutical or lifestyle interventions in diabetes prevention. These trials often run for 3 to 5 years. As these lengthy trials have prevention as their objective, the primary outcome is typically ‘incidence of diabetes’ and glycaemic control is usually a secondary outcome (Diabetes Prevention Program Research, 2009; Pan et al., 1997; The NAVIGATOR Study Group). In trials of shorter duration such as ours, the progression to diabetes is less likely to be detected and measures of glycaemic control, typically FPG and postprandial plasma glucose, or insulin are used as the primary outcome measures (Chiasson et al., 1996; Kosaka, Noda, & Kuzuya, 2005; Zhang et al., 2008).

Glycosylated haemoglobin (HbA1c) provides an estimation of the average blood sugar during the past two to three months (Kilpatrick, 2008). No data exists to define the utility of HbA1c in monitoring prediabetes (Twigg, 2007) but it has been used in some clinical trials in people with IGT (DeFronzo, et al.; Diabetes Prevention Program Research Group, 2002b; Wei, Hong, & Ye, 2008). HbA1c measurements have been recommended to replace glucose measurements for monitoring diabetes (International Expert Committee on Diabetes, 2009).

8.2.1 Fasting blood glucose and HbA1c

We found no significant differences on any of the glycaemic outcome measures between the CHM and placebo groups at completion of the treatment. However, we found a significant improvement within the CHM group on postprandial plasma
glucose levels at the completion of the treatment compared to baseline \((p = .03)\). This difference was not present at follow up. There was no significant difference relative to baseline in the placebo group at either the completion of treatment or at follow-up. Measuring change from baseline is an acceptable and meaningful statistic where baseline levels are similar, which in our case they were (Vickers 2001).

Hyperglycaemia in prediabetes is primarily postprandial in nature. The body is unable to control blood glucose adequately after a loading of ‘sugar’. It is these postprandial ‘spikes’ in blood glucose levels that are thought to be toxic to the beta-cells and cause them to dysfunction (Kahn, 2003; Robertson, Harmon, Tran, Tanaka, & Takahashi, 2003).

Overall, the results from this study are not consistent with the only previous randomised controlled trial of Jiangtang Xiaozhi (Xiyuan Hospital, 2004). This earlier trial was an eight week intervention with 60 people with type 2 diabetes. It compared Jiangtang Xiaozhi with another well documented herbal formula, Jin Qi Melbime, as the control. The fasting plasma glucose levels reduced from 9.15±2.32 mmol/L to 7.85±1.87 mmol/L in the Jiangtang Xiaozhi group, a clinically and statistically significant change from baseline. Postprandial plasma glucose and HbA1c also both showed a significant difference compared to baseline (11.41±2.63 mmol/L to 9.91±1.93 mmol/L and 7.35±1.87% to 6.73±1.02%, respectively). There are several reasons why these results may differ from our clinical trial including baseline symptoms, dosage and trial design.

In contrast to the Xiyuan Hospital trial (2004), which was conducted with a group who were all diagnosed with type 2 diabetes, our clinical trial cohort had lower FPG and HbA1c baseline levels. Higher levels of FBG, postprandial plasma glucose and HbA1c at baseline provide a greater room for improvement and therefore a better chance for detecting a significant change. In the present study the mean baseline of FPG in the CHM and placebo groups was 6.7 mmol/L and 6.3 mmol/L respectively, and the normal range for FPG is 4-6 mmol/L making a significant change difficult to detect. In other trials where a post-treatment difference was detected in the FBG, the baseline severity of symptoms has tended to be somewhat higher (Fan, Luo, & Qin, 2004), the trial has been conducted over a longer period of time (Fan, et al., 2004;
Sasaki et al., 2008; Zeng YH, 2000) or the change detected was a within-group difference not between group (Hao AZ, 2004).

HbA1c remained almost exactly the same in both groups throughout the treatment period and at follow up. Once again, it may have been that the baseline symptoms were not severe enough to detect a change. In the earlier clinical trial of Jiangtang Xiaoxhi there was a significant decrease in HbA1c levels in the treatment group from 7.05±1.25% at baseline to 6.04±1.00% after treatment (Xiyuan Hospital 2004). In the present study, however, the baseline HbA1c levels of the Jiangtang Xiaozhi and placebo groups were 6.4% and 6.3% respectively, which were lower than the previous study. Higher baseline HbA1c levels have been found to be associated with statistically significant reduction in HbA1c in clinical trials across 10 classes of glucose-lowering therapies (DeFronzo, Stonehouse, Han, & Wintle, 2010).

We conducted a subgroup analysis within our trial to examine the affect of Jiangtang Xiaozhi on participants who had mild diabetes at baseline to enable comparability with the earlier trial in China. No significant differences were found in the FPG, postprandial glucose or HbA1c measures in the Jiangtang Xiaozhi sub-group at the completion of the intervention. It is worth noting, however, this sub-group was considerably underpowered (n=30). To our knowledge, there is no evidence from any other Chinese herbal medicine RCTs that a sample of this size in a trial of this length would detect a change on fasting blood glucose.

The dosage regime in the present trial was slightly different to that applied in the earlier trial. In the earlier trial there were 5 grams of herbs per capsule with a dosage of 5 capsules 3 times a day for a total of 75 grams per day. In our study we used 3.79 grams of herbs per tablet with a dosage of 3 tablets 3 times a day for a total of 34 grams per day. While not directly comparable, animal studies of Jiangtang Xiaozhi, showed that while lipids and insulin improved at the lower dosage it was not until a larger dose was administered that blood glucose reduced (Appendix B-2).

A further difference between the earlier trial and the present trial was in the experimental design and statistical analysis which was less rigorous then our methodology. The prior investigators’ use of another herbal formula to compare the efficacy of Jiangtang Xiaozhi means that their trial should have been designed as a
‘head-to-head’ or ‘comparative effectiveness’ trial (Luce 2009). An analysis of covariance would have also increased the statistical rigor of the design and the validity of the findings.

In considering the results of our trial and other clinical trials of pharmaceutical and herbal interventions there are two striking differences: trial length and sample size. In clinical trials involving people with IGT, the intervention period is usually considerably longer thereby allowing for greater natural progression of the disease (Diabetes Prevention Program Research Group, 2002b; The DREAM Trial Investigators, 2006). In two large-scale studies of lifestyle intervention, the rate of progression from IGT to diabetes was only 38% in the control group compared to 58% in the placebo group (Tuomilehto 2001; Knowler 2002). The duration of the Finnish trial (Tuomilehto et al., 2001) was 3.2 yrs and the Diabetes Prevention Program (Diabetes Prevention Program Research Group, 2002b) was conducted over 2.8 years. Pharmaceutical interventions have also reduced progression to diabetes by 31% using metformin in a 3 year trial (DPP 2002), by 25% using acarbose in a 3.9 year trial (STOP-NIDDM trial) and by 62% using rosiglitazone in the 3 year DREAM trial (DREAM trial, 2006). A 12 month randomised controlled trial of an herbal extract, berberine, for the treatment of IGT and hyperlipidemia found a significant difference on all glycaemic measures compared to a placebo (Zhang 2008). All of these trials were conducted over a sufficient time period to allow for noticeable natural progression of the disease. In addition, some of these studies have shown that the proportion of people classified with IGT on both the first test and re-test is only 33–48%, with 39–46% being reclassified as normal and 6–13% as having diabetes on repeat testing (Santaguida, 2005). In our trial we did not have the resources or time to retest the sample at baseline to confirm diagnosis. This may have compromised our capacity to detect a change in this population.

In smaller and shorter trials, it seems that an intervention effect is more likely to be detected in postprandial plasma glucose levels (Nijpels, 2008; Hung, 2005). Our trial did detect a significant difference on postprandial levels within the intervention group compared to baseline but not when compared with the placebo group. In herbal medicine trials conducted in people with IGT in China, changes in the FPG were not typically detected but changes between and within groups in postprandial
glucose levels were commonly found (Fan 2004; Hao 2004; Li 2004; Qu 2002). Two hour post-load plasma glucose levels and fasting insulin levels have been related to the incidence of type 2 diabetes, independent of FBG (Nijpels, 1996). Further, postprandial glucose levels have been found to be more closely associated with cardiovascular risk than fasting glucose levels (The DECODE study group, 1999). This suggests that postprandial glycaemia may be a distinct therapeutic target (The NAVIGATOR group, 2010).

In summary, there are several possible reasons for the absence of a detectable between group effect of Jiangtang Xiaozhi on glycaemic measures in this trial. Firstly, this herbal medicine may be ineffective in treating elevated glucose levels in people with IGT. Secondly, it may be that the size of the sample was not sufficiently large to detect an effect, particularly given the transient nature of IGT. Thirdly, an effect might only occur with greater symptom severity at baseline. The fourth possibility is that the dosage of Jiangtang Xiaozhi was not adequate. Finally, our clinical trial cohort was largely overweight and obese with a mean BMI of 30.8 kg/m$^2$, which can affect the efficacy of an intervention (Fischer, Hanefeld, Spengler, Boehme, & Temelkova-Kurktschiev, 1998).

### 8.3 Secondary outcome measures

Despite there being no detectable effect of treatment on the primary outcome measures, the present study has yielded three positive findings on secondary outcomes. First, significant differences were found in levels of insulin in those taking Jiangtang Xiaozhi compared to the placebo. The levels of insulin resistance (HOMA-IR) were lower than those in the placebo group. Second, serum insulin slightly decreased in the treatment group compared to worsening levels in the placebo group, resulting in a borderline significant difference between groups. Third, HDL cholesterol was significantly improved in CHM group compared to the placebo group. Further, significant differences were found in the prediabetes subgroup analysis. These findings are discussed in detail below.
Chapter 8: Randomised Controlled Trial - Discussion

8.3.1 Insulin

There is little or no information from which to derive norms for insulin secretion or insulin sensitivity measures among people with IGT (Nijpels et al., 2008). This means we could not calculate a power analysis on insulin secretion or insulin sensitivity and were thus unable to determine whether the present sample size was adequately powered to detect clinically significant change.

