Effects of Chinese herbal medicine Yiqi Huaju Qingli Formula in metabolic syndrome patients with microalbuminuria: a randomized placebo-controlled trial

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BACKGROUND: Microalbuminuria (MAU) is a key component of metabolic syndrome (MetS) and is an early sign of diabetic nephropathy as well. Although routine Western medicine treatments are given to MetS patients to control high blood pressure, hyperglycemia and dyslipidemia, some patients still experience progressive renal lesions and it is necessary to modify and improve the treatment strategy for MetS patients.

OBJECTIVE: To investigate the efficacy of Yiqi Huaju Qingli Herb Formula, a compound traditional Chinese herbal medicine, in MetS patients with MAU when it is combined with routine Western medicine treatment.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: Sixty patients with MetS were randomized into the Chinese herbal formula group (CHF, Yiqi Huaju Qingli formula treatment in combination with Western medicine) and control group (placebo in combination with Western medicine). All treatments were administered for 12 weeks.

MAIN OUTCOME MEASURES: Urinary microalbumin (MA), urinary albumin-to-creatinine ratio (UACR), 24-hour total urine protein (24-hTP), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2-hPPG), glycosylated hemoglobin (HbA1c), homeostasis model assessment for insulin resistance (HOMA-IR), blood lipid profile and blood pressure were observed.

RESULTS: Compared with the control group, CHF treatment significantly decreased BMI (P<0.05), WC (P<0.01) and WHR (P<0.01). Both groups had significant decreases in FPG, 2-hPPG, HbA1c, HOMA-IR, MA, and UACR, with CHF treatment showing better effects on these parameters compared with the control treatment (P<0.05). Both treatments significantly reduced the levels of total cholesterol, low-density lipoprotein cholesterol and triacylglycerol (TAG), and a greater reduction in TAG was observed with CHF treatment (P<0.05). The level of high-density lipoprotein cholesterol did not change in the control group after treatment (P>0.05), whereas it significantly increased with CHF treatment (P<0.01). Compared with before the treatment, significant decreases in systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were observed in both groups (P<0.01). However, there was no significant difference between the two groups (P>0.05).

CONCLUSION: Combined treatment of Yiqi Huaju Qingli Formula and Western medicine significantly alleviated MAU, which may correlate with the improvement of insulin sensitivity and glucose and lipid metabolism.

TRIAL REGISTRATION IDENTIFIER: This trial was registered in the Chinese Clinical Trial Registry with the identifier ChiCTR-TRC-11001633.
KEYWORDS: metabolic syndrome X; microalbuminuria; insulin resistance; drugs, Chinese herbal; randomized controlled trials

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1 Introduction

Microalbuminuria (MAU) is one of the criteria for the diagnosis of metabolic syndrome (MetS), as established by the World Health Organization in 1998[1]. MAU is one of the most common microvascular complications of diabetic nephropathy (DN), and ultimately develops into end-stage renal disease[2]. Besides the fact that diabetes is closely associated with MAU, hypertension and obesity can also impair renal function and result in MAU. Thus, MAU is not only one of the important components of MetS, but also an independent risk factor of cardiovascular disease[3]. With the control of hypertension, hyperglycemia and dyslipidemia, some patients still exhibit MAU and progressive renal lesion, which probably result from multiple risk factors involved in patients with MetS. As shown in our previous study, Yiqi Huaju Formula treatment of the MetS subjects without MAU was effective in improving central obesity and fatty liver disease[4,5]. Traditional Chinese medicine (TCM) theory on the development of MAU regards it as “evil heat” that damages the kidneys, and blood stasis that blocks the collateral pathway. We added some heat-eliminating herbs to Yiqi Huaju Formula to compose a new Yiqi Huaju Qingli Formula[6]. The previous experiments showed that Yiqi Huaju Qingli Formula improved insulin sensitivity in rats with type 2 diabetes mellitus (T2DM) and reduced MAU[7]. In this study, we further investigated the effects on MAU subjects coupled with MetS when we added Yiqi Huaju Qingli Formula to routine treatment.

