Research Article

Efficacy and Safety of Chinese Herbal Formula Granules in Treating Chronic Kidney Disease Stage 3: A Multicenter, Randomized, Placebo-Controlled, Double-Blind Clinical Trial

Jing Zhao,1 Wei Sun,1 Jihong Chen,1 Zhuxing Sun,2 Dai Chen,3 Chunhua Cao,4 Min Yang,5 Jipei Ma,6 Ling Wang,7 Changying Xing,8 Yan Chen,9 Meixiao Sheng,1 Enchao Zhou,1 Lingdong Xu,1 Kun Gao,1 Lihua Liu,1 Qiong Liu,1 Lan Yi,1 Weiming He,1 and Yuanyuan Zhu1

1Department of Nephrology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China
2Department of Nephrology, Wuxi People’s Hospital, Wuxi, Jiangsu, China
3Department of Nephrology, Changzhou TCM Hospital, Changzhou, Jiangsu, China
4Department of Nephrology, Taizhou Hospital of TCM, Taizhou, Zhejiang, China
5Department of Nephrology, The First People’s Hospital of Changzhou, Changzhou, Jiangsu, China
6Department of Nephrology, Wuxi Hospital of TCM, Wuxi, Jiangsu, China
7Department of Nephrology, Xuzhou No.1 People’s Hospital, Xuzhou, Jiangsu, China
8Department of Nephrology, Jiangsu Province Hospital, Nanjing, Jiangsu, China
9Department of Nephrology, Jiangsu Province Official Hospital, Nanjing, Jiangsu, China

Correspondence should be addressed to Wei Sun; henosn@163.com

Received 27 August 2019; Revised 21 May 2020; Accepted 7 July 2020; Published 21 October 2020

Academic Editor: Giuseppe Caminiti

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Background. It is generally considered that traditional Chinese medicine (TCM) therapy postpones the progression of some chronic kidney diseases (CKDs). Chinese medicine herbs are widely applied in TCM therapy. We aimed to evaluate clinical efficacy and safety of Chinese herbal formula granules in patients with CKD stage 3 through a prospective randomized controlled study. Methods. A total of 343 participants with CKD stage 3 were recruited from 9 hospitals in Jiangsu Province between April 2014 and October 2016. Patients were randomly assigned to a treatment or control group. Patients in the treatment group orally took Chinese herbal formula granules twice a day, while controls received placebo granules. The duration of intervention was 24 weeks. Primary outcomes were 24-hour proteinuria, serum creatinine, and eGFR, which were measured every 4 weeks. Results. There was no statistical difference in 24-hour proteinuria between the two groups (0.97 ± 1.14 g/d vs. 0.97 ± 1.25 g/d). Patients in the treatment group had significantly lower serum creatinine level (130.78 ± 32.55 μmol/L versus 149.12 ± 41.27 μmol/L) and significantly higher eGFR level (55.74 ± 50.82 ml/min/1.73-m² versus 44.46 ± 12.60 ml/min/1.73-m²) than those in the control group (P < 0.05). There was no significant difference between two groups in the incidence of adverse events. Conclusion. The treatment adopting Chinese herbal formula granules for 24 weeks improved kidney function of patients with CKD stage 3.

1. Introduction

Chronic kidney disease (CKD) stands for a health threat around the world. Its prevalence is between 8% and 16% across regions and locates at around 11% among developed nations such as America and Australia [1]. With the exacerbation in its prevalence and relevant economic burden, this disease attracts accumulating attentions [2]. In our country, CKD prevalence among middle-age and elderly people achieves 11.5%, and merely, 8.7% of these cases are diagnosed while 4.7% experience proper treatments [3]. Some subtypes of this disease would evolve into end-stage renal disease (ESRD), ultimately leading to the implementation of kidney replacement. Until now, over 2.60
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2. Methods

2.1. Study Design. This study was an investigator-initiated, multicenter, double-blind, randomized clinical trial to analyze the efficacy and safety of herbs in treating stage 3 CKD. Patients in the treatment group received Chinese medicine herbs plus basic care, while those in the control group were treated with placebo plus basic care. The study was conducted in 9 centers across Jiangsu Province in China, including Affiliated Hospital of Nanjing University of Chinese Medicine, Wuxi People’s Hospital, Changzhou TCM Hospital, Taizhou Hospital of TCM, the First People’s Hospital of Changzhou, Wuxi Hospital of TCM, Xuzhou No.1 People’s Hospital, Affiliated Hospital of Nanjing Medical University, and Jiangsu Province Official Hospital. This study was approved by the ethics committee of Affiliated Hospital of Nanjing University of Chinese Medicine (approval number: AF/SQ140303). Full trial protocol can be accessed from this hospital.

2.2. Study Population. Recruited male and female patients were diagnosed with primary CKD and aged 18–75 years, with estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m² and <60 ml/min/1.73 m² which was calculated with chronic kidney disease epidemiology collaboration (CKD-EPI) equation and 24-hour proteinuria ≤ 2.0 g/d. Blood pressure was managed ≤130/80 mmHg. Patients with acute kidney injury, polycystic kidney disease, or secondary kidney diseases such as diabetic nephropathy were not recruited. Patients receiving glucocorticoids, immunosuppressants, and/or Tripterygium drug were excluded. Patients with concurrent serious diseases, including primary cardiac, cerebral, pulmonary, hepatic, hematological, and psychiatric disease, in pregnancy or in lactation, were not included either. All participants signed written informed consent before enrollment.

