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Study Protocol

Huangqi-Guizhi-Wuwu Decoction in the Treatment of Diabetic Nephropathy (CKD2-4): A Study Protocol for a Prospective, Open, Multicenter and Controlled Trail

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Abstract

Background: In recent years, the disease spectrum has been changing with the change of people's lifestyle. In terms of kidney diseases, the incidence of diabetic nephropathy is increasing year by year and has replaced chronic glomerulonephritis as the primary cause of uremia. Therefore, it is important to delay the progression of renal function in patients with diabetic nephropathy to reduce the occurrence of uremia.

Objective: To investigate the efficacy of the treatment of diabetic nephropathy (CKD2-4) with the addition and subtraction of Huangqi-Guizhi-Wuwu Decoction.

Method: The 100 patients with diabetic nephropathy were divided into two groups to compare the clinical efficacy. The control group was basic treatment + dapagliflozin, and the observation group was treated with Huangqi-Guizhi-Wuwu Decoction to compare the clinical efficacy, traditional Chinese Medicine (TCM) syndrome integral change, creatinine and urinary protein quantification of the two groups.

Expected results: Compared with the dapagliflozin, the addition and subtraction of Huangqi-Guizhi-Wuwu Decoction can significantly reduce the glomerular filtration rate, lower proteinuria of diabetic nephropathy (CKD2-4) and delay the progression of diabetic nephropathy.

Introduction

Epidemiological studies have shown that nearly half of the type 2 diabetes will develop diabetic nephropathy (DN), which is characterized by proteinuria and/or a persistent decline in kidney function. Currently, DN is the leading cause of end-stage renal disease (ESRD) in the western world, and about 42% of ESRD patients suffer from diabetes nephropathy. At the same time, we have observed that the percentage of chronic kidney disease (CKD) patients caused by diabetes is increasing in China, and it has been ahead of CKD caused by glomerulonephritis since 2011. It has become the main cause of CKD in China, bringing new challenges to the national medical, health system and chronic disease management. In addition, the development of DN increases the risk of morbidity and mortality of cardiovascular disease (CV). Subjects with both diabetes and DN had a mortality rate 3 to 12 times higher than those with diabetes alone [1-5]. In the 1990s, studies demonstrated the efficacy of blocking the renin angiotensin system (RAS) using angiotensin-converting enzyme inhibitors (ACE Inhibitors) or Angiotensin II receptor antagonists (ARBs) in reducing proteinuria and progression of renal function [6-7]. But there are no drugs explicitly used for the specific treatment of DN. Until recent years, glucose sodium cotransbator 2 inhibitors (SGLT2i) have emerged as drug candidates for DN. SGLT2i, initially used to help control blood glucose levels in patients with type 2 diabetes, has also been shown to reduce the risk of cardiovascular events, including major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) and hospitalized heart failure [8]. The results of cardiovascular risk trials in patients with

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type 2 diabetes also showed that SGLT2 inhibitors slowed the progression of renal failure. However, studies have reported that SGLT2i has adverse effects such as genital infections, urinary tract infections, diabetic ketoacidosis, and fractures [9-11]. Besides, guidelines recommend estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2, especially in patients with type 2 diabetes DN with albuminuria > 300 mg/g, although the U.S. prescription information for carbalaflozin has been updated to allow patients who have already received treatment with an eGFR of less than 30 ml/min/1.73 m^2 until dialysis or kidney transplantation begins. However, the study of George Bakris showed that it is not recommended to start treatment with SGLT2 inhibitors in patients with eGFR < 30ml/min/1.73m^2, although there may be a similar renal protective effect in patients with eGFR < 30ml/min/1.73m^2. Long-term clinical practice has demonstrated that Huangqi-Guizhi-Wuwu Decoction has significantly reduced proteinuria, blood creatinine, and increased glomerular filtration rate in DN patients, and some clinical studies have confirmed its effectiveness [13-15]. Therefore, our research team designed a prospective multicenter and open clinical study based on previous studies, including 9 parameters: urine routine (urine protein, red blood cell count), 24-hour urine protein quantification, urine microalbumin/urine creatinine, blood creatinine, blood routine, electrolytes, blood lipids, liver function, blood glucose status, and effectively combined subjective clinical variables and objective biochemical indicators. It aims to evaluate whether Huangqi-Guizhi-Wuwu Decoction has an advantage over dapagliflozin in protecting kidney function in patients with diabetic nephropathy (stage CKD2-4), and fill the gap in the treatment of patients with SGLT2i contraindications.