2 Materials and methods

2.1 Subjects
2.1.1 Inclusion criteria
(1) Patients from 18 to 65 years old. (2) Subjects with abdominal obesity (waist circumference (WC) > 90 cm for men and WC > 85 cm for women), triacylglycerol (TAG) ≥ 1.70 mmol/L (150 mg/dL), high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L (40 mg/dL), elevated blood pressure (systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg or previously diagnosed hypertension), elevated fasting blood glucose (fasting plasma glucose (FBP) ≥ 6.1 mmol (110 mg/dL), and 2-hour postprandial plasma glucose (2-hPG) ≥ 7.8 mmol (140 mg/dL) or previously diagnosed diabetes). Presence of at least three of the aforementioned factors (in addition to diabetes) was sufficient to establish a clinical diagnosis of MetS. MetS was defined according to the diagnostic criteria for metabolic syndrome by the Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults[8]. (3) On different days, two continuous tests of urinary albumin-to-creatinine ratio (UACR) within 30 to 300 mg/g. (4) Informed consent form was signed.

2.1.2 Exclusion criteria
Subjects were excluded from this study if they had any of the following conditions: (1) type 1 diabetes; (2) SBP > 180 mmHg or DBP > 110 mmHg; (3) severe cardiovascular, cerebrovascular diseases or chronic liver diseases; (4) UACR > 300 mg/g, or 24-hour total urine protein (24-hTP) > 0.5 g, or serum creatinine > 176 mmol/L; (5) pregnant or lactating women; (6) mental disorders; (7) cancer.

2.1.3 Participants
Sixty participants were recruited from the Department of Endocrinology at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, and the Department of Integrative Medicine at Huashan Hospital, Fudan University between December 2011 and June 2012. The participants were randomly divided into Chinese herb formula group (CHF group; n=30) and control group (n=30) according to the random number table. The study protocol was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, and was registered in Chinese Clinical Trail Registry (Trial registration identifier: ChiCTR-TRC-11001633).

2.2 Treatment
All of the participants were educated for diet control
and proper exercise as a basic treatment. Routine Western medicine treatment was maintained for all the participants with or without the addition of CHF.

### 2.2.1 CHF group

The participants from the CHF group received the routine Western medication and an additional Chinese herb formula, which was composed of Huangqi (Radix Astragali), Huanglian (Rhizoma Coptidis), Puhuang (Pollen Typhae), Zexie (Artemisiae Rhizoma Alismatis), Ludouyi (Testa Vignae Radiatae), Liuyuxue (Serissa Japonica), and Fuzi (Radix Aconiti Lateralis Preparata).

The extract of the indicated herbs in the powder form was produced by the Department of Pharmacy of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (No. 110502). The extract powder was placed into packs, each of which contained the equivalent of 23.5 g crude herbs.

### 2.2.2 Control group

Participants in the control group received placebo instead of CHF in addition to their routine Western medicine. The placebo (No. 110602) was formulated with 5% dosage of CHF and was similar to CHF in both taste and color. The placebo and CHF packaging was also identical. The participants were blinded to their treatments of CHF or placebo (one bag per dose, twice a day) for 12 weeks.

### 2.3 Clinical and biochemical measurements

#### 2.3.1 Demographic characteristics and blood pressure

At the beginning and end of the study, SBP, DBP and mean artery blood pressure (MABP) were recorded; body height, WC, and hip circumference were measured, and then body mass index (BMI) and waist-to-hip ratio (WHR) were calculated.

#### 2.3.2 Blood sample collection and analyses

Venous blood samples were collected following an overnight 12-h fast for the analyses of FPG, fasting plasma insulin (FPI), glycosylated hemoglobin (HbA1c) and lipid profile including total cholesterol (TC), TAG, HDL, and low-density lipoprotein cholesterol (LDL-C). Insulin resistance was evaluated by homeostasis model assessment for insulin resistance (HOMA-IR) (FPI (U/mL) × FPG (mmol/L)/22.5).

Venous blood samples were collected after a 75-g oral glucose tolerance test for the measurement of 2-hPPG.

FPG, 2-hPPG, TAG and TC were determined using enzymatic methods with kits from Shanghai Jingyuan Company. HDL-C was tested using enzymatic methods with kits from Japan Jishui Company. LDL-C was tested by elimination method and kits were purchased from Japanese Jishui Company. Aforementioned indexes were analyzed by the automatic biochemistry analyzer (Hitachi 7600).

HbA1c was analyzed by high-performance liquid chromatography with kits from Sysmex Corporation. Plasma insulin was analyzed by the fully automated chemiluminescent immunoassay analyzer. (CENTAUR XP, Simens, Germany).