2.3. Data Collection and Monitoring. Case report forms were filled, maintained by an appropriately qualified physician, and checked by data monitor for integrity and accuracy. The monitor reviewed all study records on a case-by-case basis and completed Monitor Review Form. All data were documented into Medroad data acquisition system using double-data entry. The data acquisition system was developed by the Jiangsu Famous Medical Technology Co., Ltd.

2.4. Interventions

2.4.1. Drugs, Doses, and Placebo. Chinese herbal formula granules were manufactured by Jiangyin Tianjiang Pharma (Jiangsu, China) and consisted of 10 Chinese herbs as shown in Table 1. Each of the adopted Chinese herbs was supplied (exercise), and dietary therapy. Among them, herbal medicine has been studied intensively. Ancient people developed many treatments for edema and hematuria, common symptoms of kidney disease. Chinese medicine herbs have been proven to be effective in treating kidney diseases in both ancient and modern times. With medical progressions, more and more studies have checked therapeutic effects of TCM, especially herbs and herbal compounds, in treating CKD [9–11]. It has been reported that some traditional Chinese herbs could reduce proteinuria, protect podocyte, and alleviate glomerulosclerosis [12, 13]. However, relevant clinical studies are rare, with poor quality. Besides, it is difficult to ascertain the efficacy and mechanism of TCM herb compound formula because of diverse active constituents and formula uniformity. TCM focuses not only on kidney injury, but also on internal balance of the whole body. A personalized herbal decoction is based on accurate identification of syndromes, the establishment of therapeutic method, and appropriate choice of herbs and doses. TCM physician will prescribe a personalized herbal formula based on a patient’s own conditions, which may repair damaged kidney tissues, improve kidney functions, and alleviate symptoms naturally. Different herbs show varied natural abilities in kidney management. For clinical practice, high quality and well-designed clinical studies would be urgently needed to ascertain the efficacy and safety of Chinese herbs.

Our previous study suggested that Chinese herbal formula granules could retard the increase of serum creatinine in early- and middle-stage CKD [14–16]. However, detailed efficacy and safety of this herbal formula need to be further studied. Accordingly, a prospective, multicenter, randomized, placebo-controlled, double-blind clinical trial was conducted to further verify the efficacy and safety of the Chinese herbal formula in treating CKD stage 3.
2.6. Outcome Assessment. Primary efficacy outcomes were estimated via changes in 24-hour proteinuria, serum creatinine, and eGFR, and the indicators were measured every 4 weeks for 24 weeks. The participants were instructed to collect urine with an interval over 24 hours (from 7:00 AM of the first day to 7:00 AM of the next day) using a study-specific container, record collection time, and total volume of urine, and then bring urine samples to the corresponding specific container, record collection time, and total volume of urine, and then bring urine samples to the corresponding study hospital for the measurement of 24-hour proteinuria between 7:00 AM of the first day to 7:00 AM of the next day) using a study-specific container, record collection time, and total volume of urine, and then bring urine samples to the corresponding study hospital for the measurement of 24-hour proteinuria determined through the methods of dye-binding (Coomassie Brilliant Blue G-250) using cerebrospinal fluid protein test kit. Blood samples were collected to examine serum creatine (Determiner L CRE kit) and to calculate eGFR.

2.7. Safety. Safety evaluation involved participants’ general conditions, incidence of adverse events, and laboratory indexes (from hematology and liver function tests and ECGs). Potential adverse events included gastrointestinal reactions, electrolyte disturbances, and abnormal liver function. Events were recorded and assessed every 4 weeks from the start to the end of the study. Once an adverse event occurred during the study, appropriate evaluation and medications were taken according to its severity. Serious adverse events were monitored up to 30 days after the final visit. Participants withdrawing from the trial due to adverse events were followed until the events were settled, and their statuses were documented in detail.

2.8. Follow-up Measurements. Participants were followed up every 4 weeks to assess their clinical condition, blood pressure, adverse events, and therapy adherence. 24-hour proteinuria was measured every 4 weeks during the 24-week trial, and blood samples were obtained at 0, 4, 12, and 24 weeks for measuring hemoglobin, red blood cell, white blood cell, platelet, alanine aminotransferase, aspartate aminotransferase, serum urea nitrogen, serum creatinine, serum albumin, and blood lipids. For measuring blood pressure, patients seated quietly for at least 5 minutes, relaxed, and did not move or speak before measurements. Their arms were placed at a level equal to that of their hearts, without constrictions by tight clothing. Measurements were implemented twice for each patient with a mercury sphygmomanometer, and average values were recorded for analysis.

2.9. Sample Size Determination. According to the published literature and previous clinical data, sample size was estimated at 300 subjects on the basis of a type I error rate of 0.049 and type II error (β) of 0.1, which contributed to the F(α, β) of 10.5 according to the F-distribution table. Assuming a dropout rate no more than 20% for each site, an additional 20% samples should be added, and sample size would be expected to be 360 in total. The formula for the number of subjects was as follows:

| Herb name | Dosage ratio in one prescription (%) |
|-----------|--------------------------------------|
| Astragali Radix (Huangqi) | 6 |
| Angelica Sinensis Radix Tostum (Danggui) | 2 |
| Polygoni Cuspidati Rhizoma et Radix (Huahang) | 3 |
| Herba Serissae (Liuyuexue) | 6 |
| Smilacis Glabrae Rhizoma (Tufuling) | 6 |
| Achyranthis Bidentatae Radix (Niuixi) | 2 |
| Pyrrosiae Folium (Shiwei) | 4 |
| Rhei Radix et Rhizoma Praeparata (Dahuang) | 1 |
| Centellae Herba (Jixuecao) | 6 |
| Polygonati Rhizoma Praeparata (Huangjing) | 4 |


\[
\text{Number of subjects} = \frac{[P_1 \times (100 - P_1) + P_2 \times (100 - P_2)]/(P_2 - P_1)}{f(\alpha, \beta)}.
\]