In the present study, we assessed serum insulin, insulin resistance, insulin sensitivity as well as beta-cell function. Insulin resistance, insulin sensitivity and beta-cell function were assessed using the homeostasis model (HOMA). Analysis of covariance demonstrated a statistically significant difference and medium effect size in serum insulin between the CHM group and the placebo group following treatment. There was a trend towards an effect of the treatment on insulin resistance levels.

*Serum insulin*

Serum insulin in the placebo group increased throughout the trial while serum insulin in the CHM group remained significantly more stable.

*Insulin resistance*

Insulin resistance is a decreased responsiveness of target tissues — skeletal and myocardial myocytes, hepatocytes, and adipocytes — to normal levels of circulating insulin (Setsi 2006). In our placebo group, higher levels of insulin resistance (HOMA-IR) accompanied higher levels of serum insulin. This is to be expected. Greater serum insulin levels are seen in those with higher insulin resistance. A smaller insulin response is anticipated in those with better insulin sensitivity. At week 16 of treatment, there was a trend for insulin resistance to improve in the CHM group compared to the placebo group, but the change narrowly missed statistical significance ($p = .06$).

However, the level of change detected in insulin resistance in our trial had marginal clinical significance. Cut-off values for normal HOMA-IR are considered to lie somewhere between 2.5 and 4.1 (Wallace 2004; Ramachandran 2003; Snehalatha 2009). At these values our clinical trial cohort would be considered to be in the non-
clinical range at the start of the trial with levels of 2.12±1.30 and 1.60±0.92 in the placebo and CHM groups respectively. The 3 month clinical trial of the herbal extract, berberine, found a clinical and statistically significant difference with HOMA-IR reducing from 3.9 to 2.44 in people with diabetes not IGT (Zhang Y 2008). In another trial conducted in people with IGT the HOMA-IR baseline levels were still markedly higher than our cohort (Snethalatha 2009). Again it seems that perhaps our clinical trial cohort was overall too well at baseline and that our sample did not allow for sufficient power to detect change from these baselines.

**Insulin sensitivity and beta-cell function**

Insulin sensitivity (HOMA%S) in the CHM group remained stable throughout the treatment period. It increased slightly in the placebo group but was not close to being statistically significant (\(p = .34\)). Like insulin resistance, poor insulin sensitivity is associated with poorer health outcomes. HOMA%S values are associated with cardiovascular disease in older women (Lawlor 2007), and an Australian study found that declining insulin sensitivity was associated with 5 year fatal or non-fatal cardiovascular events, but not with all-cause mortality (Barr et al., 2009).

In the present study, mean beta-cell function (HOMA%B) increased in the placebo group from 87% to 99% but not to a statistically significant degree while remaining stable in the CHM group (82% to 84%). These results could be interpreted as a trend towards improvement in the beta-cell function of the placebo group. However, beta-cell function needs to be interpreted in the context of serum insulin, insulin sensitivity and insulin resistance.

Typically a beta-cell or HOMA%B value that is closer to 100% is associated with better beta-cell function (Lyssenko et al., 2005; UKPDS Group, 1995; Wallace, 2004; Weyer, 1999). Why then in the placebo group, compared to the CHM group, would insulin secretion increase, insulin sensitivity decrease but beta-cell function (HOMA%B) appear to improve? One explanation may be that a ‘high’ HOMA%B does not always equate to better beta-cell functioning but perhaps the opposite.

When insulin sensitivity is improved, beta-cell activity may be reduced – the beta-cells of the pancreas simply don’t have to work as hard anymore (Wallace, 2004).
This explanation is supported by several longitudinal studies which have shown that decreased beta-cell function as represented by HOMA%B does not, on its own, seem to predict the development of diabetes. A five year study of 12,924 non-diabetic Koreans examined the role of HOMA%B in predicting the development of diabetes. They found that the HOMA%B baseline value was actually higher in those who went on to develop diabetes (Sung, 2010). Another study which utilised HOMA to predict the development of diabetes concluded that whereas low insulin secretion may be adequate for an insulin sensitive patient, the same level of beta-cell function may be inadequate for another patient (Haffner, Kennedy, Gonzalez, Stern, & Miettinen, 1996). The developers of the HOMA instrument have indeed pointed out that “HOMA-%B is a measure of beta-cell activity, not of beta-cell health or pathology” and that HOMA%B values need to be considered alongside HOMA%S and HOMA-IR (Wallace T M, 2004). Therefore what may have been happening in the placebo group was the natural progression of diabetes: an increase in insulin secretion combined with a rise in beta-cell activity (HOMA%B) coupled with a rise in insulin resistance (HOMA-IR) indicating that the beta-cells are working harder. Whereas in the CHM group the insulin measures, stable serum insulin, stable insulin sensitivity and reduced insulin resistance compared to the worsening insulin measure in the placebo group indicate that progression has perhaps stalled but not reversed.

The time series of the data gives cause for caution when considering the clinical significance of these insulin related results. The significant difference in insulin resistance and trending difference in serum insulin values occurred within the last 4 weeks of the trial.

### 8.3.2 Sub-group analysis on insulin measures

A subgroup analysis comparing prediabetic \((n = 41)\) and diabetic \((n = 30)\) participants was conducted to provide additional information about the action of Jiangtang Xiaozhi. Statistically significant and trending post-treatment differences on all insulin measures were found in the prediabetic CHM group compared to the prediabetic placebo group. At the completion of the treatment, insulin \((p = .02)\), insulin resistance \((\text{HOMA-IR} \: p = .05)\), insulin sensitivity \((\text{HOMA}%B \: p = .04)\) and beta-cell function \((\text{HOMA}%S \: p = .05)\) in the prediabetic CHM group were all
significantly better compared to placebo. In the diabetes subgroup, however, no significant group differences were detected.

Sub-group analyses should be done with caution and, likewise, the results regarded with caution. They are useful to detect if a treatment was more (or less) effective (or harmful) in a particular group of patients. Baseline data are used to derive sub-groups and it’s possible to conduct many different analyses. However ‘data-dredging’ should be avoided and whether sufficient statistical power is available to detect differences between sub-groups should be considered (Pocock, et al., 2002). As such, sub-group analyses are more appropriate in larger trials than the present study. These concerns aside, sub-group analyses may provide grounds for generating hypotheses which would then require validation in future studies (Stone, 2010). In the case of the present trial, the sub-group analysis results are ambiguous. The results were strengthened in the prediabetic sub-group and no differences were identified in the diabetic sub-group. Of note is that the current author’s earlier suggestion that higher baseline levels in symptoms are required to detect significant change is contradicted by this preliminary subgroup analysis. A likely alternative explanation is that the diabetes sub-group was simply too small to detect a change ($n = 30$).

### 8.3.3 Possible mechanisms of action

The mechanism(s) underlying the favourable insulin outcomes found in this study are not known, and the requisite further investigation to identify such mechanisms is beyond the scope of the present study. However, several possible explanations emerge when the actions of the individual herbs in the Jiangtang Xiaozhi formulation used in the current study are considered. *Astragalus membranaceus* has a known effect on insulin, and has a protective effect on beta-cells of the pancreas. *Astragalus* appears to inhibit the gene PTP1B. In animal studies, mice lacking PTP1B have increased insulin sensitivity and improved glucose tolerance (Mao 2008; Gover 2002; Mao et al 2007). Berberine, a compound purified from *Coptis chinensis*, has shown convincing antidiabetic effects (Xiao, 2002). A study found that rat β-cell islets pre-treated with *Coptis Chinensis* were protected from both apoptosis and necrosis (Kwon et al., 2005). Animal studies of berberine, an extract of *Coptis*
*chinensis*, have shown that insulin resistance is improved in diabetic mice, and that berberine can activate the AMP-activated protein kinase (AMPK) activity in the adipose tissue (Lee, Kim et al 2006). Berberine has also been found to act as an insulin secretagogue reducing post-prandial hyperglycaemia to normal levels (Ko et al 2005). A double blind placebo controlled randomised controlled trial of berberine in 116 patients with type 2 diabetes found it reduced fasting and postprandial plasma glucose as well as HbA1c levels but did not affect insulin concentrations or HOMA measures (Zhang et al 2008).

### 8.3.4 Clinical significance of insulin findings

We found that overall, insulin measures improved in the CHM group compared to the placebo group. The degree to which the intervention appeared to maintain insulin sensitivity levels, restrain insulin secretion and thereby help preserve beta-cell function is meaningful in a clinical environment. Worsening of impaired glucose tolerance, progressing to frank diabetes is generally accepted as a consequence of insulin resistance, impaired insulin secretion and pancreatic beta-cell failure (Haffner, 1995; Kanauchi, Nakajima, Saito, & Kanauchi, 2003; Levy, Atkinson, Bell, McCance, & Hadden, 1998; Li et al., 2002). While the relative contribution of each of these factors is still a subject for debate, we do know that insulin resistance plays a key role and this is evidenced by a number of longitudinal and cross-sectional studies. These studies have conclusively shown that the progression from normal glucose tolerance to IGT is associated with the development of severe insulin resistance (Haffner, 1995; Rudenski et al., 1988). In one epidemiological study of 1,449 people with IGT and normal glucose tolerance, 23.4% of those with IGT had developed diabetes within 3.5 yrs. Those that developed diabetes were more likely to have a higher HOMA-IR at baseline (Haffner, et al., 1996).