#### 2.3.3 Urine sample collection and analyses

First morning urine was collected for the detection of urinary microalbumin (MA), urine creatinine, and UACR. Twenty-four-hour urine was gathered for the analyses of 24-hTP. Kehua Biomed Company provided the kit for urine creatinine and Randox Company provided the kit for 24-h urinary albumin analysis. MA was analyzed using immunoturbidimetry with brain natriuretic peptide-specific protein detection machine (Simens, Germany).

### 2.4 Safety assessment

Routine blood test, routine urine test, liver function test, kidney function test, electrolytes and electrocardiogram were performed before and after both treatments.

### 2.5 Statistical methods

Statistical analysis was performed using SPSS (SPSS, Chicago, IL, USA; version 16). Data were presented as mean ± standard deviation if normally distributed and median (interquartile range) if distributions were skewed. Independent-samples *t* tests were used to compare normally distributed continuous variables; otherwise, Mann-Whitney test was applied. Within-group comparison between baseline and follow-up was assessed using paired *t* test or Wilcoxon signed rank sum test. Fisher exact test was used for between-group comparison and McNemar test for within-group comparison of categorical variables. *P* value less than 0.05 was considered statistically significant.

### 3 Results

#### 3.1 General information of patients

Thirty patients (17 male and 13 female) were enrolled in the CHF group with the average age of (53.17 ± 7.82) years. Another 30 patients (18 male and 12 female) were included in the control group with the average age of (53.33 ± 8.51) years. All the patients met the diabetes diagnosis criteria. Twenty-nine patients in the CHF group and 28 patients in the control group were diagnosed with hypertension prior to the study. All the patients, regardless of whether they had hypertension, were treated with angiotensin receptor blockers due to their positive MAU. Some of them received additional calcium channel blocker treatment for better control of their blood pressure. The baseline data, including the application of the hypoglycemics and antihypertensives, were comparable, and there was no statistical difference between the CHF group and the control group (*P* > 0.05) (Table 1). See Figure 1 for flowchart of the recruitment process.

#### 3.2 Changes in BMI, WC and WHR

As shown in Table 2, there were no significant changes in terms of BMI, WC and WHR in the control group after treatment (*P* > 0.05). In contrast, significant decreases in BMI, WC and WHR were observed in the CHF group after treatment (*P* < 0.01). Significantly decreased BMI
3.4 Changes in TC, TAG, LDL-C and HDL-C

As shown in Table 4, both the CHF and control treatments resulted in significant reduction of the levels of TC, TAG and LDL-C, respectively ($P<0.01$). A more significant reduction of TG was observed after CHF treatment compared with that after control treatment ($P<0.05$). The level of HDL-C was not altered in the control group after treatment ($P>0.05$), whereas it was significantly increased by CHF treatment ($P<0.01$), although there was no significant difference of HDL-C between the CHF group and the control group after treatment ($P>0.05$).

3.5 Changes in MA, UACR and 24-hTP

As shown in Table 5, both CHF and control treatment significantly reduced the levels of MA and UACR ($P<0.01$, $P<0.05$). The reductions of MA and UACR in the CHF group were much greater than those in the control group ($P<0.05$). The level of 24-hTP was not altered by the control treatment ($P>0.05$), whereas it was significantly decreased by the CHF treatment ($P<0.01$). There was a significant difference of 24-hTP between the CHF group and the control group after treatment ($P<0.05$).

3.6 Changes in SBP, DBP and MABP

As shown in Table 6, significant decreases in SBP, DBP and MABP were observed in patients from both CHF and control groups as compared with before treatment ($P<0.01$). However, there was no significant difference between the two groups ($P>0.05$).

3.7 Safety evaluation of CHF treatment

Two patients undergoing the CHF treatment had displayed mild diarrhea and gastrointestinal discomfort, but completed the treatment after these symptoms were alleviated. No other adverse reactions were observed. There were no abnormal manifestations regarding blood biochemistry,
Table 2  BMI, WC, and WHR before and after treatment (Mean ± standard deviation)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>BMI (kg/m²) Before treatment</th>
<th>After treatment</th>
<th>WC (cm) Before treatment</th>
<th>After treatment</th>
<th>WHR Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>30</td>
<td>26.81±2.11</td>
<td>23.34±2.43**</td>
<td>94.71±6.98</td>
<td>87.30±8.60**</td>
<td>0.95±0.06</td>
<td>0.87±0.05**</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>26.43±2.57</td>
<td>26.81±2.75</td>
<td>94.45±11.20</td>
<td>94.67±10.87</td>
<td>0.95±0.06</td>
<td>0.94±0.05</td>
</tr>
</tbody>
</table>

**P<0.01, vs before treatment; △P<0.05, △△P<0.01, vs control group. BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio.