(1)

2.10. Randomization and Masking. Block randomization scheme was used and stratified by site. Random sequence stratified by site was randomly generated adopting the SAS system. Consecutive numbers were assigned to each site, and the subjects were randomly assigned in the order of their enrollment into the study, with a 1:1 ratio to receive Chinese herbal formula granules (the treatment group) or placebo (the control group). Patients, investigators, and site staff were blind to treatment assignment throughout the study.

2.11. Statistical Analysis. SAS software v9.2 (SAS Institute Inc., NC, USA) was used for all statistical analyses. All statistical tests were two-sided, and \( P < 0.05 \) was considered to represent the presence of statistical significance. Descriptive statistics on quantitative variables were described as the number of observations, measure, standard deviation, median, minimum, and maximum. The number of observations and percentages were recorded for categorical variables. Comparisons on quantitative variables between treatment and control groups were performed through grouped T-test, while the chi-square test was adopted to compare categorical variables. Meanwhile, repeatedly measured data on 24-hour proteinuria, creatinine, nitrogen, etc. were compared, and their differences were analyzed by variance analyses of repeated measurement. Baseline was defined as the screening period. For parameters not measured at baseline, screening values were used.

3. Results

3.1. Follow-up. From April 2014 to October 2016, a total of 343 patients with CKD stage 3 were enrolled from 9 centers and randomly assigned into the treatment group (\( n = 171 \)) and control group (\( n = 172 \)). 300 participants completed the 24-week follow-up. 21 subjects were deleted from the treatment group, including 2 subjects with serious adverse events, while 22 from the control group (Figure 1). Full analysis set (FAS) was performed in all patients. Per-protocol set (PPS) was 87.72% in the treatment group and 87.21% in the control group and was 87.46% for the total enrolled participants (Table 2). There were no statistically significant differences in safety profile, dropout rate, or patient compliance between the two groups (Table 3).

3.2. Baseline Characteristics. Gender, age, disease course, blood pressure, and the levels of 24-hour proteinuria, eGFR, urea nitrogen, and serum creatine were compared between treatment and control groups before treatment. The results showed that there was no significant difference between two groups in any characteristics at baseline (\( P > 0.05 \), Table 4).

3.3. Outcome Evaluation

3.3.1. Evaluation of 24-Hour Proteinuria. There was no statistical difference in 24-hour proteinuria between the treatment and control groups at the end of treatment (24 weeks later). However, percentage changes in proteinuria were slight at week 8, 12, 16, and 20 in the treatment group, and differences in 24-hour proteinuria before and after treatment were not statistically significant, according to pairwise comparisons. In contrast, differences in the proteinuria level before and after drug administration were statistically significant in the control group at week 12, 16, 20, and 24 (\( P < 0.05 \), Table 5).

3.3.2. Serum Creatinine. Serum creatinine was gradually decreased from the start of treatment and such trend continued throughout the treatment period in the treatment group, showing significant difference at week 16, 20, and 24 (\( P < 0.05 \)); while this index remained stable in the control group (\( P > 0.05 \)). Moreover, statistically significant difference was found between the two groups after drug administration (\( P < 0.001 \), Table 6, Figure 2). At the final visit, the median change in serum creatinine level before and after treatment was \(-13.15\, \mu\text{mol/L} \) (range: \(-42.05\)–\(-40.77\, \mu\text{mol/L}\)) in the treatment group and \(0.48\, \mu\text{mol/L} \) (range: \(-96.73\)–\(-320.82\, \mu\text{mol/L}\)) in the control group. \( P \) value for grouped T-test was less than 0.0001, indicating that renal function was improved and therapeutic efficacy in the treatment group was obviously better than that in the control group (Table 7).

3.3.3. Subgroup Analysis. The participants were further divided into CKD stage 3a (eGFR 45–59 ml/min/1.73 m²) and stage 3b (eGFR 30–44 ml/min/1.73 m²) groups. As a result, 153 patients with CKD stage 3a (75 in the treatment group and 78 in the control group) were analyzed. Serum creatinine level in the treatment group started to decline from week 4 after treatment, and such tendency maintained throughout the rest of the treatment period. Differences between two groups were statistically significant at all timepoints after treatment (\( P < 0.001 \), Table 8, Figure 3). 180 subjects were in stage 3b (92 in the treatment group and 88 in the control group). Significant differences were also found in serum creatinine level between the treatment and control groups at any detection time points after drug administration (\( P < 0.001 \), Table 9, Figure 4).