An improvement in insulin resistance has health benefits independent of glucose metabolism (Martens, Visseren, Lemay, de Koning, & Rabelink, 2002; Pavo et al., 2003). For example, higher than normal HOMA-IR values have been associated with a higher incidence of cardiovascular disease (Hanley, Williams, Stern, & Haffner, 2002; Hedblad, Nilsson, Engström, Berglund, & Janzon, 2002).
If Jiangtang Xiaozhi improves insulin function, it may have a beta-cell protective effect. The findings of the present study are not convincing enough to justify clinical recommendations but certainly warrant further investigation.

### 8.3.5 Dyslipidemia findings

People with diabetes often have abnormally low levels of HDL cholesterol and high levels of triglycerides (Taskinen 2003; Martens, et al., 2002). There is also a strong association between dyslipidemia and insulin resistance (Festa, Hanley, Tracy, D’Agostino, & Haffner, 2003). We found that high-density lipoprotein cholesterol (HDL), otherwise known as the ‘good’ cholesterol, improved post-treatment in the CHM group compared to the placebo group. No post-treatment differences were found between the groups on total cholesterol or triglyceride measures. Cholesterol lowering medication was being taken by nearly all our clinical trial participants. When analysed as a covariant there was no significant effect exerted by cholesterol lowering medication consumption on any of the lipid results.

The mean post-treatment increase of 0.10 mmol/L in HDL-cholesterol in the CHM group represents a 6% change from baseline and is thus of some clinical significance. This finding supports the earlier trial of Jiangtang Xiaozhi which found a mean increase of 0.06 mmol/L in HDL over an 8 week period (Xiyuan Hospital 2004). In a pooled analysis of four clinical trials of statins, individuals with a ≥7.5% increase in HDL cholesterol in conjunction with lowered LDL had a reduced incidence of coronary artherosclerosis (Nicholls 2007).

### 8.3.6 The mechanism for improving HDL cholesterol

HDL plays an important role in cardioprotective and antiatherogenic processes (Lan 2007). This occurs in part by the reverse clearance transport capacity of HDL. HDL is lipid poor and excess cholesterol binds to HDL to be transported to the liver and excreted in the bile. Insulin resistance reduces HDL by an increase in fractional clearance and catabolism of HDL (Horowitz 1993). A new approach toward treating dyslipedemia alongside high blood glucose levels has been to target insulin resistance (Pavo, et al., 2003). Thus, a possible explanation for the improved HDL levels in the CHM group may have been improved insulin resistance.
Three of the herbs in the Jiangtang Xiaozhi formula, *Curcuma longa*, *Coptis chinesis* and *Astragalus membranaceus*, have been found to have an effect on lipids. Of these *Coptis chinesis* and its extract, berberine has demonstrated this effect in both animal and clinical studies (Zhang 2007; Yin 2008; Ko 2005). Although these studies found that berberine reduced cholesterol, triglycerides and LDL, no results were available for HDL cholesterol.

The results indicate Jiangtang Xiaozhi both improves HDL levels and stabilises insulin. This is a particularly encouraging clinically relevant finding as it signifies the potential of the Jiangtang Xiaozhi to treat two conditions and thus avoid some of the problems inherent with polypharmacy.

### 8.3.7 Anthropometric measures

Weight loss has been shown to improve beta-cell function and insulin sensitivity (Dixon, Dixon, & O'Brien, 2003). In the earlier clinical trial of Jiangtang Xiaozhi, waist girth, waist-hip ratio, and BMI all reduced post-treatment (Xiyuan Hospital 2004). Clinically, these changes were marginal. BMI reduced by a mean of 0.56, and waist-hip ratio decreased from 0.93±0.80 to 0.89±0.64 in females. Waist girth showed a more pronounced reduction in females from 98.89±8.29 to 93.00±7.39 cm.

In our study, there was no difference between the CHM and the placebo group on any of the anthropometric measures.

In the clinical trial of berberine, BMI and body weight reduced compared to placebo but only to a small degree and there was no change in waist-hip-ratio (Zhang 2008). Animal studies of berberine have reported promising potential for reducing body weight (Lee 2006). BMI was measured in only five of 17 clinical trials of Chinese herbal medicines in people with IGT reviewed by the author; three found a post-treatment improvement in BMI (Grant, 2009).

The possible cause of conflicting evidence about the effect of interventions on anthropometric measures may be lack of measurement precision. Several studies have found that intra- and inter-observer waist-hip measurement had low reliability (Nordhamn, 2000; Sebo, 2008). These findings were more pronounced in the measurement of overweight and obese people.
8.3.8 C-reactive protein

Chronic inflammation may trigger insulin resistance and eventually type 2 diabetes. Elevated C-reactive protein has been found to predict the development of Type 2 diabetes independent of any other risk factors (Festa et al., 2004; Hung et al., 2006). Festa and colleagues (2004) propose several reasons for the presence of chronic inflammation in diabetes. Firstly, the presence of other disease such as atherosclerosis may cause raised inflammatory markers. Secondly, a decrease in insulin sensitivity may lead to enhanced C-reactive protein expression by counteracting the physiological effect of insulin on hepatic acute-phase protein synthesis. Finally, the effect could be caused by excess body fat as a strong and independent association of C-reactive protein levels with measures of body fat and triglycerides has been observed.

In the previous study of the Jiangtang Xiaozhi in people with diabetes, there were post-treatment improvements in three inflammatory markers, C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor (TNF) (Xiyuan Hospital 2004). We only measured one inflammatory marker, C-reactive protein, and did not find any significant between-group differences during the course of the trial or at completion. Both groups showed a reduction in C-reactive protein compared to their baseline levels, with a more pronounced decrease in the CHM group compared to baseline ($p = 0.09$).

We may not have found a significant difference in the inflammatory marker, C-reactive protein for several reasons. If inflammation is a product of excess body fat then the lack of weight loss in our CHM group may have left C-reactive protein unaffected. It should be noted however, that we did not measure body fat directly and instead used BMI and bodyweight as proxy measures. While we have no reason to believe that body fat may have reduced in the absence of any change in bodyweight or BMI, this is possible (American College of Sports Medicine, 2010) Another explanation may be that our clinical trial cohort had only mildly elevated triglycerides and these levels were not high enough to be associated with elevated C-reactive protein. An improvement in inflammatory marker interleukin-6 (IL-6) but not C-reactive protein was found after three months of berberine in people with
diabetes (Zhang 2008). Lifestyle intervention and metformin have both been found to reduce C-reactive protein (Chu 2002). In the lifestyle group, weight loss rather than increased physical activity seemed to account for most of the changes in C-reactive protein (The DPP 2005).

### 8.3.9 Health related quality of life (SF-36)

Diabetes is associated with a poorer quality of life compared to the general population. Recent research has established that a reduced quality of life is apparent with impaired glucose tolerance and impaired fasting glucose (Chittleborough, 2006; Tapp et al., 2006). There are no validated tools for assessing health related quality of life (HRQoL) in people with impaired glucose tolerance but previous studies have used the 36-item short-form health survey (the RAND 36-Item Health Survey) and evidence exists for its use in an Australian population (Hawthorne 2007).

We found no post-treatment or mid-course differences in any of the eight dimensions of the SF-36 between the CHM group and the placebo group. It is of interest however, that our clinical trial cohort had poorer quality of life on three of the eight dimensions of the SF-36: vitality, role limitations due to emotional problems and mental health when compared with the age relevant cohort (55-64 yrs) and all-age Australian norms (Hawthorne 2007).

Our results differ from the three other studies examining quality of life in people with IFG and IGT (Chittleborough, 2006; Hakkinen 2009; Tapp, Dunstan et al 2006). These studies found that health-related quality of life was reduced in the areas of physical functioning (Chittleborough 2006; Tapp, Dunstan et al 2006), social functioning (Tapp, Dunstan et al 2006) and in the Finnish study, diminished on all dimensions of the SF-36 with the exception of mental health and role limitations due to emotional problems (Hakkinen 2009). These studies were all population based studies and included people with IFG as well as IGT which may have contributed to the difference in findings between our studies.

Finding reduced functioning among an IGT sample in the dimensions of mental health and role limitations due to emotional problems is supportive of the growing interest in depression as a risk factor for the development of diabetes. Our findings
are consistent with those of a meta-analysis of 14 studies which provided evidence for an association between depression and subsequent onset of diabetes (Cosgrove, 2008). Similarly, two longitudinal studies found a greater than twofold increase risk for developing diabetes in individuals who had depression disorder at the baseline (Eaton, 1996; Kawakami 1999).

One interpretation of our results may involve the relations among dimensions on which functioning was reduced (vitality, mental health and role limitations due to emotional problems). In a study of physical activity in people at high risk of developing diabetes, less physically active participants reported more depression than more active participants (Hakkinen, 2009). Hakkinen and colleagues suggest that, as the vitality of less physically active participants was lower, there was no energy to be physically active or motivation to follow a healthy diet. This likely leads to decreased energy expenditure increasing body weight leading to a vicious cycle of energy depletion and weight gain. Examination of SF-36 findings according to physical activity was beyond the scope of our study, so we cannot say if there was a relation between physical activity and reduced functioning. However, we do know that the overall level of physical activity in our sample was poor.

8.3.10 Diet and exercise

The level of vegetable intake and physical activity of the participants at the onset and throughout the trial was poor. Although the trial was not metabolically controlled, participants were encouraged at each assessment to consume the recommended levels of fruit and vegetables, and to exercise. However, there was no change in exercise or nutrition in either group. In interpreting the data on fruit and vegetable intake, it should be noted that some respondents indicated they found it difficult to estimate the quantities consumed.