Table 3  FPG, 2-hPPG, HbA1c and HOMA-IR before and after treatment (Mean ± standard deviation)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FPG (mmol/L) Before treatment</th>
<th>After treatment</th>
<th>2-hPPG (mmol/L) Before treatment</th>
<th>After treatment</th>
<th>HbA1c (%) Before treatment</th>
<th>After treatment</th>
<th>HOMA-IR Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>30</td>
<td>8.20±2.72</td>
<td>6.20±1.31**</td>
<td>12.02±3.79</td>
<td>8.48±2.56**</td>
<td>7.98±1.49</td>
<td>7.02±1.26**</td>
<td>4.40±1.24</td>
<td>2.40±1.92**</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>8.11±2.46</td>
<td>7.02±1.41**</td>
<td>13.43±3.74</td>
<td>10.20±3.24**</td>
<td>8.10±1.38</td>
<td>7.62±1.36**</td>
<td>4.38±1.83</td>
<td>3.55±1.88**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, vs before treatment; △P<0.05, △△P<0.01, vs control group. FPG: fasting plasma glucose; 2-hPPG: 2-hour postprandial plasma glucose; HbA1c: glycosylated hemoglobin; HOMA-IR: homeostasis model assessment for insulin resistance.

Table 4  TC, TAG, LDL-C and HDL-C before and after treatment (Mean ± standard deviation, mmol/L)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TC Before treatment</th>
<th>After treatment</th>
<th>TAG Before treatment</th>
<th>After treatment</th>
<th>LDL-C Before treatment</th>
<th>After treatment</th>
<th>HDL-C Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>30</td>
<td>4.69±0.78</td>
<td>4.22±0.77**</td>
<td>1.52±0.58</td>
<td>2.51±0.71**</td>
<td>3.04±0.85</td>
<td>2.56±0.52**</td>
<td>1.07±0.28</td>
<td>1.19±0.30**</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>4.65±0.54</td>
<td>4.22±0.66**</td>
<td>1.85±0.44</td>
<td>2.56±0.52**</td>
<td>3.01±0.76</td>
<td>1.13±0.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P<0.01, vs before treatment; △P<0.05, vs control group. TC: total cholesterol; TAG: triacylglycerol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 5  MA, UACR and 24-hTP before and after treatment (Mean ± standard deviation)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MA (mg/L) Before treatment</th>
<th>After treatment</th>
<th>UACR (mg/g) Before treatment</th>
<th>After treatment</th>
<th>24-hTP (g per 24 h) Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>30</td>
<td>101.58±75.39</td>
<td>47.11±27.85**</td>
<td>120.54±75.75</td>
<td>63.32±39.86**</td>
<td>0.14±0.04</td>
<td>0.07±0.03**</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>98.50±66.92</td>
<td>78.87±60.65</td>
<td>121.45±88.72</td>
<td>101.83±74.56</td>
<td>0.13±0.06</td>
<td>0.11±0.07</td>
</tr>
</tbody>
</table>

**P<0.05, **P<0.01, vs before treatment; △P<0.05, vs control group. MA: urinary microalbumin; UACR: urinary albumin-to-creatinine ratio; 24-hTP: 24-hour total urine protein.

Table 6  SBP, DBP and MABP before and after treatment (Mean ± standard deviation, mmHg)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>SBP Before treatment</th>
<th>After treatment</th>
<th>DBP Before treatment</th>
<th>After treatment</th>
<th>MABP Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>30</td>
<td>139.23±8.66</td>
<td>125.93±5.32**</td>
<td>83.53±7.39</td>
<td>79.03±5.66**</td>
<td>101.43±6.10</td>
<td>95.30±4.81**</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>137.00±11.15</td>
<td>127.97±6.91**</td>
<td>82.93±7.60</td>
<td>79.77±5.26**</td>
<td>101.73±7.19</td>
<td>96.77±4.97**</td>
</tr>
</tbody>
</table>

**P<0.05, △P<0.01, vs before treatment. SBP: systolic blood pressure; DBP: diastolic blood pressure; MABP: mean artery blood pressure.
urine biochemistry, liver function, kidney function, electrolytes and electrocardiogram after both CHF and control treatments.