3.3.4. eGFR. At week 24, eGFR was \(55.74 \pm 50.82\, \text{ml/min/1.73 m}^2\) and \(44.46 \pm 12.60\, \text{ml/min/1.73 m}^2\) in treatment and control groups, respectively. The difference between groups was statistically significant, with \( P < 0.0001 \) (Table 10, Figure 5). Statistical analysis indicated that eGFR changes were \(17.95 \pm 21.86\, \text{ml/min/1.73 m}^2\) and \(0.04 \pm 19.83\, \text{ml/min/1.73 m}^2\) in the treatment and control groups, respectively, and the difference between groups was statistically significant (\( P < 0.0001 \)) (Table 11).
Table 2: Participant disposition.

| Variable                                      | Treatment group no. (%) | Control group no. (%) | Total no. (%) |
|-----------------------------------------------|-------------------------|-----------------------|--------------|
| Randomization                                 | 171 (100.00)            | 172 (100.00)          | 343 (100.00) |
| Safety analysis set (SS)                      | 171 (100.00)            | 172 (100.00)          | 343 (100.00) |
| Full analysis set (FAS)                       | 171 (100.00)            | 172 (100.00)          | 343 (100.00) |
| Dropouts during the study                     | 21 (12.28)              | 22 (12.79)            | 43 (12.54)   |
| Serious adverse events                        | 2 (1.17)                | 0 (0.00)              | 2 (0.58)     |
| Nonadherence to medication, e.g., discontinuation from study drug for more than 2 weeks without permission | 0 (0.00) | 2 (1.16) | 2 (0.58) |
| Withdrawal by subject                         | 16 (9.36)               | 17 (9.88)             | 33 (9.62)    |
| Others (reasons)                              | 3 (1.75)                | 3 (1.74)              | 6 (1.75)     |
| Per-protocol set (PPS)                        | 150 (87.72)             | 150 (87.21)           | 300 (87.46)  |

Table 3: Dropout rate and compliance in the enrolled participants.

| Variable                  | Treatment group | Control group | Statistics          | P value |
|---------------------------|-----------------|---------------|---------------------|---------|
| Dropout                   | 150 (87.72)     | 150 (87.21)   | 0.02 (CHISQ test)   | 0.8866  |
| No                        | 21 (12.28)      | 22 (12.79)    |                     |         |
| Yes                       | 92.57 ± 24.99   | 94.18 ± 22.67 | −0.62 (grouped T-test) | 0.5338  |

Figure 1: Trial flowchart.
Table 4: Patient demographics and baseline characteristics (full analysis set).

| Variable                          | Treatment group | Control group | Statistics   | P value |
|----------------------------------|-----------------|---------------|--------------|---------|
| Gender                           |                 |               |              |         |
| Male 106 (61.99)                 | 121 (70.35)     |               |              |         |
| Female 65 (38.01)                | 51 (29.65)      |               |              |         |
| Age (years) 51.89 ± 13.12        | 52.03 ± 12.62   | −0.10 (grouped T-test) | 0.9197     |
| Disease duration (months) 59.92 ± 84.69 | 62.81 ± 77.05   | −0.33 (grouped T-test) | 0.7424     |
| Systolic blood pressure (mmHg) 124.57 ± 7.24 | 123.84 ± 7.90   | 0.89 (grouped T-test) | 0.3730     |
| Diastolic blood pressure (mmHg) 76.94 ± 5.24 | 76.56 ± 6.12   | 0.61 (grouped T-test) | 0.5408     |
| 24-hour proteinuria (g/24h) 0.73 ± 0.61 | 0.72 ± 0.67   | 0.22 (grouped T-test) | 0.8298     |
| Urea nitrogen (mmol/L) 8.93 ± 3.26 | 8.89 ± 3.10   | 0.09 (grouped T-test) | 0.9291     |
| Serum creatinine (µmol/L) 150.27 ± 37.12 | 147.56 ± 29.46 | 0.75 (grouped T-test) | 0.4540     |
| eGFR (ml/min/1.73 m²) 43.57 ± 9.29 | 44.37 ± 9.09   | −0.81 (grouped T-test) | 0.4171     |

*Compared with pretreatment, the difference was significant in the control group, P < 0.05.

Table 5: Change from baseline in 24-hour proteinuria over the 24-week follow-up period.

| Time                   | Treatment group | Control group | Effect            | F value | P value |
|------------------------|-----------------|---------------|------------------|---------|---------|
| Pretreatment (g/24h)   | 0.72 ± 0.61     | 0.66 ± 0.58   | Time effect      | 4.19    | 0.0009  |
| Week 4 (g/24h)        | 0.81 ± 0.83     | 0.72 ± 0.70   | Difference between groups | 3.10 | 0.0792  |
| Week 8 (g/24h)        | 0.82 ± 0.89     | 0.85 ± 1.16   |                 |         |         |
| Week 12 (g/24h)       | 0.84 ± 1.01     | 1.01 ± 1.59*  |                 |         |         |
| Week 16 (g/24h)       | 0.81 ± 0.95     | 0.99 ± 1.39*  |                 |         |         |
| Week 20 (g/24h)       | 0.87 ± 1.02     | 1.01 ± 1.47*  |                 |         |         |
| Week 24 (g/24h)       | 0.97 ± 1.14     | 0.97 ± 1.25*  |                 |         |         |

*Compared with pretreatment, the difference was significant in the control group, P < 0.05.