Methods and analysis

A total of 100 patients with diabetic nephropathy were enrolled into the observation group (Huangqi-Guizhi-Wuwu Decoction group), and the control group (dapagliflozin group) in a 1:1 ratio by open grouping. The treatment cycles are all 12 weeks. All the participants will be followed up at the 0, 2, 4, 6, 8 and 12 weeks by the investigator to understand the changes of symptoms, signs, glomerular filtration rate and 24-hour urinary protein quantification, and evaluate the efficacy. The above data will be recorded on a standardized electronic case report. The primary endpoint was a 15% decline in eGFR; The secondary end point was the doubling of the quantitative change in 24-hour urinary protein.

Strengths and limitations of this study

- This study is the first prospective, open label, multicenter clinical study comparing the efficacy of a Chinese herbal decoction with an SGLT2 inhibitor (dapagliflozin) in the treatment of diabetic nephropathy.
- TCM Decoction has fewer contraindications than dapagliflozin, and it increases the selectivity of drugs for patients with end-stage diabetic nephropathy.
- Participants will be recruited from 2 hospitals in China, which may introduce sample selection bias.

Study design

The study on Huangqi-Guizhi-Wuwu Decoction is a prospective, multicenter and open clinical study. Patients will be divided into" Huangqi-Guizhi-Wuwu Decoction group " and " dapagliflozin group ", and the study will be implemented in 2 tertiary care hospitals. Each participating center systematically followed up the participants with DN and can provide dietary preaching, etc. Participants will be followed up at weeks 2, 4, 6, 8, 12. A flow diagram of the entire trial is shown in Figure 1. The protocol of the study was designed according to the standard protocol items: recommendations for intervention trials (spiritual) reporting guidelines.

Inclusion criteria

1. Patients diagnosed as diabetic nephropathy
2. TCM syndrome differentiation is Qi deficiency and blood stasis type
3. Male or female 18 ≤ age ≤ 75
4. 25 ml/min/1.73 m^2 ≤ eGFR < 90 ml/min/1.73 m^2
5. 24-hour urine protein ration ≤ 3.5g/24h
6. Participants must understand and abide by the agreement and sign written informed consent.

Exclusion criteria

1. Exposure to immunosuppressors and glucocorticoid, no one week washing period.
2. Urinary tract infeution(leukocytes in urinary sediment >5/HP