Vegetable intake was inadequate in both the CHM and the placebo groups. Only eight participants in the placebo group and fourteen in the treatment group were having the recommended level of five serves of vegetables per day. The poor vegetable intake reflects that of the general population where just over 1 in 10 adults (10.2 per cent) consume the recommended minimum of 5 serves of vegetables a day in 2008 (NSW Health, 2008).
Fruit consumption was adequate in both groups for 20 and 22 participants in the placebo and CHM groups respectively.

Physical activity in the both groups was poor. Only 11 participants in the placebo and 9 in the CHM group undertook the prescribed minimum of physical exercise necessary for health benefits (150 minutes of physical exercise per week comprising five separate occasions of at least 10 minutes duration (Australian Department of Health and Ageing, 1999). This is consistent with the data for the Australian population, where 70% of adults are classified as sedentary or insufficiently active (Australian Bureau of Statistics 4835.0.55.001 - Physical Activity in Australia: A Snapshot, 2004-05). The links between physical activity and reduced risk for diabetes are well documented (DPP 2002; Erikkson 1998; Laaksonen 2005).

8.4 Safety and adverse events

There was no significant difference between the two groups on any of the safety parameters. Tolerability was assessed at every visit and included adverse events. Only one adverse reaction was reported. This was dizziness reported by one participant in the treatment group. Symptoms stopped when the medication was discontinued indicating a possible causal relationship. No other symptoms were reported.

8.5 Clinical significance of findings

Our findings that Jiangtang Xiaozhi improved insulin sensitivity and HDL-cholesterol compared to placebo over a 16 week treatment period are encouraging but it is difficult to determine the clinical significance. Indeed in contrast to the well-established standards regarding statistical significance, no particular guidelines exist for deciding what magnitude of difference is “clinically significant” or “practically important” (Haynes, 2006; Kaul & Diamond, 2010).

The positive results of Jiangtang Xiaozhi in the treatment of people with diabetes in the Xiyuan study combined with our results in postprandial glucose and insulin indicate that a higher level of baseline severity in blood glucose symptoms might yield more reliable findings. Although, our sub-group analysis of people with
diabetes did not yield statistically significant differences, we have found a trend on all measures in favour of the CHM group. Our analysis was considerably underpowered. A longer study, in line with other interventions in this population group, to allow for the natural progression of the disease may also bring forth an effect on fasting blood glucose.

The improvement in HDL-cholesterol combined with the positive impact on insulin make Jiangtang Xiaozhi a candidate for treating this metabolic syndrome.

The safety of this herbal formulation and its components have been demonstrated in animal and human studies. The lack of, or minimal, side effects provide a considerable advantage over many of the current pharmaceutical treatments used for the treatment of prediabetes and mild diabetes.

In summary, the positive effect of Jiangtang Xiaozhi found for insulin and HDL are promising but not substantial enough to warrant a recommendation to use this herbal medicine in a clinical setting, particularly without a stronger finding on glucose metabolism. This clinical trial does, however, contribute to the growing evidence base of high quality clinical trials of Chinese herbal medicines for the treatment of diabetes and impaired glucose tolerance.

### 8.6 Limitations

Our study has several limitations. Firstly, we failed to recruit the 100 participants required for sufficient statistical power to detect a clinically significant change in FBG. Further, it is likely that even this sample size may not have adequately accounted for the transient nature of people with IGT. People classified as IGT may revert – without intervention - to apparently normal glucose metabolism. One review stated that up to 53% of dysglycaemic individuals may revert to normal glycaemia within a year (Santaguida P, 2005). It has previously been demonstrated that subjects wax and wane over time in their glycaemic response to OGTT and that repeated testing would be expected to lead to variable results (Harris, 1989; Harris et al., 1998).
Secondly, the intervention period may have been too short to allow for the natural progression of impaired glucose tolerance. Typically studies in this population target changes in postprandial glucose or run for a minimum of 12 months and have incidence of diabetes as the primary outcome.

Thirdly, slow recruitment meant that we needed to expand our criteria to include people with mild diabetes. This diluted our original IGT population and reduced power to detect a difference in the IGT group alone.

A fourth limitation relates to the methodology of the outcome measures. We used HOMA to assess insulin resistance and sensitivity as a cost effective method with validity for clinical trials (Wallace 2004). The use of the euglycaemic clamp method to assess insulin sensitivity may have provided a more accurate result. Clamp methods are not feasible in large studies. Likewise we used only one insulin measure and this may not have sufficiently accounted for intra-individual variation. The accuracy of HOMA-IR has been thought to suffer from intra-individual variation and lessen in individuals with pronounced hyperglycaemia (Mari 2001; Matsuda M, DeFronzo R 1999). The latter limitation is unlikely to have affected study results as all participants had only moderate hyperglycaemia. However, intra-individual variation would be compounded by the variation of the fasting blood glucose levels in prediabetic populations (Motala, Omar, & Gouws, 1997).

HOMA%S is more suited to assessing change in larger sample sizes and is not powered to detect small differences in insulin sensitivity (Pavo, et al., 2003). A larger sample may have shown more significant HOMA%S results.

Insulin assay variation between different laboratories can be large (Wallace, Levy, & Matthews, 2004). We tried to limit any impact of this variation by utilising the same pathology service throughout the trial, but the assays were determined at different laboratories.

A fifth limitation was our use of last observation carried forward (LOCF) for data analysis. The LOCF principle assumes that data are missing completely at random although this is rarely the case for all missing data, carrying observations forward
may therefore bias results (Siddiqui and Ali 1998; Verbeke and Molenberghs 2000; Mallinckrodt et al., 2003).

A final limitation was compliance and dosage. It is likely that therapeutic doses weren’t reached by some participants. The regime of three tablets three times a day is a difficult dosage regime. Although a final pill count was undertaken not all participants returned leftover medication. Simpler, less frequent dosing regimens result in better compliance (Claxton, 2001). The dosage used in our trial was significantly less than that used in the trial of Jiangtang Xiaozhi in people with diabetes. While not directly comparable, animal studies of Jiangtang Xiaozhi, showed that while lipids and insulin improved at the one dosage level it was not until a larger dose was administered that blood glucose reduced.

8.7 Strengths

The strength of this study was that it was a robust double-blinded, placebo controlled trial conducted according to rigorous scientific methodology.

Bias was minimised by good clinical trial design. A computerised random sequence generator at a centralised location was used by a person uninvolved in the clinical trial to assign cases to groups. A robust placebo was used to blind participants to their group allocation. Blinding was effective with only 27% of participants identifying their group in the final four weeks of the intervention. The intervention provider and outcome assessor were also blinded until data analysis was completed. All data was reported for all participants on all nominated outcome measures. Participants who did not complete the trial were accounted for.

Our statistical analysis was robust. The integrity of randomisation was maintained by employing an intention-to-treat analysis for all participants in the groups to which they were assigned. The main statistical tool was an analysis of covariance (ANCOVA). The inclusion of covariants in our analysis reduced the likelihood of within-group error variance and minimises some confounding factors.

The study had clear outcome variables and, where possible, used validated scales. The use of HOMA in clinical trials of people with impaired glucose tolerance and
Chapter 8: Randomised Controlled Trial - Discussion

diabetes has been validated elsewhere (Wallace 2004). The use of the SF-36 in an IGT population has not been validated. However, there are no validated QoL measures for this group and the SF-36 has been used in previous studies.

The study’s findings may be generalised to the wider impaired glucose tolerant population. The study population was drawn from people with a wide range of ethnic and socio-economic backgrounds in three locations in urban and coastal New South Wales. Gender and age was representative of the demographic of people with IGT in the broader community.

8.8 Conclusion

The null hypothesis that the Chinese herbal formula, Jiangtang Xiaozhi, has no added value in treating impaired glucose tolerance or insulin resistance in persons with prediabetes and early diabetes compared to placebo is partially rejected. We found evidence that Jiangtang Xiaozhi showed benefits in improving insulin resistance, maintaining insulin levels and improving HDL-cholesterol compared to a placebo. We also found that Jiangtang Xiaozhi was able to improve postprandial glucose compared to baseline levels. But we found no evidence that Jiangtang Xiaozhi was effective in lowering fasting blood glucose or HbA1c in a 16 week trial in people with impaired glucose tolerance and mild diabetes.

Chinese herbal medicine has been reported to improve impaired glucose tolerance and reduce the incidence of diabetes (Grant et al., 2009). These trials were either longer or larger than the clinical trial we conducted of Jiangtang Xiaozhi. The only other clinical trial of Jiangtang Xiaozhi found evidence for the treatment of fasting blood glucose in people with diabetes compared to baseline levels. This trial was shorter in length and in a smaller sample. The two critical differences seem to have been the more severe baseline symptoms of participants and the dosage. However, our trial supports the findings of this earlier on the capacity of Jiangtang Xiaozhi to improve insulin measures and HDL cholesterol compared to a placebo.

There is evidence that Jiangtang Xiaozhi exerts a positive effect on serum insulin and insulin resistance warrant further investigation. The role of insulin resistance in the pathogenesis of diabetes is well documented. Pharmacological interventions that are
well tolerated with minimal side effects for treating insulin resistance are few. Jiangtang Xiaozhi was well tolerated and, with further research, may provide an option for treatment. However, the benefits of Jiangtang Xiaozhi on insulin were not adequate to flow onto effect glycaemic control. This may be due to a number of factors: the trial was inadequately powered to detect a change, the dosage was not adequate, or the improvements in insulin resistance may eventually manifest in changes in glycaemic control over a longer period of time. The latter explanation reflects the intent of Chinese medicine treatment, that the body is brought gradually back to balance or homeostasis. However it is more likely that the former two explanations were closer to what occurred in the trial.