4 Discussion

The incidence of MetS, which is characterized by abdominal obesity, hyperglycemia, dyslipidemia and elevated blood pressure, is increasingly on the rise. With it, the risks of cardiovascular diseases and diabetes increase, and the development and progression of renal damage resulting from the concomitant multiple risk factors increase as well. MAU, an important component of MetS, is a sensitive sign not only of early stages of DN, but also of extensive vascular dysfunction. Renal function in patients with MetS is more vulnerable, as compared to that of the patients with diabetes or hypertension alone, due to the MetS patients’ multiple risk factors. A previous study showed that the number of patients with MAU was 14% greater in diabetic patients coupled with MetS, as compared to that in diabetic patients without MetS. Increasing numbers of MetS components corresponded with increased prevalence of MAU[9]. Now MAU is considered one of the strongest predictors for cardiovascular diseases. In the Copenhagen Prospective study[10], the prevalence of coronary heart disease with albumin excretion rate (AER) > 5 mg/min was 11% and the mortality was 28%, while the prevalence of coronary heart disease with AER < 5 mg/min was 5% and the mortality was 13% (P<0.001). Obviously, AER above 5 mg/min was a strong risk factor for coronary heart disease and cardiovascular death. Therefore, early intervention on MAU is critical to the prevention, or delaying the onset, of renal lesions in MetS, and to the prevention of cardiovascular disease as well.

The patients in this study had been receiving routine treatments to control high blood pressure, hyperglycemia, and dyslipidemia, and their blood pressure, glucose and lipid levels were controlled to a certain extent. However, they still developed MAU. This indicates that there were some unidentified or uncontrolled factors resulting in the renal lesion besides the known and controlled factors in MetS patients. These unknown factors caused the patients to experience residual risk such as MAU. This indicates the need for improving clinical treatment strategies to enhance the therapeutic efficacy for MAU.

Insulin resistance, one of the essential mechanisms of MetS, was previously considered to have some indirect impact on the membrane permeability of renal glomeruli through hyperglycemia, dyslipidemia and elevated blood pressure; the direct impact of insulin resistance on renal damage was thought to be low. In fact, MAU is closely associated with insulin resistance[11,12]. Chan et al[13] found that among patients with T2DM, insulin resistance was more severe in those with MAU compared with those without MAU. Moreover, insulin resistance was positively correlated to the urinary albumin excretion rate (r=0.25, P<0.002). In non-diabetic patients, MAU was positively correlated with insulin resistance as well[14]. In a prospective study, insulin resistance and the number of MetS components were demonstrated as critical factors that impact the prevalence of chronic renal lesions even after adjustment of hypertension and diabetes[15]. These findings can help us to understand why there were 5% to 10% patients with MAU among the newly diagnosed diabetics[16-18]. Patients with MAU prior to diabetes may have experienced long-term insulin resistance and hyperinsulinemia. Insulin resistance and hyperinsulinemia lead to glomerular hyperfiltration, hyperperfusion, hypertension, proinflammatory and prothrombotic states, which can activate the renin-angiotensin system, and damage renal function. Moreover, abdominal obesity, the anthropometric symbol of insulin resistance, is also an independent risk factor of MAU[19]. Thus, increasing insulin sensitivity may be an important step in reducing renal lesions in MetS. However, currently there is no safe or ideal insulin-sensitizing agent. The typical insulin sensitizer rosiglitazone may increase cardiovascular risks (myocardial infarction, stroke, congestive heart failure and death) and has been restricted in its clinical usage[20]. In contrast, TCM offers new possibilities in safely improving insulin sensitivity.