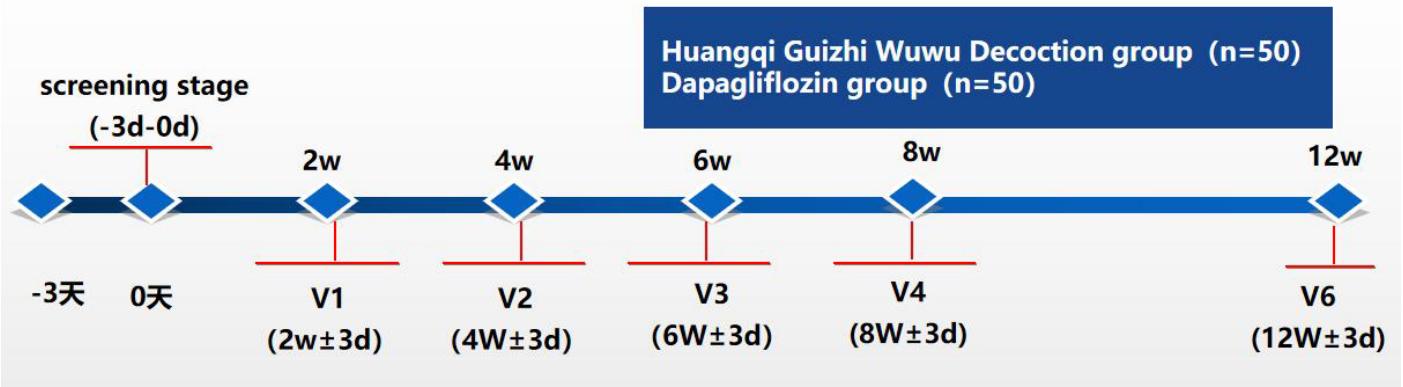

Figure 1. *Trial flow diagram of the Huangqi-Guizhi-Wuwu Decoction study. The overall trial flow, including a screening phase within 3 days, initiation of medication and end of 6 visit phases, was assessed. Enrolled subjects will be assigned 1:1 in an open label fashion to either the Huangqi-Guizhi-Wuwu Decoction group or the dapagliflozin group. Participants will be followed up at baseline (visit 0) for 2 weeks.*

3. Serum potassium >5.5mmol/L
4. Serum albumin <30g/L
5. Pregnant or lactating women, and participants (including males) who were unable or unwilling to take adequate contraception during the study period
6. Having comorbidities that affect the progression of diabetic nephropathy (including but not limited to malignant tumors, systemic autoimmune diseases, liver cirrhosis)
7. Participating in another clinical trial
8. Investigators holding it is not suitable for a participant to join this study.

Sample size

Discussed by clinical experts and combined with literature findings, the average change rate of EGFR from baseline in the study group is expected to be μ T = 27%, and the change rate of EGFR in the control group compared with baseline was μ C = 5.0%, i. e. , Δ = μ T- μ C=22%. Taken α= 0.05 (two-sided), β= 0.20, power = 0.80, the ratio of observation group and control group was assigned 1:1, and the statistical sample size was 39 cases per group. Considering exfoliation and other factors, the total sample size was increased by 20%, and 50 cases each between the observation group and the control group, resulting in the sample size of this study is no less than 98 cases. Therefore, the total number of cases for this clinical trial was determined to be 100.

Randomisation and allocation

Researchers will assign numbers to eligible participants according to the order of enrollment, assigning 1:1 for the Huangqi-Guizhi-Wuwu Decoction and Dapagliflozin groups.

Patient and public involvement

We will establish a reference group of patients and public involvement (PPI) including patients with DN, their partners, caregivers and representatives from the volunteer sector. A PPI reference panel will meet quarterly throughout the duration of the protocol. Panel members were consulted at all stages of work to make this recommendation and provided valuable insights and suggestions. The trial was designed in collaboration with PPIs to help maximize patient benefit. Our PPI representative had a significant impact on the decisions of the study population, promotion and recruitment. They will also continue to contribute throughout the pilot study in reviewing ethics approval documents, reading reports, and facilitating dissemination activities.

Treatment

All participants will receive routine treatment as usual, including regular dietary advice, hypertension, and diabetic disease management [16-17]. Huangqi Guizhi Wuwu Decoction group: Basic treatment + oral administration of the addition and subtraction of Huangqi-Guizhi-Wuwu Decoction 100ml in water decoction, twice-daily, oral Dapagliflozin group: base therapy + dapagliflozin 10mg,once-daily,oral. Medications from different hospitals were available to all participants. This period also created possible treatment differences.