Jiangtang Xiaozhi has potential to treat elevated cholesterol in addition to serum insulin. The mean increase in the Jiangtang Xiaozhi group is only slightly less than the increase found in a pooled analysis of four clinical trials of statins, where individuals with a $\geq 7.5\%$ increase in good HDL cholesterol had a significant regression in coronary artherosclerosis.

To our knowledge this is the first study outside of China and Japan to investigate a Chinese herbal medicine for the treatment of prediabetes using a rigorous RCT design. In conclusion, small sample of participants with IGT and early diabetes exhibited significant benefits in terms of both insulin and HDL cholesterol over a relatively short intervention period using Jiangtang Xiaozhi. It was also well tolerated.

In light of the growing epidemic of diabetes worldwide, preventing or delaying the onset of diabetes may likewise reduce the microvascular and macrovascular complications of the disease. It is worthwhile investigating the potential of Jiangtang Xiaozhi to decrease blood glucose levels and reduce or prevent the incidence of diabetes in a longer, adequately powered trial.

This robust study further contributes to the growing body of scientific knowledge of Chinese herbal medicine. Findings from quality RCTs are important to inform the community, health professionals and regulatory authorities on the role of Chinese herbal medicine in health care.
CHAPTER 9

Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

When conducting a randomised controlled trial (RCT) to determine the efficacy of an acupuncture or Chinese herbal intervention there are many methodological challenges. These methodological challenges multiply when a Traditional Chinese Medicine (TCM) differential diagnosis is incorporated into the RCT design. Clinically, the TCM diagnostic framework is used to identify individual imbalances by careful gathering of symptoms through inquiry, observation, palpation and smell. The imbalances form a ‘pattern of disharmony’ and an individualised formulation of herbs or acupuncture along with diet and lifestyle advice such as Qi gong or Tai Chi is prescribed as appropriate. A change in a symptom or sign can change the diagnosis and therefore the treatment regardless of the ‘disease’. This diagnostic process is central to the practice of TCM in most clinical settings. The literature reviewed in Chapter 3 identifies a challenge for future trials to design conditions that more closely mimic the delivery of acupuncture and Chinese herbal medicine in clinical practice. In this way, research should deliver individualized treatment informed by its own diagnostic traditions that reflect clinical practice (Hammerschlag, 1998; MacPherson, Thorpe, Thomas, & Campbell, 2004). To do this, diagnosis and prescribed treatment need to be reliable and consistent.

This study sought to assess the inter-rater reliability of Chinese medicine diagnosis of people with prediabetes using a structured assessment instrument. There are several potential benefits of this study: (a) to contribute to a growing body of knowledge about the reliability of TCM diagnostic techniques, (b) to expand our understanding of the main TCM patterns of disharmony present in people with prediabetes, and (c) assist in the development of a valid and reliable instrument that enables TCM diagnosis to be incorporated into clinical trials of traditional Chinese medical therapies.
9.1 The use of TCM diagnosis in current research

Theoretical elements from Chinese medicine are being incorporated into the design of RCTs, but most research is still based on biomedical diagnosis (Shea, 2006). A review of Chinese medicine trials from Chinese language literature found that diagnostic categories and measurements tend to be set in a western biomedical context with traditional Chinese medicine featuring only on a small scale (Tang, Zhan, & Ernst, 1999). This was reflected in our review of the clinical trials conducted in China in people with prediabetes (see Chapter 3). Only a small number of the trials reviewed incorporated either TCM diagnosis or treatment principles into the trial design. Six of the 36 RCTs utilised TCM differential diagnosis to enrol people diagnosed with a specific pattern of disharmony for a disease. The most commonly encountered clinical trial design was the use of a standard herbal formula, coupled with a loose treatment principle, administered to a cohort of people with prediabetes without any pattern discrimination. The option to modify the formula to take into account individual symptoms such as constipation or insomnia was available in only a small number of trials.

Different people respond differently to Chinese herbs or acupuncture points (Allen, 1998; Bensoussan, 1998; Langevin et al., 2004). Treatment according to a differential diagnosis is arguably the most effective way in which to use the *materia medica* of Chinese medicine. Differential diagnosis and treatment is the way in which TCM is practiced in most clinical settings with some exceptions such as medical acupuncture or trigger point acupuncture. If clinical trials are to reflect clinical practice then TCM principles need to be integrated into trial design. TCM diagnosis has been incorporated into past clinical trials in a number of ways:

1. individual TCM diagnosis of participants and individualized treatment based on the diagnosis (Diener et al., 2006);

2. TCM diagnosis and allocation to a group receiving a set standard Chinese treatment (Bensoussan, 1998; Joos, Schott, Zou, Daniel, & Martin, 2000);
3. Assignment of groups to TCM diagnoses using algorithms that are then matched to a specific Western condition (Bensoussan et al., 1998; Hammerschlag, 1998; Schnyer & Allen, 2002).

Without assessing the consistency of the diagnoses used in these trials, the interpretation of positive or negative results are confounded.

Schnyer and colleagues have been developing ‘manualization’ as an approach to assist in providing a reliable and consistent TCM diagnosis and treatment in clinical trials (Schnyer & Allen, 2002). ‘Manualization’ is the documentation of the diagnostic framework and treatment to be undertaken within a clinical trial. It guides the diagnosis and treatment of a clinical trial participant through a series of adjustments to the herbal formula. This allows the diagnosis and treatment to reflect as closely as possible what would occur in clinical practice, while being replicable.

The utilisation of TCM diagnosis and treatment in clinical trials facilitates the convergence of Western biomedicine and TCM. It enables the investigation to determine if individualised treatments based on TCM diagnosis produce a more significant result than standard treatments, and if the TCM diagnostic framework has any meaningful alignment with Western biomedicine.

9.2 Previous inter-rater reliability studies

A growing number of studies have undertaken to evaluate the validity and reliability of TCM diagnoses. O’Brien and Birch (2009) conducted a review of these studies and identified fourteen studies that assessed inter-rater reliability of pattern diagnosis. The purpose of undertaking these inter-rater reliability studies has been to assess the reliability of diagnosis within a clinical trial setting (MacPherson, Thorpe et al. 2004; O’Brien, Abbas et al. 2009); and to understand the effectiveness of training on inter-rater reliability of TCM practitioners (Mist, Ritenbaugh, & Aickin, 2009; Zhang et al., 2008).

Methodology, design and size varied considerably across these studies making conclusions about inter-rater reliability in TCM diagnosis difficult to reach. The range of disorders examined were also dissimilar and included menopause (Zell, et
al., 2000), headache (Coeytaux, Chen, Lindemuth, Tan, & Reilly, 2006), rheumatoid arthritis (Zhang GC, 2004), high cholesterol (O'Brien et al., 2009a) and irritable bowel syndrome (Sung, 2004). A few studies looked at the same disorder such as those that examined TCM diagnosis of lower back pain (Kalauokalani, Sherman, & Cherkin, 2001; MacPherson, et al., 2004; Sherman, Cherkin, & Hogeboom, 2001). However, variable design and statistical methods prohibit any meta-analysis. Nonetheless insights can be gained from looking at common findings, problems encountered and strategies that were employed to address these.

Common across these studies was the variation in practitioner diagnostic assessment techniques and the diagnostic categories that were assigned. These variations were the product of differences in training, education and clinical experience. This presents a number of potential problems. The TCM diagnostic categories and subcategories that are presented may use different terminology or hold different meaning to different practitioners. Data collection techniques that are practitioner centric are not replicable or reliable across groups of practitioners and therefore not suited for trials or study. The way in which these issues were addressed depended to some extent on the objective of the study and whether standardisation was sought or simply a consensus on diagnosis on a particular disease. The strategies that some of the inter-rater reliability studies employed to address these issues are discussed below.

Methods of minimising variability in the diagnostic process included sharing the same patient history form to ensure that all practitioners had the same information (O’Brien, et al., 2009a; Zhang et al., 2005), and using set practitioner questionnaires (MacPherson, et al., 2004; Mist, et al., 2009). Some studies thought it appropriate to reflect clinical practice and allowed practitioners to use their own style of diagnostic assessment (Kalauokalani, et al., 2001) or a minimal data collection and diagnosis form (Coeytaux, et al., 2006). However, the lack of an adequate data collection instrument limits the precision with which a diagnosis can be consistently obtained by different practitioners, and repeated.

To address the issues of variability in the expression of the final TCM diagnosis, some studies developed a list of key diagnostic patterns for a disease (Zhang, et al.,
Kalauokalani, et al., 2001; Kalauokalani D, 2001; MacPherson, et al., 2004; Sung, 2004; 2005). Although this wasn’t always suited to the study design and in some studies diagnosis was left open to as many syndromes as required (O'Brien, et al., 2009a) or a combination of both (Zell, et al., 2000).

Study design varied but using two-three different practitioners to assess the same patient within a short period of time was the most common (MacPherson, et al., 2004; O'Brien, et al., 2009a). One study incorporated a Latin square design in which six practitioners assessed the same six patients but found the outcomes too complex to analyse using a statistical method (Hogeboom, Sherman, & Cherkin, 2001).

The issue of practitioner education and clinical experience as possible confounding factors was addressed in several studies (Sung, 2004; Zhang, et al., 2008). Some studies utilised practitioners with similar training and clinical experience (Sung, 2004). Although one study found that utilising TCM practitioners from a similar background and clinical experience made little or no difference to the average agreement of TCM diagnosis (Zhang, et al., 2005).