Table 6: Change from baseline in serum creatinine over the 24-week follow-up period.

| Time                   | Treatment group | Control group | Effect            | F value | P value |
|------------------------|-----------------|---------------|------------------|---------|---------|
| Pretreatment (µmol/L)  | 148.42 ± 35.90  | 147.26 ± 28.71 | Time effect      | 3.11    | 0.0086  |
| Week 4 (µmol/L)        | 138.80 ± 31.62  | 148.06 ± 34.99 | Difference between groups | 54.69 | 0.0001  |
| Week 8 (µmol/L)        | 133.28 ± 30.95  | 150.22 ± 36.70 |                 |         |         |
| Week 12 (µmol/L)       | 132.59 ± 30.42  | 147.73 ± 39.02 |                 |         |         |
| Week 16 (µmol/L)       | 130.19 ± 29.79* | 150.50 ± 38.23 |                 |         |         |
| Week 20 (µmol/L)       | 130.08 ± 30.57* | 151.10 ± 36.18 |                 |         |         |
| Week 24 (µmol/L)       | 130.78 ± 32.55* | 149.12 ± 41.27 |                 |         |         |

*Compared with pretreatment, the difference was significant in the treatment group, P < 0.05.

Figure 2: Change from baseline in serum creatinine over the 24-week follow-up period.
When eGFR data were further analyzed after stratification by CKD stages (3a or 3b), eGFR values increased from baseline in the treatment group, but no obvious change was observed in the control group. Difference in eGFR change between the two groups was statistically significant, and such trend persisted throughout the treatment (Tables 12–14, Figures 6 and 7).

### 3.4. Transfer in Stages of CKD Disease.

Among subjects with CKD stage 3a in the treatment group, the proportion of individuals progressing from stage 3a to stage 3b or 4 was 4.35%, 37.68% of them showed no change, and 57.97% of them were reversed to stage 2 or 1. The proportions of CKD stage 3a subjects showing progression, stabilization, and reversion were 20.59%, 61.76%, and 17.65%, respectively, in the control group. The differences were statistically significant. Among participants with CKD stage 3b in the treatment group, the proportion of individuals progressing from stage 3b to stage 4 was 9.21%, 50.00% of them showed no change, and 40.79% of them were reversed to stage 3a, 2 or 1. The proportions of CKD stage 3b subjects showing...
progression, stabilization, and reversion were 17.11%, 60.52%, and 22.37%, respectively, in the control group (Figure 8).

3.5. Safety and Adverse Events. There were no statistically significant differences between groups in laboratory parameters, either hematology, liver function, or electrolytes, after treatment (Table 15). During 24-week follow-up, the incidence of adverse events was 14.04% in the treatment group and 9.3% in the control group, without significant difference (Table 16). Two subjects in the treatment group, one experiencing 1 serious adverse event and the other suffering from benign meningioma and duodenal tumor (adenocarcinoma), were admitted to hospital. These serious adverse events were judged to have nothing to do with the study drug, by physicians. According to the analysis on adverse events (Table 17), the most prevalent events were mild abnormal liver function and mild elevation of blood potassium. However, overall incidence of adverse events was not significantly different between groups, suggesting that the study drug did not elevate the occurrences of adverse events.

4. Discussion

Our study indicated that Chinese herbal formula granules improved renal function as evidenced by decrease in serum creatinine and increase in eGFR in patients with CKD stage 3. 24-hour proteinuria was not reduced by TCM formula and was not significantly different between the two groups. The incidence of adverse events was not statistically different
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Table 11: Analysis of the change of eGFR in pre- and post-treatment.

| Variable | Treatment group | Control group | Statistics | P value |
|----------|-----------------|---------------|------------|---------|
| Change   | 7.40 (grouped T-test) | <0.0001 |
| N (missing) | 149 (1) | 148 (2) |
| Mean ± SD (ml/min/1.73 m²) | 17.95 ± 21.86 | 0.04 ± 19.83 |
| Median (ml/min/1.73 m²) | 17.93 | -0.72 |
| Min-max (ml/min/1.73 m²) | -33.85–88.97 | -58.75–63.27 |

Table 12: Change from baseline in eGFR over the 24-week follow-up period in the CKD stage 3a subgroup.

| Time          | Treatment group | Control group | Effect | F value | P value |
|---------------|-----------------|---------------|--------|---------|---------|
| Pretreatment (ml/min/1.73 m²) | 52.18 ± 4.14 | 51.85 ± 4.44 | Time effect | 2.08 | 0.0664 |
| Week 4 (ml/min/1.73 m²) | 58.06 ± 9.04 | 53.18 ± 8.45 | Difference between groups | 33.59 | <0.0001 |
| Week 8 (ml/min/1.73 m²) | 60.45 ± 10.28 | 52.04 ± 10.41 |
| Week 12 (ml/min/1.73 m²) | 60.43 ± 10.64 | 53.56 ± 11.24 |
| Week 16 (ml/min/1.73 m²) | 61.54 ± 11.18 | 52.17 ± 10.48 |
| Week 20 (ml/min/1.73 m²) | 61.60 ± 10.82 | 52.61 ± 10.65 |
| Week 24 (ml/min/1.73 m²) | 61.77 ± 10.78 | 52.63 ± 11.63 |

Table 13: Change from baseline in eGFR over the 24-week follow-up period in the CKD stage 3b subgroup.