Table 1. *√ 'indicates selected subsequent items; "" - "" indicates an unselected subsequent item.*

Follow-up items	1	2	3	4	5	6
Time	-3d-0d	2w±3d	4w±3d	6w±3d	8w±3d	12w±3d
Informed consent was obtained	√	-	-	-	-	-
Medical history, emographic data	√	-	-	-	-	-
Physical examination	√	√	√	√	√	√
Syndrome ifferentiation and scoring in TCM	√	-	-	-	-	-
24h urinary protein quantification	√	-	√	-	√	√
Urinaryalbumin/ urinary creatinine	√	√	√	√	√	√
Urine routine,	√	√	√	√	√	√
Blood routine	√	-	√	-	√	√
Biochemical liver work	√	-	-	-	-	√
Renal function,	-	√	√	√	√	√
Electrolytes	√	-	-	-	-	√
Serum potassium	-	√	√	√	√	√
Fasting glucose	√	√	√	√	√	√
Glycated Hemoglobin	√	-	-	-	-	√
Cystatin C	√	-	-	-	-	√
Ascertainment ofinclusion, exclusion criteria,	√	-	-	-	-	-
Concomitant medications	√	√	√	√	√	√
Adverse Events	-	√	√	√	√	√
Exit criteria	-	√	√	√	√	√

Outment measurement

All the participants will be followed until the criteria for termination are met (primary endpoint criterion: 15% and greater reduction in eGRF from baseline value; secondary endpoint criterion: doubling of 24-h urinary protein quantification), or 12 weeks after enrollment of the last patient. Participants in both the Huangqi-Guizhi-Wuwu Decoction group and the dapagliflozin group underwent follow-up assessments every 2 or 4 weeks, and detailed follow-up items at different follow-up stages are shown in Table 1.

Comprehensive demographic data (age, gender, ethnicity, height, weight, TCM syndrome collection, medical history, symptom signs, physical examination, etc.) will be collected on all the participants at baseline. Blood routine, urine routine, 24-h urine protein quantification, urine albumin/creatinine, blood lipids, liver and kidney function, eGFR, fasting plasma glucose are included.

At each follow-up visit, including vital signs, temperature, heart rate, respiratory rate, noninvasive blood pressure, and collection of data from syndrome differentiation in TCM, will be monitored for TCM syndrome scoring. Biochemical parameters, including urine microalbumin/urine creatinine, urine routine (urine protein, urine occult blood), renal function, serum potassium, fasting plasma glucose and 24-h urine protein quantification and blood routine were tested every 4 or 8 weeks. Glycated hemoglobin, Cystatin C, electrolytes, blood biochemistry (serum albumin, alanine transaminase, glutaryl transaminase and total bilirubin), urine microalbumin / urine creatinine, urine routine (urine protein, urine occult blood), renal function, serum potassium, fasting plasma glucose, 24-hour urine protein quantification and blood routine will be tested at week 12. Among them, urinary microalbumin / urinary creatinine was measured by the Central Laboratory of the Institute of kidney disease, Dalian Medical University. Concomitant medications, including calcium channel blockers, statins, ACE inhibitors, angiotensin receptor blockers and erythropoiesis stimulating agents and medications to treat other diseases, will be recorded during baseline and follow-up. Medical costs will be recorded during the visit phase and post study visit phase using questionnaires and participants' medical insurance records, including medication costs and outpatient costs of treatment. All of the above data will be recorded on standardized online electronic case report forms (eCRFs) based on an electronic data capture system. All adverse events (AEs) will be recorded on eCRFs and on a specific page retained for this purpose. Adverse events refer to adverse medical events that arise after a patient or a clinical trial subject take a drug, but they are not necessarily causally related to the treatment. Clinical adverse events include all unintended clinical manifestations such as malaise, abnormal laboratory values, and unexpected events (cerebrovascular accident, car accident, death, etc.), and should be reported as adverse events as long as these occur after signing informed consent, regardless of whether they are related to the test drug. All adverse events had to be presented in the form of clinical reports. The completed ECRF will be entered into a secure central database for independent quality control and centralized analysis.

Endpoint measurements

1. Patient reaching the endpoint event:
    - Main endpoint events: the eGRF is 15% or more lower than the baseline value;
    - Urinary protein was quantified and doubled at 24h.
2. The study cannot be carried out due to force majeure;
3. Large-scale and unexpected adverse reactions or serious adverse events occurred during the study;
4. The ethics committee or the sponsor decides to stop the trial.