To improve inter-rater reliability some studies incorporated training or a period of refinement or calibration before or during the inter-rater reliability study (Mist, et al., 2009; Zhang, et al., 2008).

Data analysis methods to assess inter-rater reliability included Cohen’s Kappa statistic (MacPherson, et al., 2004; O'Brien, et al., 2009a; Sung, 2004; Zhang, et al., 2005), or Fliess’ kappa (Mist, et al., 2009) or in some cases no statistical method was used (Kalauokalani, et al., 2001).

Overall, the results of these studies vary from low to good level of agreement. Common findings were a moderate to high level of agreement on the primary diagnosis but poor agreement on the secondary syndromes (Hogeboom, et al., 2001). Conclusions are limited by small sample sizes, variable methodology and lack of validity of the instruments used to collect data. A reliable and valid TCM diagnostic instrument is required that can be incorporated in clinical trials of traditional Chinese medical therapies.
A structured assessment instrument, the Traditional East Asian Medicine Structured Instrument – Traditional Chinese Medicine (TEAMSI-TCM), is being developed against this background by the Harvard Medical School Division for Research and Education in Complementary and Integrative Medical Therapies and the New England School of Acupuncture (NESA) in the United States\(^1\). It uses the pattern differentiation model characteristic of TCM. It is a prescriptive instrument that guides practitioners to use the proper indicators, combine them in a systematic manner, and generate conclusions (Kalauokalani, et al., 2001; Schnyer et al., 2005). The hypothesis is that this instrument will increase the inter-rater reliability of Traditional Chinese Medicine (TCM) diagnosis when used in clinical trials. The validity and reliability of the TEAMSI-TCM instrument is currently being tested in two trials in the United States.

A further enhancement to the reliability of the TCM diagnostic process may be the use of pathology tests. The use of pathology tests and their congruence to TCM patterns of disharmony is limited but has increasingly been investigated in China (Xu 1993; Lu Y 2003; Chen 2007). These studies found that pathology results had associations with the TCM diagnostic categories of particular diseases. It has been proposed that integrating TCM diagnosis with biomarkers may improve reliability (Zhang, Bausell, Lixing, Handweger & Berman, 2003). To this author’s knowledge the usefulness of pathology results in improving the inter-rater reliability of TCM diagnosis has not been formerly investigated. While investigating the utility of biochemical data in increasing the reliability of TCM diagnosis is beyond the scope of this paper, there is certainly value in continuing to explore the relations among TCM diagnoses and biomarkers.

### 9.3 Method

An inter-rater reliability study was conducted as part of a clinical trial investigating the effectiveness of *Jiangtang Xiaozhi* in the treatment of impaired glucose tolerance and insulin resistance in persons with prediabetes or mild diabetes. The developers

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\(^1\) see [http://www.nesa.edu/research/currentresearch/dcrc3.html](http://www.nesa.edu/research/currentresearch/dcrc3.html) for details: the Traditional East Asian Medicine Structured Interview, TCM version (TEAMSI-TCM)
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

of the TEAMSI-TCM agreed to the diagnostic instrument being used to assess reliability in this study, albeit the instrument is still in the developmental stage.

Two TCM practitioners used TEAMSI-TCM to provide a diagnostic assessment and a final diagnosis of 27 people with prediabetes. Practitioners were blinded to each other’s diagnoses throughout the study.

9.3.1 Participants

Twenty-seven participants had all been diagnosed with impaired glucose tolerance (prediabetes) by blood test prior to enrolment in the study. Participants were required to complete the TEAMIS-TCM patient questionnaire and to be interviewed by two practitioners. This inter-rater reliability study was conducted as part of a larger clinical trial where biomarkers were collected at baseline. The biomarkers were collected within a week of the TCM diagnosis being conducted.

9.3.2 Practitioners

Two accredited TCM practitioners with 4-year Bachelor degrees from the same institution and more than 4 years clinical experience in Australia conducted the TCM diagnosis. Both practitioners were accredited with the Australian Acupuncturists and Chinese Medicine Association. The practitioners were both aware that the patient had been diagnosed with prediabetes. They were not required to provide a treatment plan. The practitioners were required to use the TEAMSI-TCM instrument for diagnosis. Practitioners were provided with the same patient questionnaire. The practitioners were blind to each other’s diagnosis until data entry was complete.

9.3.3 Data collection and diagnostic framework

The Traditional East Asian Medicine Structured Interview, TCM version (TEAMSI-TCM) was used for data collection (Appendix H.1). The TEAMSI-TCM instrument is specifically designed for use in clinical trials, it is not designed for use in usual clinical settings. It utilises the Eight Principle Pattern Differentiation model as a framework and the identification of patterns according to the Internal Organs. The Eight Principles are applicable to the diagnosis of all patient presentations. It allows for the differentiation of patterns according to Exterior-Interior, Hot-Cold, Full-
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

Empty and Yin-Yang (Maciocia, 1989). The Identification of Patterns allows for the identification of disharmony of a particular Internal Organ.

The TEAMSI-TCM data collection instrument was designed to guide practitioners to use clinical signs, combine them in a systematic way and generate a conclusion. It is designed to be used in conjunction with education and training. It is structured in two parts.

A patient questionnaire was first completed by the participant. This provided subjective data on the participant’s symptoms. Practitioner 1 and Practitioner 2 read a copy of the same completed questionnaire prior to commencing the interview with the participant. The interviews were usually conducted within an hour of each other. Neither practitioner had access to each other’s examination notes and which practitioner was seen first was altered in a pseudorandom manner to control for order effects on patient reporting during interviews.

The practitioners’ package consisted of a section for recording notes taken during the interview and which related to the participant’s questionnaire. This was where practitioners recorded general symptoms, and symptoms related to the main complaint. An evaluation section provided guidance for recording observations relating to tongue, pulse, body, constitution, and complexion.

A pattern differentiation form specifically designed for people with prediabetes allowed for a primary pattern and accompanying pattern to be selected from a list of single and complex patterns (Appendix H.2). An option was provided for practitioners to list additional diagnoses where necessary or comment to modify the patterns described on the form.

9.3.4 Statistical analysis

A kappa coefficient was used as the main statistic to determine inter-rater reliability. A kappa is a measure of agreement between raters which is corrected for chance. A kappa of zero means there is no agreement or less than chance agreement and a kappa of one means there is complete agreement.
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

The approach used by Macpherson et al (MacPherson, et al., 2004) to determine inter-rater reliability was adopted. Their study presents both a percentage and a kappa coefficient based on Steinijans demonstration that Cohen's kappa coefficient of agreement between 2 raters or 2 diagnostic methods based on binary (yes/no) responses does not parallel the percentage of patients with congruent classifications (Steinijans, Diletti, Bömches, Greis, & Solleder, 1997). MacPherson and colleagues recommended presenting both, the percentage of patients with congruent classifications, and Cohen's kappa coefficient with 95% confidence limits.

To describe the range between zero and one, Landis and Koch (1977) have suggested the scale represented in Table 9-1.

<table>
<thead>
<tr>
<th>Kappa</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>Less than chance agreement</td>
</tr>
<tr>
<td>.01-.20</td>
<td>Slight agreement</td>
</tr>
<tr>
<td>.21-.40</td>
<td>Fair agreement</td>
</tr>
<tr>
<td>.41-.60</td>
<td>Moderate agreement</td>
</tr>
<tr>
<td>.61-.80</td>
<td>Substantial agreement</td>
</tr>
<tr>
<td>.81-.99</td>
<td>Almost perfect agreement</td>
</tr>
</tbody>
</table>

For the analysis of biomarkers and patterns of disharmony, the participants included were only those where both practitioners agreed on the primary diagnosis. Independent $t$-tests were used to calculate any significant difference between the patterns of disharmony and the biomarker variables. Analyses were performed in
SPSS version 18.0 (SPSS Inc), and CIs for values were calculated using the generic formula for 95% confidence intervals: estimate $\pm 1.96SE$.

### 9.3.5 Definition of agreement on TCM pattern diagnosis

There are no defined TCM patterns for prediabetes. In Western medicine it is a biomedical entity. In TCM it does not appear in classical texts and few modern texts discuss prediabetes. Flaws et al (2002) found that, in clinical experience, people at the early stage of diabetes or prediabetes more commonly present with spleen deficiency then with yin deficiency and dry heat (Flaws, Kuchinski, & Casanas, 2002).

The results of a search of Chinese journals identified eight reviews of pattern differentiation in people with IGT, as was discussed in Chapter 3:

1. Spleen deficiency with Damp (or Damp-Heat)
2. Qi and Yin deficiency
3. Qi deficiency
4. Yin deficiency (with Empty-Heat or Blood stasis)
5. Phlegm-Damp
6. Qi and Phlegm stagnation
7. Liver qi stagnation (with Blood stasis)
8. Yang xu with blood stasis

The most common identified pattern was Spleen deficiency with Damp, and Qi and Yin deficiency. Blood stasis was a common accompanying pattern (Lu Y 2003; Lian 2004; Wu 2004; Dong 2005; Li SL 2006; Chen 2007; Song 2007; Chai 2008).

In clinical trials of Chinese herbal medicine in the treatment of people with prediabetes it is common for the Spleen to be the main target of treatment (Fan, Luo, & Qin, 2004; Ja, 2003; Mang, 2000)
Hence, the pathogenesis and patterns are likely to be complex. These patterns formed the basis of a list of diagnostic patterns practitioners were asked to select from. Practitioners were directed to select only one primary pattern, but multiple accompanying patterns if required. Practitioners were advised to add patterns or comment and modify the sheet if necessary.