| Time          | Treatment group | Control group | Effect | F value | P value |
|---------------|-----------------|---------------|--------|---------|---------|
| Pretreatment (ml/min/1.73 m²) | 36.53 ± 4.36 | 37.53 ± 4.34 | Time effect | 3.4 | 0.0043 |
| Week 4 (ml/min/1.73 m²) | 38.76 ± 0.68 | 38.22 ± 7.50 | Difference between groups | 23.68 | <0.0001 |
| Week 8 (ml/min/1.73 m²) | 41.49 ± 9.64 | 38.16 ± 8.49 |
| Week 12 (ml/min/1.73 m²) | 41.80 ± 8.85 | 38.73 ± 8.65 |
| Week 16 (ml/min/1.73 m²) | 43.01 ± 9.40 | 37.55 ± 7.81 |
| Week 20 (ml/min/1.73 m²) | 43.23 ± 9.54 | 37.11 ± 7.42 |
| Week 24 (ml/min/1.73 m²) | 43.97 ± 9.66 | 37.53 ± 8.23 |

Table 14: Change from baseline in urea nitrogen over the 24-week follow-up period.

| Time          | Treatment group | Control group | Effect | F value | P value |
|---------------|-----------------|---------------|--------|---------|---------|
| Pretreatment (mmol/L) | 8.75 ± 3.06 | 8.69 ± 2.69 | Time effect | 0.25 | 0.9388 |
| Week 4 (mmol/L) | 8.90 ± 2.68 | 8.24 ± 2.76 | Difference between groups | 4.26 | 0.0399 |
| Week 8 (mmol/L) | 9.02 ± 2.85 | 8.25 ± 2.61 |
| Week 12 (mmol/L) | 9.12 ± 2.75 | 8.22 ± 2.40 |
| Week 16 (mmol/L) | 8.94 ± 2.73 | 8.24 ± 2.25 |
| Week 20 (mmol/L) | 8.93 ± 2.72 | 8.34 ± 2.38 |
| Week 24 (mmol/L) | 8.76 ± 2.67 | 8.40 ± 2.54 |

between groups either, indicating the safety of Chinese herbal formula granules. Several factors may contribute to the progression of kidney damage, including hypertension, ageing, hemodynamic dysregulation, proteinuria, and high intake of dietary protein. Apart from kidney disease, proteinuria has been identified as a strong risk factor for CKD progression, and cardiovascular and all-cause mortality. Effective control over proteinuria may be renoprotective, and proteinuria is a crucial indicator for the measurement of treatment response in a variety of kidney diseases. Renin angiotensin-aldosterone system (RAS) blockers, glucocorticoids, and immunosuppressants are commonly used for primary glomerular diseases. Immunosuppressive therapies have been mainly adopted to treat patients with heavy proteinuria, but they are not entirely suitable for those with non-nephrotic-range proteinuria. Furthermore, long duration of treatment and high incidence of severe adverse effects limit the use of glucocorticoids and immunosuppressants. Therefore, in addition to RAS inhibitors, identifying other therapeutic agents would be necessary for patients with minor- to moderate-range proteinuria. TCM is widely regarded as a potential cost-effective alternative. The efficacy of Chinese medicine has been confirmed in some randomized controlled studies in recent years [9, 10]. However, studies on Chinese herbal compound formula are limited. Measurement on proteinuria could predict renal outcomes, including dipstick urinalysis, urine albumin-to-creatinine ratio (ACR) or protein-to-creatinine ratio (PCR), and 24-hour urinary albumin or protein excretion. 24-hour
urine collection for protein measurement is still considered to be the golden standard for measuring protein. ACR showed no superiority to PCR in predicting prognosis or detecting CKD in nondiabetic subjects [17]. Urine PCR, ACR, and 24-hour protein were reported to have equal utility to predict the doubling of serum creatinine, the commencement of renal replacement therapy, and all-cause mortality, according to a single-center retrospective cohort study [18]. In our study, due to heterogeneity in relevant standards across 9 hospitals, 24-hour proteinuria instead of ACR or PCR was adopted as a primary outcome to evaluate proteinuria. In the current study, Chinese herbal formula granules did not reduce proteinuria in patients with CKD stage 3. This might be ascribed to the short-term therapy and the fact that it was more difficult to lower proteinuria among patients with targeted CKD stage 3 which is more severe. It should be noted that changes in 24-hour proteinuria was much less in the TCM group than in control at every 4-week follow-up timepoint. So, the effectiveness of Chinese herbal formula granules on proteinuria needs to be further investigated.

Serum creatinine level is inversely correlated with GFR and is considered as an indirect marker of GFR. It can be used in estimation equations for GFR to approximate GFR. Notably, there was a gradual decline in serum creatinine in the TCM group. These results revealed that serum creatinine was obviously decreased and eGFR, calculated by the serum-based CKD-EPI equation, was significantly increased in the treatment group. Moreover, blood urea nitrogen remained unchanged. The accuracy of the eGFR equation is difficult to guarantee in a heterogeneous population. The CKD-EPI equation using creatinine, which is adopted widely, has such an accuracy that 80.6% of estimated GFR values are within 30% of measured GFR [19]. In day-to-day clinical practice, accuracy may be not necessary, and establishing an eGFR trend for an individual patient with CKD is probably more important. These outcomes demonstrated the efficacy of Chinese herbal formula granules in delaying the deterioration of kidney function in patients with CKD stage 3 for 6 months. This renal-protective function independent of proteinuria-lowering effects of TCM raises the question of how TCM compounds slow the progression of CKD.

Recently, accumulating clinical studies have focused on Chinese herbs for the treatment of CKD [20–22]. Since 2003, our group has been dedicated to characterizing the pathogenesis of CKD and to exploring the efficacy of TCM therapies [23, 24], and has proposed a complete TCM theory for the pathogenesis and treatment of CKD [25, 26]. As a result, several clinical trials and basic studies have been conducted to date [16, 27, 28]. The present study in patients with CKD stage 3 was the first prospective randomized controlled trial to evaluate clinical efficacy and safety of Chinese herbal formula compound which could tonify the kidney, clear away dampness, regulate circulation, and eliminate turbidity, according to TCM classic theory.