Statistical analysis

General principle: All statistical tests were performed with a two-sided test, and p values less than 0.05 will be considered significant.

Statistical description: Example, mean, standard deviation, median, minimum and maximum values; frequency and frequency (%).

Statistical content analysis: The enrollment and completion number of each center are summarized, and the shedding cases are listed. Distribution of various central cases, comparison of total shedding rate, and detailed list of unfinished reasons. The patient demographic characteristics (age, height, vital signs, etc.), medical history and medication history were described. T test or Wilcoxon for rank sum test is used for measuring indicators; x2 test or Fisher's exact probability method is adopted for classification indicators, and Wilcoxon for rank sum test or CMH x2 test for rank data.

Ethics and dissemination

The trial received ethical approval from the ethics committee of the First Affiliated Hospital of Dalian Medical University, China (Registration no: pj-ks-ky-2021-228 (x2)) and the ethics committees of all participating centers. The findings will be disseminated through peer-reviewed journals, clinical practice guidelines and scientific conferences. ClinicalTrial.gov. Registry (NCT05418465); pre-results.

Informed consent and withdrawal from the study

Each participant or their authorised surrogates will sign an informed consent form. The process of informed consent will be in accordance with the Declaration of Helsinki. Participants will be fully informed about the ADIFE study by the investigators, and will be able to discuss the trial process with their nephrologists and contact the investigator directly to request further information. Participants and authorised surrogates will receive the related materials of informed consent. Participants will be informed of their right to withdraw from the study, either at their own request or at the discretion of the investigator, at any time without their care being affected in any way.

Dissemination plan

Survey data will be exported directly from the eCRFs as a text file and imported in electronic form for scoring and analysis using statistics software. A detailed data base will track participants' progress through the trial, including the scheduling of assessments and reminders to complete assessments. Detailed strategies, including phone or text message reminders, will be used to remind participants about upcoming assessments. All members of the research team and other associated personnel will have access to the final trial dataset in both identified and reidentifiable forms.

Printed data will be stored in locked filing cabinets, which

is accessible only to the research team. Electronic data will be stored on password-protected computers or servers that are only accessible to the research team. All paper and electronic records will be retained and disposed in accordance with the requirements of the Criteria for the Quality Control of Clinical Trial from Drugs China Food and Drug Administration.

The results from the outcome measures will not be presented in a way that compromises the confidentiality of the participants. Descriptions of participants will not allow identification of individual participants, and individual results and names will not be revealed. Final reports and publications will only comprise aggregated results. After the study, participants will receive a summary of the results in Chinese. Scientific reports of the main outcomes, secondary outcomes and process evaluation will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

Data management

All the information concerning the participants will be recorded on standardised online eCRFs, which will be anonymised and saved on password-protected computers.

The data monitoring committee, which will be independent from the sponsor and any other competing interests, will meet twice yearly to review the efficacy and safety data.

Oversight committees

A Trial Steering Committee has been set up and will include an independent chairperson, 25 independent members, and investigators of the study.

Safety monitoring

AEs will be closely monitored. These events are likely to affect the safety or physical or mental integrity of the participants in the trial to a significant degree. SAEs must be reported to the sponsor (the First Affiliated Hospital of Dalian Medical University, China) and the State Food and Drug Administration promptly, by fax or telephone, by the investigators, followed by a written report within 24hours.