9.4 Results

9.4.1 Patient characteristics

The mean age of the 11 male and 16 female participants was 57.3 yrs (range 36-75 yrs). The mean fasting blood glucose was 6.2 mmol/L, 2hr-OGTT was 10.6 mmol/L. All participants had good glycaemic control as evidenced by a mean HbA1c of 6.2% (range 5.2 – 7.2%). The majority of participants had hypertension (n = 16) and high cholesterol (n = 14).

9.4.2 TCM diagnostic patterns

Three TCM patterns of disharmony for people with prediabetes featured as the primary diagnosis: Yin deficiency, Qi and Yin deficiency and Spleen qi deficiency. The two practitioners agreed on 70% of the primary diagnoses for individual participants (see Table 9-2). The three patterns were fairly evenly distributed among the participants.

The inter-rater reliability for the practitioners was found to be Kappa = .56 (p < .001), 95% CI (0.25 to 0.81). While this is statistically significant it only represents a moderate level of agreement.

While the differentiation of prediabetes is not well-researched, the most prevalent understanding of diabetes is that the root of diabetes is qi and yin deficiency and the branch is heat, blood stasis, phlegm, liver qi stagnation, damp-heat or phlegm-dampness (Wei-bin, 2008).

There was agreement between practitioners on primary and accompanying diagnosis in eleven participants (40.7%). These patterns were:
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

- Yin deficiency with Spleen qi deficiency \( (n = 1) \)
- Yin deficiency with Damp heat \( (n = 1) \)
- Yin deficiency with Blood stagnation \( (n = 1) \)
- Qi and Yin deficiency with Damp and Blood stagnation \( (n = 1) \)
- Qi and Yin deficiency with Damp \( (n = 1) \)
- Spleen qi deficiency with Damp and Liver qi stagnation \( (n = 4) \)
- Spleen qi deficiency with Damp Heat and Liver qi stagnation \( (n = 1) \)
- Spleen qi deficiency with Damp Heat \( (n = 1) \)

Table 9-2 Frequency of Agreement of Primary TCM Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Practitioner 1</th>
<th>Practitioner 2</th>
<th>Agreement(^a) n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney yin deficiency</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>(22% of participants given equivalent diagnosis by both practitioners)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qi and Yin deficiency</td>
<td>10</td>
<td>9</td>
<td>7</td>
<td>70%</td>
</tr>
<tr>
<td>(26% of participants given equivalent diagnosis by both practitioners)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen qi deficiency</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>55%</td>
</tr>
<tr>
<td>(22% of participants given equivalent diagnosis by both practitioners)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>27</td>
<td>19</td>
<td>70.3%</td>
</tr>
<tr>
<td>(70.3% of participants given equivalent diagnoses by both practitioners)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes \(^a\)agreement refers to the equivalent diagnosis for one participant by both practitioners

Accompanying patterns identified by practitioners were primarily accompanying Damp, Damp Heat, Liver qi stagnation and Blood stagnation. As multiple accompanying patterns were identifiable for each participant, no attempt has been
made to calculate levels of agreement among accompanying patterns other than to ascertain that 24 participants (89%) received at least one accompanying or a secondary diagnosis by both practitioners.

<table>
<thead>
<tr>
<th>Accompanying patterns</th>
<th>Practitioner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damp heat</td>
<td>7</td>
</tr>
<tr>
<td>Spleen qi deficiency</td>
<td>3</td>
</tr>
<tr>
<td>Plus Damp</td>
<td>11</td>
</tr>
<tr>
<td>Blood stagnation</td>
<td>5</td>
</tr>
<tr>
<td>Liver qi stagnation</td>
<td>10</td>
</tr>
<tr>
<td>Yang xu</td>
<td>1</td>
</tr>
<tr>
<td>Phlegm</td>
<td>0</td>
</tr>
<tr>
<td>Yin deficiency</td>
<td>2</td>
</tr>
</tbody>
</table>

9.4.3 The TEAMSI-TCM instrument

The face, content and ecological validity of the TEAMSI-TCM instrument was not formally assessed. Nonetheless feedback was requested. Both practitioners found the forms for patient and practitioner comprehensive and thorough. However, in general the process of moving through the form was complex and hindered usability for both practitioner and patient.

The primary difficulty patients voiced was using the codes (recurrent, chronic etc) to grade the nature of a symptom, followed by the length of the document. Many patients struggled to use these codes appropriately. Most were not able to “correctly” complete the questionnaire without assistance throughout.

The primary difficulty for practitioners was using the step-by-step diagnosis form. The number of symptoms ‘ticked’ within one pattern of disharmony does not necessarily equate to the same diagnosis across practitioners. The severity and
nature of the symptoms combined with clinical judgement were cited as more relevant to determining a final diagnosis. The patient-practitioner interaction was considered central to making the diagnosis while the TEAMSI-TCM tool was useful to refine and enunciate the diagnosis.

9.4.4 TCM patterns of disharmony and biomarkers for people with prediabetes

Chapter three examined some of the biochemical markers that were predominant in certain patterns of disharmony in this sample of people with prediabetes. This study repeated this analysis with the small sample of participants where there was diagnostic agreement on the pattern of disharmony ($n = 18$). The results are shown in Table 9-3.


Table 9-3 *TCM diagnosis for prediabetes and biomarkers*

<table>
<thead>
<tr>
<th>Marker</th>
<th>TCM Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yin deficiency (n = 6)</td>
</tr>
<tr>
<td>Hypertension^</td>
<td>3</td>
</tr>
<tr>
<td>FBG mmol/L (SD)</td>
<td>5.8 (0.81)</td>
</tr>
<tr>
<td>GTT mmol/L (SD)</td>
<td>9.8 (2.2)</td>
</tr>
<tr>
<td>Insulin mmol/L (SD)</td>
<td>12.5 (8.3)</td>
</tr>
<tr>
<td>HOMA-IR (SD)</td>
<td>1.8 (1.1)</td>
</tr>
<tr>
<td>HbA1c % (SD)</td>
<td>6.1 (0.6)</td>
</tr>
<tr>
<td>Trigs mmol/L (SD)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>TC mmol/L (SD)</td>
<td>4.8 (0.7)</td>
</tr>
<tr>
<td>HDL mmol/L (SD)</td>
<td>1.8 (0.53)</td>
</tr>
<tr>
<td>Body Mass Index (SD)</td>
<td>27.7 (2.5)</td>
</tr>
</tbody>
</table>

*Notes:*

^refers to participants who were currently taking medication for hypertension.

*significant difference between Spleen qi deficiency with Damp & the other two diagnostic categories.

**significant difference between Spleen qi deficiency with Damp and Qi and yin deficiency.

^**significant difference between Spleen qi deficiency with Damp and Yin deficiency.
There was a significant difference between the Spleen qi deficiency with Damp cohort and Qi and yin deficiency on the variables of fasting blood glucose \( (p = .03) \), insulin \( (p<0.01) \), insulin resistance (HOMA-IR \( p=0.01 \)), and HbA1c \( (p = .01) \). There was also a significant difference between the Spleen qi deficiency with Damp group and the Yin deficiency group on the variables of fasting blood glucose \( (p<0.05) \), insulin \( (p = .05) \) BMI \( (p = .01) \), and HDL cholesterol \( (p = .03) \). There was no significant variation in the biomarkers of people with Yin deficiency and Qi and yin deficiency \( (p>0.05 \text{ on all variables}) \).

**9.5 Discussion**

This study aimed to assess the inter-rater reliability of Chinese medicine diagnosis of people with prediabetes using a structured assessment instrument; and contribute to an understanding of TCM patterns of disharmony in people with prediabetes.

*Reliability of TCM diagnosis*

The analysis of 54 diagnoses of 27 participants found a moderate level of agreement between the two practitioners on the primary diagnosis. That is, the practitioners agreed on nearly 6 out of 10 diagnoses. In terms of the number and percentage of congruent classifications on the primary diagnosis, it was slightly higher at 70%. This level of agreement is consistent with some of the other inter-rater reliability studies where two practitioners were considered (Kalauokalani D, 2001; MacPherson, et al., 2004; O'Brien et al., 2009b; Sung, 2004). It should be noted that in general when a diagnosis or clinical judgement requires a subjective assessment than the inter-rater reliability between assessors is generally low (Zhang, et al., 2005). This applies to Western medicine also where a subjective component is involved (Hand, Haisma et al. 2006; Eversole 2009; Rask, Borg et al. 2009).

The moderate level of agreement on the primary diagnosis achieved between the two practitioners in this study may be attributed to several factors - the similar backgrounds of the practitioners, the use of a thorough diagnostic instrument and the limited number of practitioners involved.
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

Probably one of the most remarkable results of this study was that the TCM diagnostic framework exhibited a modest level of reliability for what is seen purely as a biomedical disorder. In Western medicine, people with prediabetes are not diagnosed according to any overt symptoms or signs with the exception of elevated blood glucose levels. Hence it would seem less likely to exhibit common symptoms compared to disorder such as lower back pain which tended to receive a common pattern diagnosis involving qi stagnation (Sherman, et al., 2001) or Kidney yin deficiency for women with menopause (B Zell et al., 2000).

O’Brien et al. (2009) note that caution should be exercised in drawing any conclusions about the reliability and applicability of bian zheng (TCM differential diagnosis) to a biomedical entity. They concluded that inter-rater reliability might be higher in a classical TCM disease where diagnosis and sub-groups are more commonly understood and accepted by practitioners, where there is a substantial history of treatment. Such caution should perhaps apply to this study also. However, a further finding was that the patterns of disharmony that were identified as prominent through differential diagnosis in this research reflect those that had been found in the earlier Chinese studies. Of the few studies that have examined the prevalence of a TCM pattern of disharmony in people with prediabetes, two population studies firmly indicate that Spleen qi deficiency with Damp (or similarly Damp Heat and Phlegm damaging the Spleen) and Qi and yin deficiency are the main patterns (Chen, Zhou, & Jau, 2007; Lu Y, 2003). Lian’s (2004) study also points to the central role of the Spleen in the disorder (Lian, 2004). While in Dong’s (2005) analysis Qi and Yin deficiency were seen as the main pattern (Dong, 2005).