According to TCM principles, the pathogenesis of insulin resistance involves “spleen-deficiency resulting in obstruction of transformation”. This illustrates the pathological condition under which the absorbed nutrients (glucose, lipids and others) are unable to be converted into the energy required for normal function, which is promoted by spleen qi. This abnormality results in the accumulation of glucose and lipids, subsequently causing elevated levels of lipids, glucose, blood pressure and adipocytic infiltration of internal organs. These elevated parameters are transformed into pathological factors resulting in target organ injuries, abdominal obesity, hyperglycemia, hypertension and dyslipidemia as well. Yiqi Huaju Formula was designed under the guidance of this principle to prevent and treat MetS component diseases[21]. The previous study demonstrated that the formula significantly increased insulin sensitivity, improved abnormal body fat distribution, hyperglycemia, and dyslipidemia as well. Yiqi Huaju Formula was designed under the guidance of this principle to prevent and treat MetS component diseases[22]. The previous study demonstrated that the formula significantly increased insulin sensitivity, improved abnormal body fat distribution, hyperglycemia, and dyslipidemia, inhibited inflammatory cytokines, and effectively promoted fibrinolysis[23-25]. In order to address MetS coupled with MAU, in which endothelial function and renal local microcirculation are affected by insulin resistance, we added some heat-eliminating herbs and kidney-tonifying herbs to the Yiqi Huaju Formula to compose a new herb formula Yiqi Huaju Qingli Formula for the treatment of MetS coupled with MAU. As to Yiqi Huaju Qingli, “Yiqi” means improving insulin resistance and promoting the
transformation of nutrients to energy such as adenosine triphosphate. “Huaju Qingli” means rectifying the abnormal body fat distribution, hyperglycemia, and dyslipidemia caused by insulin resistance and regulating levels of adipokines, inflammatory cytokines, prothrombotic factors, and oxidative stress molecules, thus improving endothelial function and local renal microcirculation and alleviating MAU. In this study, MetS patients coupled with MAU were treated with CHF or placebo respectively for 12 weeks. After treatment, patients treated with placebo in addition to hypoglycemic and antihypertensive medications in the control group had significant reductions in MA and UACR, but no statistical changes in 24-hTP. These results indicate that the medications are effective for MetS coupled with MAU, but they do not satisfactorily address the entire picture. In contrast, applying Yiqi Huaju Qingli Formula in addition to hypoglycemic and antihypertensive medications in the CHF group resulted in more significant reductions in MA and UACR, and a significant reduction in 24-hTP. And there were significant differences between the two groups after treatment. These results demonstrate clear improvement gained when CHF treatment is added to the routine Western medications in the treatment of MetS patients couple with MAU.

The routine treatment resulted in reductions in FPG, 2-hPPG, HbA1c, TC, TAG and LDL-C in the control group, but the reductions were much greater with the addition of Yiqi Huaju Qingli Formula in the CHF group, and there were significant differences between the two groups after treatment. Additionally, the level of HDL-C in the CHF group increased significantly, but remained nearly unchanged in the control group. These findings showed that, when treating glucose and lipid profiles in MetS patients with MAU, combining CHF and Western pharmaceutical medications is superior to the routine Western medicine treatment alone. Hypertension in both groups was well controlled before the study initiated because of the application of antihypertensives. However, SBP, DBP and MBP in both groups were further significantly decreased after the 12-week treatment, and there was no statistical difference between the two groups at the end of the study. These results suggest that the decrease in blood pressure was involved in the improvement of renal function in the patients; however, blood pressure changes may not be the main mechanism of the Chinese herb formula in the improvement of MAU.

HOMA-IR was significantly decreased in both groups, though more reduction was seen in the CHF group, which suggests that CHF has a superior effect in improving insulin sensitivity. The effect of the CHF treatment in increasing insulin sensitivity was supported by the changes in anthropometric parameters. Significantly decreased BMI, WC and WHR were noted in the CHF group after treatment, while there were no significant changes in the control group. Obesity, and especially central obesity, is a hallmark of insulin resistance. Our previous study investigated the effects of the major components of the formula and found that atractylodes macrocephalum, berberine, and pollen typhae flavonoids increased insulin sensitivity through phosphatidylinositol 3-kinases or β-arrestin-2 signal transduction and enhanced the consumption of glucose in adipocytes. We also observed that Yiqi Huaju Qingli Formula increased insulin sensitivity and decreased MAU in diabetic rats, and the results were consistent with the clinical outcomes in the present study.

It is very important to control hyperglycemia and hypertension for the treatment of MAU subjects coupled with diabetes or with MetS. All the patients enrolled in this study were treated with hypoglycemic and antihypertensive medications before the study initiated; however, they still had positive MAU, which suggested that the routine treatment did not address all aspects of MetS and MAU diseases. When we added Yiqi Huaju Qingli Formula to the routine medications for the subjects in the CHF group, the therapeutic effect for MAU was improved more greatly. The most significant differences between the CHF group and the control group were the dramatic increased insulin sensitivity and significant improvement on anthropometric parameters, which represent abnormal body fat distribution in the CHF group. Much more significant reductions in plasma glucose and the lipid profile were also observed. All the results suggest that the insulin-sensitizing effects of CHF can explain the main difference between the two groups.

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6 Competing interests

The authors declare that they have no competing interests.

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