Discussion

Treatment measures for diabetes are being progressively improved, yet the number of patients with diabetes progressing to end-stage renal disease continues to increase, so diabetes is now the most common reason for classification into renal replacement therapy programs worldwide. With the current explosion in the incidence of diabetes, especially the type 2 diabetes, we are at risk of an epidemic of ESRD in diabetes [18]. However, the diagnosis of DN is an exclusion diagnosis, depending on proteinuria in patients with at least 5 years' history of diabetes. Kidney biopsy is the gold standard for a clear diagnosis, treatment guidance, and prognosis of other types of kidney disease. However, it is not applicable to diabetic patients because of the risks associated with this intervention. This is mainly because there is no other treatment option for DN, except for the current optimal control of diabetes, hypertension, dyslipidemia, and lifestyle changes [19]. Unfortunately, these care standards may delay but do not prevent disease progression or the significant emotional, physical, and economic costs associated with the disease. Therefore, there is an urgent need to develop a new therapy for what is both effective and safe [20]. SGLT2 inhibitors increase urinary glucose excretion in an insulin-independent manner and reduce blood glucose and HbA1c in an insulin-dependent manner. To date, three large cardiovascular outcome trials have demonstrated the beneficial effects of these drugs extend beyond the control of glycemic [9,21]. However, some studies have noted that in the subgroup of patients with eGFR below 30ml/min/1.73m^2, the patients receiving dapagliflozin had a similar incidence of adverse events, serious adverse events, hyperkalemia and hypoglycemia compared with the treated control patients, and relevant contraindications also exist in the patients with eGFR>30ml/min/1.73m^2. Therefore, for patients with end-stage DN or contraindication, the dilemma of no specific drugs is returned. In recent years, renal fibrosis has emerged in the public as a new therapeutic target. The essence of renal fibrosis is the scar accumulation caused by pathological fiber repair. Meanwhile, the deposition of matrix protein separates the renal tubular basement membrane from the peritubular capillary, resulting in the renal tubulointerstitial fibrosis [22]. Biological research believes that chronic kidney disease refers to the breaking of the vascular niche balance caused by various pathological factors, changing the living environment of the cells, causing the disorder of the microenvironment of the vascular niche, which can cause ischemia and hypoxia of the kidney, forming fibrosis. This process also exists in the DN. Moreover, through clinical and animal experiments, it is clearly pointed out that [23]: collaterals are highly correlated with the capillary network and the surrounding environment, and it can be considered that the concept of renal fibrosis is related to the collaterals theory of TCM [24-25]. Therefore, we can conduct the treatment of promoting blood circulation and remove the blood stasis according to the theory of kidney complex disease. Its representative prescription is Huangqi-Guizhi-Wuwu Decoction,whose composition includes: Huanagqi, Guizhi, Chishao, Shengjiang and Dazao. Huangqi is sovereign drug, whose pharmacology effects are antiphlogosis, antioxidant, immune regulation, improve cardiovascular, inhibit tumor proliferation; Containing volatile oil components, Guizhi can expand blood vessels, promote microcirculation, antiphlogosis, sedation and analgesia; As an assistant drug, Chishao can expand blood vessels, improve microcirculation, and protect vascular endothelium. Besides, Shengjiang and Dazao can dilate blood vessels, improve the body surface circulation, increase myocardial contractility, and improve myocardial nutrition. The above drugs have the effect of improving microcirculation and dilating blood vessels. In recent years, studies on the treatment of DN under the guidance of collateral pathogenesis have shown that Huangqi-Guizhi-Wuwu Decoction can significantly reduce proteinuria and blood creatinine in DN patients, and increase glomerular filtration rate, effectively improving symptoms and signs and protecting renal function. For the past few years, TCM has been paid wide attention as a source of novel therapeutic agents due to its various efficacy, non-toxicity and / or side effects [26]. On the basis, we designed a multicenter controlled trial on DN (CKD stage 2-4) patients to compare the effectiveness of Huangqi-Guizhi-Wuwu Decoction and dapagliflozin in the treatment of DN, thus further reporting its therapeutic effect.

Trial status

Recruitment has commenced using digital social media networks and print-based advertising nationwide in November 2021. The recruitment is expected to be completed in October

2022. The study will be completed by December 2022.. The study will be completed by December 2022.

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Competing interests

None declared.

Patient consent for publication

Parental/guardian consent obtained.

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