The studied Chinese herbal formula consists of 10 Chinese medicine herbs. According to TCM classic theory, Astragali (Huangqi) plus Angelica sinensis (Danggui), Polygonati cuspidati (Huangjing), and Achyranthis bidentatae (Niuxi) could benefit qi, nourish yin, and tonify the kidney and spleen to nourish blood. Astragali (Huangqi) plus Angelica sinensis (Danggui) can tonify the kidney and benefit qi. Astragali (Huangqi) combined with Polygonati (Huangjing) could benefit qi and nourish yin. Angelica sinensis (Danggui) accompanied by Achyranthis bidentatae (Niuxi) could replenish blood and promote blood circulation. Smilacis Glabrae (Tufuling), Serissa (Liuweixue), Centella (Jixuecao), Polygoni cuspidati (Huzhang), Pyrosideae (Shiwei), and Rhei (Dahuang) all could clear away damp-heat, promote blood circulation to remove blood stasis, boost uresis, and alleviate strangury. Collectively, these 10 Chinese medicine herbs tonify the kidney, clear away dampness, regulate circulation, and eliminate turbidity. With the development of modern TCM pharmacology, therapeutic targets and effective constituents of herbs are identified, which fills important gaps in our knowledge on herbs. Astragali and Angelica have been reported to be able to delay the progression of renal diseases by improving local tissue perfusion, balancing vasoactive substances, and directly improving endothelial function [29]. Polygoni cuspidate, whose major ingredient is polydatin, inhibits the expression of intercellular adhesion molecule 1 (ICAM-1) and serum tumor necrosis factor-alpha (TNF-α) in the process of renal ischemia-reperfusion injury [30]. In addition, Polygoni Cuspidati could lower lipid level and relieve renal impairment [31, 32]. Polygonati Regulates renal hemodynamics and slows the progression of
Smilacis Glabrae and Serissae can decrease serum uric acid and protect the kidney [33]. Centella ameliorates tubular interstitial fibrosis [34]. Rhei has been documented to delay the loss of renal function in both in vivo and in vitro studies [35]. By far, detailed mechanisms of the current TCM compound are still not completely understood. Possible mechanisms by which Chinese herbal formula granules preserve renal function may be ascribe to antirenal fibrosis, anti-inflammation, antioxidative stress, regulating microcirculation, and improving metabolism.

This clinical trial had some limitations. Firstly, the patients enrolled in this study had not been confirmed through renal biopsy. Secondly, proteinuria status varied among enrolled participants, even less than 2.0 g/d, and patients

Table 15: Change from baseline in safety outcomes over the 24-week follow-up period.

| Variable                        | Treatment group | Control group | P value time effect | P value group comparison |
|---------------------------------|-----------------|---------------|---------------------|-------------------------|
| White blood cell (×10^12/L)     |                 |               |                     |                         |
| Pretreatment                    | 6.49 ± 2.16     | 6.49 ± 1.81   | 0.2003              | 0.9694                  |
| Week 24                         | 6.53 ± 1.99     | 6.51 ± 1.86   | 0.0013              | 0.8842                  |
| Red blood cell (×10^12/L)       |                 |               |                     |                         |
| Pretreatment                    | 4.40 ± 0.54     | 4.53 ± 0.62   | 0.0842              | 0.1398                  |
| Week 24                         | 4.46 ± 0.56     | 4.69 ± 0.64   | 0.0842              | 0.1398                  |
| Platelet count (×10^12/L)       |                 |               |                     |                         |
| Pretreatment                    | 178.23 ± 49.27  | 190.31 ± 51.67| 0.2136              | 0.2415                  |
| Week 24                         | 192.03 ± 53.51  | 197.12 ± 53.75| 0.2136              | 0.2415                  |
| Albumin (g/L)                   |                 |               |                     |                         |
| Pretreatment                    | 42.92 ± 3.92    | 42.87 ± 6.03  | 0.2117              | 0.3561                  |
| Week 24                         | 44.28 ± 3.01    | 43.16 ± 3.90  | 0.2117              | 0.3561                  |
| ALT (IU/L)                      |                 |               |                     |                         |
| Pretreatment                    | 26.60 ± 15.62   | 23.91 ± 12.27 | 0.8650              | 0.2324                  |
| Week 24                         | 26.52 ± 15.46   | 26.03 ± 11.39 | 0.8650              | 0.2324                  |
| AST (IU/L)                      |                 |               |                     |                         |
| Pretreatment                    | 25.83 ± 13.00   | 23.33 ± 10.15 | 0.6925              | 0.5820                  |
| Week 24                         | 26.14 ± 12.69   | 23.72 ± 8.72  | 0.6925              | 0.5820                  |
| Blood potassium (mmol/L)        |                 |               |                     |                         |
| Pretreatment                    | 4.38 ± 0.62     | 4.34 ± 0.65   | 0.4012              | 0.8847                  |
| Week 24                         | 4.58 ± 0.59     | 4.33 ± 0.53   | 0.4012              | 0.8847                  |

Table 16: Analysis of adverse events.