All participants with the exception of three received at least one accompanying or secondary diagnosis. Diagnosis of multiple patterns or syndromes was a feature of previous research on inter-rater reliability (MacPherson, et al., 2004; Sherman, et al., 2001). The diagnosis of secondary patterns of disharmony tends to be subject to lower levels of inter-rater reliability (Zhang GC, 2004). In this study there was complete agreement between practitioners on both the primary and the accompanying diagnoses in 41% of cases or in eleven participants. It is possible that a higher rate of agreement may have been reached if the diagnostic categories were constructed differently or training conducted to ensure a shared understanding. For
example in one instance one practitioner diagnosed a patient as having primary Spleen qi deficiency and accompanying yin deficiency. This may have been more appropriately marked as a single primary diagnosis only, depending on the emphasis or weight accorded to the accompanying symptoms.

The understanding by practitioners of the three patterns of disharmony that dominated diagnosis in our study (Spleen qi deficiency, Yin deficiency and Qi and Yin deficiency) may have affected inter-rater reliability. As shown in Figure 9-1 the lines distinguishing the differences between these patterns are blurred and may have led to some overlaps. It is possible that training and calibration to ensure a shared understanding of the nominated TCM syndromes may have increased inter-rater reliability.

*Figure 9-1* Primary TCM Diagnosis for Prediabetes Symptom Overlap
Relative importance of education and training

Previous studies have found that differences in training affect the way a diagnosis is communicated (Zhang, Lee et al. 2005; Coeytaux, Chen et al. 2006). This confounding factor was limited in our study by selecting practitioners who were trained in the same institution and with a similar length of practice experience. Nonetheless, there was no training given on the patterns of disharmony nominated in the TEAMSI-TCM tool. There may have been improved inter-rater reliability if practitioners were taken through consensus training or similar to ensure that practitioners were all ‘speaking the same language’ (Sung, 2004; Zhang, et al., 2008).

Use of a structured diagnostic instrument (TEAMSI-TCM)

One of the strengths of this study was the use of the diagnostic TEAMSI-TCM tool. The benefits were manifold. The comprehensive patient questionnaire provided both practitioners with the same starting point, ensuring that a substantial amount of information was shared and thereby limiting variations of what was divulged in the patient-practitioner interview. Practitioners were guided to use a thorough assessment protocol rather than rely on pulse and/or tongue alone. A rationale for a diagnosis could clearly be seen through examining patient questionnaires and practitioner notes and evaluations. Zhang et al (2008) found that inter-rater reliability increased with the use of more objective tools such as ‘inquiry’, it is likely this was the case in our study also (Zhang, et al., 2008).

An examination of the practitioners’ TEAMSI-TCM notes from patient interviews and evaluations revealed some obvious reasons for different diagnoses. The main reasons appeared to be differences in what was divulged by a patient to one practitioner and not the other; differences in tongue and pulse evaluations; and varying levels of importance or weight accorded to certain symptoms. This clinical judgement is difficult to control for and is likely to be the main confounding factor in reaching high levels of inter-rater reliability in TCM diagnosis. Perhaps the best solution is to utilise methods to guide diagnosis using a validated instrument, educate...
and train practitioners on these instruments and the nominated diagnostic categories but anticipate that clinical judgement will confound the result. Where the priority is to reach consensus for a clinical trial, a further strategy, suggested by O’Brien and Birch, may be to have two practitioners examine each patient and commence treatment only when diagnostic consensus has been reached (O’Brien & Birch, 2009).

**Patterns of disharmony and biomarkers**

The use of biomarkers integrated with TCM diagnosis has been proposed as a strategy that may improve reliability (Zhang GC, 2003). This small but emerging area of research has found correlations between certain patterns of disharmony and certain biomarkers. For example, eosinophils which play an important role in the pathogenesis of bronchial asthma and allergic rhinitis, have been found to be more elevated in the patients with typical heat (‘zheng’) (Yu, 1999). Xu et al (1993) found that high levels of platelet aggregation activity corresponded to blood stagnation (Xu, 1993). Another study found that diagnosing blood stagnation in people with rheumatoid arthritis was possible through using a combination of proteomic and bioinformatics-based classification methods (Matsumoto et al., 2008).

TCM patterns of disharmony for prediabetes are not well documented as shown in Chapter three, nonetheless there is some research that has been conducted on linking biomarkers to these patterns.

The three main organs involved in diabetes are the Kidneys, Spleen and Lungs and central to the diagnosis is the deficiency of Qi and Yin (Flaws B, 2002; Wei-bin, 2008). When examining the literature for patterns of disharmony in people with prediabetes, Spleen and Kidney are prominent. Reported patterns of disharmony typically include Spleen qi deficiency (with or without Damp or Damp Heat), Qi and Yin deficiency, Yin deficiency with Empty Heat, and occasional references to Liver qi stagnation, Yang deficiency and Blood stasis (Chen, et al., 2007; Fang WB, 2008; Fang ZH, 2007; Lu Y, 2003).

In our research diagnosis was fairly evenly distributed between three categories: Spleen qi deficiency, Yin deficiency and Qi and Yin deficiency. There were marked
Chapter 9  Inter-Rater Reliability of Traditional Chinese Medicine Diagnosis

differences between two TCM groups who showed very similar biomarker profiles (Yin deficiency and Qi and Yin deficiency) and the Spleen qi deficiency group.

The Spleen qi deficiency group had higher fasting blood glucose (FBG), insulin, greater insulin resistance and higher HbA1c then the Qi and Yin deficiency group. This group also had higher FBG, insulin, BMI, and worse HDL cholesterol then the Yin deficiency group. The biomarker pathology for people with prediabetes diagnosed with Spleen qi deficiency may therefore constitute a quite distinct group. This biochemical characterisation of Spleen qi deficiency is similar to previous studies of biomarkers in prediabetes (Chen, et al., 2007; Fang WB, 2008; Lu Y, 2003). Chen and colleagues analysed the biomarkers of 156 people, 56% who were diagnosed with Damp heat & Spleen qi xu. This group had higher BMI, higher triglycerides, higher insulin and larger waist measurements. These findings are a good indication of possible biomarkers that may be included in a TCM differential diagnosis where an integration of methods was thought feasible, but require further validation.

Chen and colleagues also found that people with prediabetes diagnosed with Qi and yin deficiency tended to have hypertension and elevated LDL. We found that there was no significant variation in the biomarkers of people with Yin deficiency compared to those with Qi and yin deficiency. This may have been that these groups were too similar or that the sample was too small.

Further research on the relations between TCM diagnosis and biomarkers may facilitate the incorporation of a set of objective criteria with differential diagnosis for use in clinical trials.

Limitations

There are some limitations to the design of this study. We used two practitioners to perform the diagnoses. Using a smaller number of raters was likely to result in higher percent agreement. More practitioners involved doing diagnoses of each patient would also have increased the statistical power of this study. However this study was conducted pragmatically within the time and constraints of a clinical trial.
Patients were diagnosed on one occasion only. This has been raised as a limitation in previous research as being seen only once by a practitioner does not reflect clinical practice (Sung 2004; Zhang, Lee et al. 2005). Typically a TCM diagnosis will be refined over a few visits as signs and symptoms become more or less apparent through ‘inquiry’, ‘observation’ and ‘palpation’. However, the cost and time involved in performing a diagnosis over two to three visits would be prohibitive in even well-resourced trials.

There are several well-described limitations to the use of the kappa statistic that can influence the interpretation of results (Brennan and Silman 1992; Watkins and Pacheco 2000; Karanicolas, Bhandari et al. 2009). Very low (or high) prevalence results in high levels of expected agreement, and consequently the value is often low despite near perfect agreement. In this study it would appear kappa reflected the level of agreement based on an inspection of prevalence.

It is a small exploratory study. Our sample size was small and as such the external validity of these findings is limited.

This study does not consider other diagnostic traditions of Chinese medicine. *Bianzheng lunzhi* or “determining treatment on the basis of discerning the syndrome” has achieved central position as the method for diagnosis in Chinese medicine. But in clinical practice this is one of many diagnostic and therapeutic strategies employed by clinicians (Scheid, 2002).

**9.6 Conclusion**

TCM practitioners diagnosing patients with prediabetes commonly selected one of three patterns: Qi and Yin deficiency, Spleen qi deficiency or Yin deficiency. There was a moderate level of inter-rater reliability between practitioners. From the diagnostic data clear patterns of disharmony or TCM categories and sub-categories of people with prediabetes are apparent.

The methodology of inter-rater reliability studies of TCM diagnosis would benefit from further refinement, building on research that has already been conducted. Methodology should address differences in training, education and clinical
experience, conducting training and ‘calibration’ exercises to ensure a shared understanding of what is meant by each proposed TCM diagnosis, and the inclusion or exploration of biochemical measures where appropriate and the use of an instrument such as the TEAMSI-TCM.

The continued improvement of the face and content validity of the TEAMSI-TCM instrument will result in a robust tool for the conduct of inter-rater reliability studies and, in the future, clinical trials.

This research contributes to the growing body of knowledge about the reliability of TCM diagnostic techniques; expanding the understanding of the main TCM patterns of disharmony present in people with prediabetes; and to the development of a valid and reliable instrument that enables TCM diagnosis to be incorporated into clinical trials of traditional Chinese medical therapies.


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