| Variable     | Treatment group (n, %) | Control group (n, %) | Statistics | P value |
|--------------|------------------------|----------------------|------------|---------|
| Adverse event|                        |                      | 1.86 (CHISQ test) | 0.1721  |
| Total (missing) |                    | 171 (0)             |            |         |
| No           | 147 (85.96)           | 156 (90.70)         |            |         |
| Yes          | 24 (14.04)            | 16 (9.30)           |            |         |

CKD [31]. Smilacis Glabrae and Serissae can decrease serum uric acid and protect the kidney [33]. Centella ameliorates tubular interstitial fibrosis [34]. Rhei has been documented to delay the loss of renal function in both in vivo and in vitro studies [35]. By far, detailed mechanisms of the current TCM compound are still not completely understood. Possible mechanisms by which Chinese herbal formula granules...
without proteinuria were recruited. Thirdly, we used 24-hour proteinuria and serum creatinine instead of the incidence of ESKD and cardiovascular disease as primary outcomes. Besides, short follow-up duration also represented a limitation. Additionally, ARBs were adopted to control blood pressure, but calculated dosages of ARBs were not recorded or compared between treatment and control groups. Given the function of ARBs on protecting the kidney, the application of ARBs might influence analysis results. Therefore, further investigations are required to improve our findings.

In conclusion, Chinese herbal formula granules could preserve renal function in patients with CKD stage 3, independent of proteinuria reduction, and could be employed as an effective and safe therapy for patients with CKD stage 3.

Data Availability

All data generated or analyzed during this study are included in this article.

Ethical Approval

This study was approved by the ethics committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (approval number: AF/SQ140303). Study procedure was in accordance with the Declaration of Helsinki.

Consent

All subjects signed the written informed consent.

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

Table 17: Analysis of adverse events by frequency.

| Item                                      | Treatment group | Control group |
|-------------------------------------------|-----------------|---------------|
| Abnormal liver function tests             |                 |               |
| No. of patients with event                | 8               | 8             |
| No. of events                             | 8               | 10            |
| Event rate (%)                            | 4.55            | 4.47          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 3               | 3             |
| No. of events                             | 3               | 3             |
| Event rate (%)                            | 1.70            | 1.12          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 4               | 2             |
| No. of events                             | 6               | 3             |
| Event rate (%)                            | 2.27            | 1.12          |
| Mild                                      |                 |               |
| No. of patients with event                | 3               | 0             |
| No. of events                             | 5               | 0             |
| Event rate (%)                            | 1.70            | 0.00          |
| Moderate                                  |                 |               |
| No. of patients with event                | 1               | 3             |
| No. of events                             | 1               | 5             |
| Event rate (%)                            | 0.57            | 1.67          |
| General Clinical Symptoms and Discomforts |                 |               |
| No. of patients with event                | 0               | 1             |
| No. of events                             | 0               | 3             |
| Event rate (%)                            | 0.00            | 0.56          |
| Abnormal liver function tests             |                 |               |
| No. of patients with event                | 8               | 8             |
| No. of events                             | 8               | 10            |
| Event rate (%)                            | 4.55            | 4.47          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 3               | 3             |
| No. of events                             | 3               | 3             |
| Event rate (%)                            | 1.70            | 1.12          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 4               | 6             |
| No. of events                             | 6               | 8             |
| Event rate (%)                            | 2.27            | 3.35          |
| Mild                                      |                 |               |
| No. of patients with event                | 3               | 2             |
| No. of events                             | 5               | 2             |
| Event rate (%)                            | 1.70            | 1.12          |
| Moderate                                  |                 |               |
| No. of patients with event                | 1               | 0             |
| No. of events                             | 1               | 0             |
| Event rate (%)                            | 0.57            | 0.00          |
| Abnormal liver function tests             |                 |               |
| No. of patients with event                | 8               | 8             |
| No. of events                             | 11              | 11            |
| Event rate (%)                            | 5.11            | 5.11          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 3               | 3             |
| No. of events                             | 5               | 5             |
| Event rate (%)                            | 0.57            | 0.57          |
| Mild                                      |                 |               |
| No. of patients with event                | 1               | 2             |
| No. of events                             | 1               | 2             |
| Event rate (%)                            | 0.57            | 1.12          |
| Abnormal liver function tests             |                 |               |
| No. of patients with event                | 2               | 2             |
| No. of events                             | 2               | 2             |
| Event rate (%)                            | 1.14            | 1.14          |
| Abnormal hematology                       |                 |               |
| No. of patients with event                | 1               | 1             |
| No. of events                             | 1               | 1             |
| Event rate (%)                            | 0.57            | 0.57          |
| Abnormal liver function tests             |                 |               |
| No. of patients with event                | 0               | 0             |
| No. of events                             | 0               | 0             |
| Event rate (%)                            | 0.00            | 0.00          |

Authors’ Contributions

Jing Zhao, Wei Sun, Jihong Chen, Zhuxing Sun, Dai Chen, Chunhua Cao, Min Yang, Jipei Ma, Ling Wang, and Changying Xing conceived and designed the experiments and analyzed the data. Yan Chen, Meixiao Sheng, Enchao Zhou, Lingdong Xu, Kun Gao, Lihua Liu, Qiong Liu, Lan Yi, Weiming He, and Yuanyuan Zhu performed the experiments, wrote the paper, and organized the funding. All authors read and approved the final manuscript. Jing Zhao and Wei Sun contributed equally to this work.

Acknowledgments

This work was funded by the Key Clinical Study Projects of Science and Technology Department of Jiangsu Province.

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